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Life-Threatening Dermatoses and Emergencies in Dermatology

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Preface

For many reasons, dermatology has acquired a special status among medical specialties. As the most accessible organ, skin was from the origin of humanity frequently exposed to therapeutic interventions and manipulations by spouses, wizards, physicians, artists and scientists. With the tremendous development of science in the 19th century, dermatology benefited early from the most advanced technologies. Photography, bacteriology, and pathology proved especially efficient for studying skin diseases. The "clinical-pathological" method arose as the gold standard for describing a myriad of diseases. As a consequence, dermatology textbooks became two to three times thicker than internal medicine textbooks.

As a heritage from this caricatural historical background, the definitions and boundaries of dermatological diseases are more complicated and controversial than the borders of Caucasian countries and regions.

Too many physicians, rebuffed by its confusion and complexity, have a poor knowledge of dermatology, and seldom appreciate the impact and consequences of skin disease. Most of them underestimate the physiological role of the skin as an organ, as important for life as any other one. Nearly all, including some dermatologists, are skeptical regarding the very concept of "dermatological emergencies".

This concept of emergency in dermatology is nevertheless very familiar to patients. Who would not be frightened by the brutal occurrence of fever and a painful rash? Family physicians and emergency physicians are therefore frequently confronted with acute skin lesions. It matters little if they do not give an adequate diagnosis to the 90% that are benign or not clinically significant. On the other hand, they should not miss those that are dangerous, either through a direct impact on the function of the skin or as marker of a serious systemic disease. The editors of this book, all of whom have worked in hospital units specialized in life-threatening dermatological diseases, have the common experience that diagnoses with prominent cutaneous manifestation are often delayed, resulting in less than adequate management.

One major aim of this book was therefore to help general practitioners, emergency room physicians, and intensive care specialists to recognize life-threatening dermatoses and to better interpret the skin symptoms of acutely ill patients. Another important goal was to remind dermatologists that they may, like every other medical specialist, be on the front line to fight life-threatening diseases, and that they

should not miss the occasional dangerous disease that may hide behind a common skin manifestation.

The format of this book was designed to support these aims. There are often several entries for a single disease: (1) by dermatological diagnosis, (2) by presenting skin symptoms with a decisional tree emphasizing urgent diagnoses that should not be missed, and (3) by risk factors (associated diseases, immunosuppression, etc.)

As any multi-authored book, this one has not avoided duplications, expression of different points of view and, occasionally, contradictions. As far as contradictions concerning matters of classification, mechanisms of action and investigation priorities, they were respected by the Editors. In settings where emergency management was concerned, we tried to solve all discordant point of views based on the best available evidence, even if often the evidence was poor.

September 2008

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Part I

Skin Physiology

Skin Barrier

1

Joachim W. Fluhr and Razvigor Darlenski

Core Messages

- Skin accomplishes the protection of the mammalian organism against exogenous physical, chemical, and biological agents, as well as sustaining the organism's homeostasis.
- The majority of the barrier mechanisms of the skin are attributed to the stratum corneum.
- The concept of 'bricks-and-mortar' organisation of the stratum corneum comprises the corneocytes with their cornified envelope and the intercellular bilamellar lipids.
- The regulation of the skin barrier homeostasis involves different mechanisms: skin surface pH, hydration of the stratum corneum, calcium ion gradient in the epidermis, nuclear hormone receptors and their ligands, and immune-cell mediators.
- The cutaneous barrier is perturbed in skin diseases such as atopic dermatitis, irritant dermatitis, and psoriasis, as well as in certain life-threatening dermatoses, e.g. toxic epidermal necrolysis, staphylococcal scalded skin syndrome, and Netherton syndrome.
- Skin barrier function can be assessed by non-invasive methods in vivo, e.g. transepidermal water loss, stratum corneum hydration, and skin surface pH measurement.

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Abbreviations: aSMase Acidic sphingomyelinase, AMP Antimicrobial peptide, BCs Barrier creams, β-Gluc-Cer'ase Beta glucocerebrosidase, Ca Calcium, CS Cholesterol sulphate, CLE Corneocytes-lipid envelope, CE Cornified envelope, DM Diabetes mellitus, ET Exfoliative toxins, FFA Free fatty acids, KVE Kaposi's varicelliform eruption, LB Lamellar bodies, LXR Liver X receptor, LEKTI Lymphoepithelial-Kazal-type 5 inhibitor, NMF Natural moisturing factor, NS Netherton syndrome, NHR Nuclear hormone receptors, PPAR-α Proliferator-activated receptor alpha, PS Psychological stress, sPLA2 Secretory phospholipase A_2, SLS Sodium lauryl sulfate, SSSS Staphylococcal scalded skin syndrome, SS'ase Steroid sulfatase, SC Stratum corneum, TJ Tight junctions, TEN Toxic epidermal necrolysis, TG Transglutaminase, TEWL Transepidermal water loss

1.1 Introduction: Skin as a Reflection of Internal Milieu

The epidermal barrier is the outermost part of our body, or more precisely, of our skin. Approximately 90% of the barrier function can be attributed to the stratum corneum. A barrier separates two distinct areas or compartments, or as defined in the Merriam-Webster Online Dictionary [1] is either (a) 'something material that blocks or is intended to block passage', or (b) 'a natural formation or structure that prevents or hinders movement or action'. The importance of the epidermal barrier, and more specifically the stratum corneum with its major components the corneocytes, the intercorneoal bilamellar lipids and the cornified envelope, has become increasingly evident over the last years. The mutation in the cornified envelope protein, namely the gene encoding for filaggrin in atopic dermatitis has brought

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a broad interest to the epidermal barrier [2]. With additional knowledge on the skin barrier, its link to inflammation, disease induction and disease activity will be more at the centre of clinical and basic research.

The skin separates the inner part of our body from the potentially harmful external environment. During fetal development and after birth, the epidermal barrier with its respective functions develops [3]. The skin barrier protects the human body against many external stressors, namely physical stress (e.g. mechanical, thermal, UV radiation), chemical stress (e.g. tensides, prolonged water exposure, solvents) and environmental conditions [4]. Furthermore, the skin as a barrier prevents the organism from loss of essential components such as ions, water and serum proteins. The epidermal barrier also reflects internal processes, diseases, disease activity, and some of the lifestyle manifested in intrinsic and extrinsic aging. The skin has also socio-cultural functions and plays an important role in communication and self-expression. On the other hand, many skin diseases are not only aggravated by psychological factors [5] but also reflect psychosomatic conflicts [6].

The stratum corneum became 'alive' over the last decades and its understanding evolved from the simple two-compartment system (bricks-and-mortar model) to a system with a regulated metabolic activity and, ultimately, as a biosensor for external factors to regulate (e.g. proteolytic activity, DNA-synthesis, and lipid-synthesis) [7]. Recently the new concept of 'Dermatoporosis' has been suggested, comparable to osteoporosis [8]. This term implies the progressive alteration of the skin with the clinical signs of senile purpura, stellate pseudoscars, and skin atrophy. The functional expression of skin fragility results in minor traumas such as frequent skin laceration, delayed wound healing, unhealing atrophic ulcers, and subcutaneous bleeding with the formation of dissecting hematomas leading to large areas of necrosis.

Ontogenetically, the epidermal barrier is formed relatively late during embryogenesis [3]. The establishment of the barrier is completed at approximately 34 weeks gestational age [9]. Premature infants show increased transepidermal water loss (TEWL) and high susceptibility to infections, both indicating immaturity of the epidermal barrier. Independently from the gestational age, further maturation processes take place in the first weeks after birth, e.g. formation of the surface acidity of the skin [10]. The incomplete acidic mantle in neonates is one element in the vicious cycle of susceptibility to developing diaper dermatitis [11].

1.2 Components and Structural Organization of the Skin Barrier

The concept of the bricks-and-mortar model is schematically presented on Fig. 1.1. In this model, the major components of the SC barrier are corneocytes with their cornified envelope ('bricks') and the intercellular bilamellar lipids ('mortar'). The mechanical strength of the skin is provided by the corneocytes, embedded in a cornified envelope (CE) consisting of extensively cross-linked proteins such as loricrin, involucrin and filaggrin. The adjacent lipid bilayers are responsible for the repletion of water and regulate electrolyte movement.

1.2.1 Lipids

The major biochemical compounds of the SC barrier include lipids and proteins. The lipids of SC comprise approximately 50% ceramides, 25% cholesterol, 15% free fatty acids, and some minor lipid components [12]. The composition of SC lipids differs markedly from the biomembrane lipids. Ceramides represent a family of structurally heterogeneous lipids, containing long-chain base components and omega-hydroxyacids

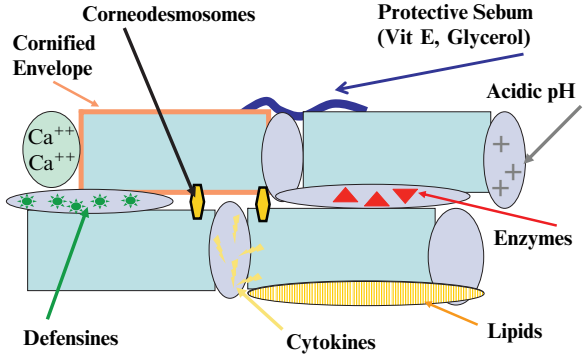

Fig. 1.1 Schematic overview of the *bricks-and-mortar* model of the organization of SC. Link to protective functions of the epidermal barrier and their biochemical correspondence

and 6-hydroxysphingosine as binding blocks. Although new members continue to be discovered, ceramide 1 is the least polar of SC ceramides and plays a major role in the organization of the intercorneocyte lipid bilayers [13]. There is also evidence that covalently-bound bilayers of omega-hydroxyceramides on the exterior surface of the CE form the so-called corneocytes–lipid envelope (CLE) [14]. The functions of CLE are to sustain SC cohesion, to serve as a scaffold for extracellular lamellar organization, and/or to keep the osmotically active material inside the corneocyte.

The three major classes of SC lipids originate from their precursors (phospholipids, glucoceramides, sphingomyelin, free sterols) derived to the SC by ovoid membrane-bilayer-enriched secretory organelles, named lamellar bodies (LB) or Odland bodies [12]. The LB contain enzymes including lipid hydrolases and proteases important for further extracellular lipid processing and desquamation. Once secreted into the intercellular space of the SC, the precursor lipids are transformed by the enzymes delivered from LB themselves (Fig. 1.2). This process is known as 'lipid processing'. Different factors affect this step in lipid transformation, e.g. changes in surface acidity and barrier disruption. Inhibition of phospholipase A_2, responsible for conversion of phospholipids to free fatty acids, results in defective structure of the intercorneocyte lipid membranes [15]. Experimental perturbation of the skin barrier leads to a rapid increase in the epidermal cholesterol synthesis associated with increased activity and mRNA levels of HMG CoA reductase, a key enzyme in the cholesterol biosynthesis [12]. Deficiency in beta glucocerebrosidase (β-Gluc-Cer'ase) and acidic sphingomyelinase (aSMase) activity, respectively in Gaucher's and Niemann Pick disease, leads to defects in the extracellular lipid bilayers and disturbance in the skin barrier function [12].

In lipid processing the polar lipid precursors are enzymatically converted into non-polar products and assembled into lamellar structures. Different models for the organisation of the membrane sheets have been proposed, e.g. a 'domain-mosaic' model [16], a 'sandwich' model [17] and a 'single gel phase' model [18]. Electron microscopy studies using ruthenium tetroxide as postfixation reagent have revealed the unique lamellar arrangement of the intercellular lipids. The electron-lucent lamellae appear as pairs of continuous leaflets, altering with a single fenestrated lamella, and each electron-lucent lamella separated from electron-dense lamella. According to the sandwich model, ceramide 1 plays a key role in the formation of the interstitial SC structure. Cholesterol may provide some necessary

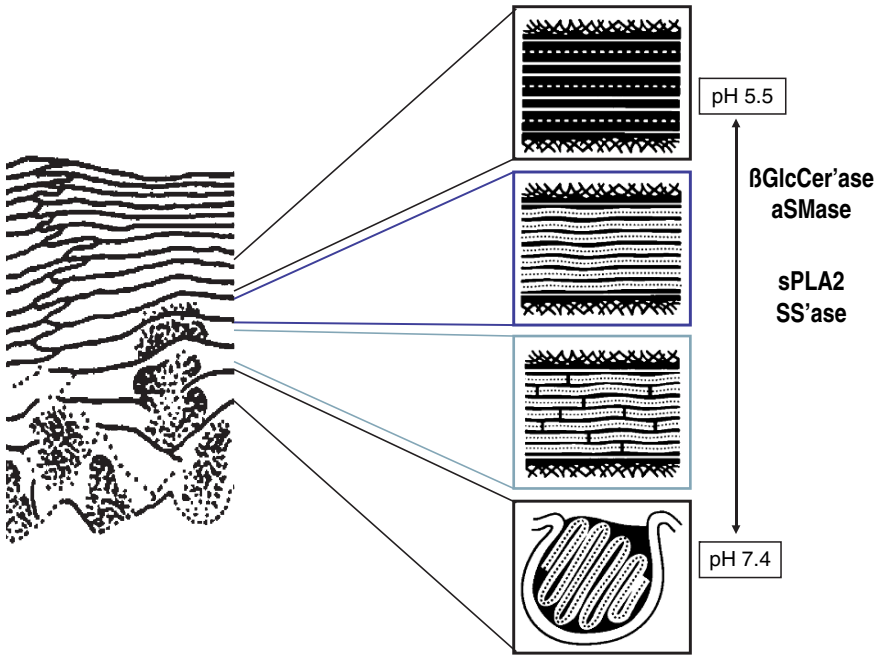

Fig. 1.2 Lipid processing of the lipids in SC

fluidity to the membranes, thus facilitating the elastic properties of the skin [19, 20].

1.2.2 Proteins

Proteins, such as keratins, loricrin, involucrin, fillagrin and corneodesmosine, play an important role in the structuring of corneocyte cytosol, as well as in the formation of the CE and the intercorneocyte junctions.

Keratins form the intermediate filaments of the cytoskeleton. The major keratins expressed in the suprabasal layers of the skin are K1, K2e and K10. They form approximately 80% of the corneocyte's mass [21]. In forming the corneocyte scaffold, K1 and K10 are bound to the corneodesmosomal desmoglein 1 and desmocollin 1, via desmosomal plaque proteins, e.g. plakoglobin and desmoplakins. Moreover, keratins interact with the cross-linked proteins of the CE, thus providing further stability of the SC barrier. Frameshift mutations of K1 genes in ichthyosis hystrix resulted in defective intermediate filament bundling [22].

Filaggrin is a member of the S100 Ca^{2+} binding protein family. The enzymatic transformation of profilaggrin, packed in the keratohyalin granules of stratum granulosum, generates two end products — filaggrin and a N-terminal peptide. In the lower layers of SC, filaggrin aggregates keratin filaments into macrofibrils. Approaching the skin surface, filaggrin is mostly degraded into free amino acids, thus forming a major part of the highly hygroscopic complex called natural moisturing factor (NMF). NMF is important for maintaining SC hydration and skin flexibility [23]. The profilaggrin N-terminal peptide plays a role in the process of programmed epidermal cell differentiation [24]. A small amount of filaggrin has been found cross-linked to loricrin as a component of the CE [25].

Members of distinct protein families are cross-linked in the formation of CE, e.g. involucrin, loricrin, envoplakin, filaggrin and small praline-rich proteins [25, 26]. Loricrin is the major protein composition of the CE, and constitutes around 70% of its mass [26]. It is derived from the keratohyalin granules. Patients with mutations of the loricrin gene alleles demonstrate a different disease pattern, known as Vohwinkel syndrome, with digital constrictions (pseudo-ainhum), honeycomb keratoderma, and mild to moderate generalized ichthyosis [27]. Involucrin predominates in the outer portion of the CE. It is supposed to be the first envelope precursor cross-linked in the formation of the CE. The process of cross-linking is regulated by the calcium-dependent enzyme, transglutaminase-1 (TG1) [28, 29]. Although there are at least two other isophorms of TG, their activity has been demonstrated insufficient to compensate the TG1 insufficiency in lamellar ichthyosis [28, 29].

Corneodesmosomes (desmosomes of SC) are comprised of different proteins, i.e. desmosomal cadherins, desmogleins, and desmocollinis, of desmosomal plaque proteins, and of extracellular protein (corneodesmosin) [30]. Corneodesmosin, an LB-secreted protein, is bound to the outer part of the CE in regions corresponding to corneodesmosomes [30]. This protein plays a central role in SC cohesion, as an association between its degradation and the shedding of corneocytes is observed [31]. It has been proposed that the sites of corneodesmosome hydrolysis correspond to the 'aqueous pore pathway' for water, drug and xenobiotic movement in the epidermis [32].

Although SC physically separates the living organism form the environment, barrier function can not only be attributed to this layer. Knockout mice deficient in claudin-1 showed elevated TEWL [33]. Claudins are transmembrane components of the tight junctions (TJ) of the viable epidermis. SC and TJ cooperate in formation of the skin barrier. Transgenic mice overexpressing claudin-6 developed barrier defects resulting from changes in both TJ and SC [34].

1.3 Protective Functions of the Skin

Skin, being the largest and the outermost organ, accomplishes the interface of the living organism with the surrounding environment. Major functions of the skin are dedicated to maintaining the homeostasis of the organism against external changes. As the potentially 'hazardous' components of the environment are of different nature the protective functions of the skin barrier can be summarized as: (1) defence against exogenous physical (mechanical stress, thermal changes, UV light) and chemical (xenobiotics, toxic chemicals, allergens) insults, (2) antimicrobial protection, (3) antioxidant defence, (4) water loss restriction and hydration, (5) permeability barrier (selective absorption), and (6) integrity/cohesion/desquamation/programmed renewal.

The distinct defensive functions of the skin barrier are not performed independently from each other. The opposite is true: molecular and biochemical interactions, and common regulatory mechanisms fulfil the integrated and interrelated protective functions of the skin barrier. For example, barrier permeability and antimicrobial function are interrelated on the molecular level. Protection against pathogenic microorganisms of the skin is accomp-lished by the mechanical barrier of SC, antimicrobial lipids and peptides, enzyme inhibitors, receptors, and chemokines. Beyond these, some SC lipids exhibit antimicrobial activity, i.e. free fatty acids, sphingosine and glucosylceramides. A critical component of the innate immune response in the skin can be attributed to three antimicrobial peptides: the cathelicidins, defensins, and dermcidins. These three classes of peptides have been shown to act as antimicrobials by directly inhibiting pathogen growth as well as by potentiating other branches of the innate, humoral, and cell-mediated immune system [35, 36]. Human beta-defensin 2 is an antimicrobial peptide (AMP), which is co-packaged along with lipids within epidermal LB before their secretion [37]. As it was previously noted, LB lipid and enzyme contents are essential for forming the permeability barrier homeostasis. Conversely, LB-derived AMPs are also related to the permeability barrier homeostasis. A delayed permeability barrier recovery has been demonstrated in cathelin-related AMP −/− mice [37]. This abnormality was attributed to defective LB contents and abnormalities in the structure of the lamellar membranes that regulate permeability barrier function [37]. Finally, the levels of human beta-defensin and LL37 (human analogue of cathelin-related AMP) were significantly decreased in acute and chronic lesions from patients with atopic dermatitis. A deficiency in the expression of AMPs may account for the susceptibility of patients with atopic dermatitis to skin infection with Staphylococcus aureus [38].

Another example of functional interrelations is the diverse effect of psychological stress (PS) on the protective functions of the epidermal barrier. Delayed skin barrier recovery has been demonstrated in experimental animals exposed to PS [39]. Pre-treatment with phenothiazine sedatives restored the kinetics of barrier recovery toward normal, suggesting that PS is the basis for this alteration in barrier homeostasis. Furthermore, the results showed that PS stimulates endogenous production of glucocorticoids, which, in turn, adversely affects permeability barrier homeostasis. Additionally, pre-treatment with a glucocorticoid receptor antagonist blocks the delay in barrier recovery [39]. The integrity of SC is decreased by PS. An animal model of insomniac PS revealed compromised SC integrity, as well as disturbed epidermal barrier homeostasis [40]. The authors showed the mechanisms of the barrier abnormalities caused by PS: reduction in the number of LB in the granular layer, inhibition of the synthesis of epidermal lipids, decreased desmoglein 1, diminution in both the size and number of corneodesmosomes, and decline in the expression of epidermal differentiation-related proteins (involucrin, loricrin, filaggrin) [40]. PS also influences the antimicrobial defence function of the skin barrier. Recent results showed downregulation of two AMPs (murine epidermal cathelicidin and moues beta-defensin 3) in both the epidermis and the skin appendages of animals exposed to PS [5]. PS-induced decline in epidermal AMPs correlates with increased susceptibility to cutaneous infections, and is mediated by an increase in endogenous glucocorticoids.

The effects of PS on the skin barrier functions have clinical implications. A large number of skin diseases associated with abnormalities in the epidermal barrier, including atopic dermatitis and psoriasis, are precipitated by PS [41]. During periods of PS, the homeostatic and the defensive functions of the skin are disturbed, which results in disease exacerbation.

1.4 Regulation of Skin Barrier Homeostasis and Functions

Several regulatory mechanisms and signal pathways interact in the formation and the maintenance of the intact skin barrier.

1.4.1 SC Hydration

Water is essential for the normal functions in the living organism. Mammalian skin is exposed to a relatively dry surrounding environment. Retaining water, a function predominantly attributed to SC, ensures skin flexibility and elasticity. Water distribution is not homogenous in the epidermis. A novel technique, *in vivo* confocal

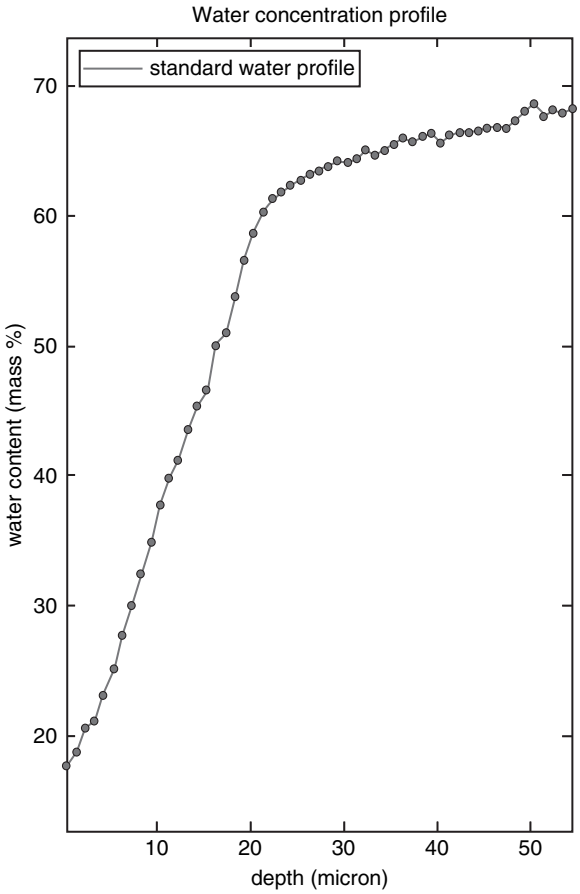

Fig. 1.3 A typical curve for the water distribution in the epidermis as a function of depth in the epidermis. The values are obtained by *in vivo* Raman microspectroscopy of the volar forearm

Raman microspectroscopy, confirmed the epidermal water gradient [42, 43]. The authors showed a continuous rise in water concentration in the SC from 15 to 25% at the skin surface to about 40% at the SC/stratum granulosum border. This is followed by a steep rise to a constant level of about 70% in the viable epidermis [43]. A typical curve for the water distribution in the epidermis as a function of depth is demonstrated on Fig. 1.3.

Water acts as a plasticizer of the corneocyte proteins and the intercellular medium [44]. Skin hydration is responsible for the resistance to mechanical stress. At reduced hydration, SC is less extendable [45]. Furthermore, SC in aged skin (which tends to be less hydrated) shows reduced elasticity [44].

The process of corneocyte desquamation on the skin surface depends on SC hydration. Corneodesmolysis is regulated by several enzymes, i.e. serine proteases and glycosidases. Water in SC is required for the normal function of these enzymes, thus resulting in normal cornecyte desquamation [46]. Impaired desquamation occurs in diseases with reduced SC hydration, e.g. ichthyosis vulgaris and winter xerosis [47]. Furthermore, visual scaling has been linked to decreased SC ceramide levels [44]. It was shown that the barrier properties of intercellular lipid membranes contribute to the water-binding properties of the SC [48]. Thus reduction in the structural components of the intercellular space is an important element of impaired water retention in scaly skin. The degradation of filaggrin is also catalyzed by hydrolytic enzymes, a process that produces the free amino acids and amino acid derivatives that, together with specific salts, form the NMF (essential for maintaining SC hydration) [49]. Proteolytic activity of these enzymes is modulated by the SC water content. Studies have shown that high water content in the SC prevents the production of NMF by filaggrin proteolysis. Decreased water content triggers the proteolysis of filaggrin, and subsequently the generation of NMF [50]. Reduction of NMF generation in ichthyosis vulgaris leads to impaired barrier repair after disruption [46].

The formation of rigid CE is impaired in dry skin, related to the level and the activity of transglutaminase (TG, key enzyme in the cross-linking of CE proteins) [47]. Patients with lamellar ichthyosis due to TG1 deficiency have abnormal CE and are clinically presented with scaly skin [51]. Low humidity exposure directly increases epidermal interleukin-1 (IL-1) [52]. SC contains a preformed pool of this proinflammatory cytokine, the latter playing a key role in skin inflammation [53]. This could be an explanation of the exacerbation of certain inflammatory dermatoses in a dry and cold environment. Water content of SC is also important for the repair of disrupted barrier. The induction of lipid biosynthesis after barrier disruption was shown to be reduced at high humidity [54]. The barrier recovery was faster in animals acclimatized to a dry environment, in comparison to those acclimated to a humid environment [54, 55].

1.4.2 Calcium Ion Gradient

Calcium (Ca) is important for the normal functions of biological barriers. For example, disturbance of

the Ca homeostasis has been correlated to the disruption of the blood–brain barrier in stroke [56]. Under basal conditions, low levels of Ca in the basal and spinous layers are observed, followed by an increase with a peak in the SG [57]. Calcium ion gradient plays a key role in the restoration processes after skin barrier disruption. The recovery process was impeded when immersing the barrier-disrupted skin into Ca-containing bathing solutions. Moreover, perturbations of the permeability barrier homeostasis resulted in alteration of the normal Ca gradient, with decrease of Ca levels in the outer epidermis [58]. The restoration of the perturbed barrier was parallel to the normal Ca gradient recovery. It has been postulated that the decrease of Ca concentration after acute barrier disruption stimulates the secretion of preformed pool of LB at the SG/SC boundary. Hence, the required components for the barrier recovery are delivered. It was further demonstrated that lowering the Ca levels can regulate directly the exocytosis of the LB, independent from disruption of the skin barrier [59].

Increasing the Ca concentration in the media resulted in induction of cell differentiation and stratification. Calcium is also necessary for the formation of intercellular contacts. The synthesis of cadherin-mediated cell-to-cell junctions is compromised in the absence of Ca [60].

Internalization of the extracellular Ca is required for completing the regulatory functions. Protein kinase C (PKC) is proposed as a signal transducer that regulates the Ca transport between extra- and intracellular compartments [61]. Selective inhibition of PKC-delta impedes barrier-repair responses by increasing intracellular free Ca [62]. Dysfunctions in the epidermal Ca gradient have a clinical implication. Diseases such as X-linked ichthyosis and psoriasis demonstrate both defective permeability barrier and abnormalities in epidermal Ca gradient [63, 64].

1.4.3 Nuclear Hormone Receptors and Their Ligands

The functions of nuclear hormone receptors (NHR) are connected to regulation of the process of transcription. The role of NHRs has been proven in the regulation of epidermal development and permeability homeostasis. Glucocorticoids and estrogens bind NHRs and stimulate skin barrier ontogenesis [65]. However, administration of supraphysiologic systemic or topical glucocorticoids leads to delayed barrier recovery after acute disruption [66]. Such an effect has been observed in psychological stress, linked to an increase of the endogenous steroid levels [39]. On the other hand, androgens delay the ontogenetic development of the epidermal barrier, stimulate epidermal hyperplasia and suppress the barrier permeability function [67].

Several NHRs are activated by lipids and their metabolites, hence being called ‘liposensors’. The role of peroxisome proliferators-activated receptor alpha (PPAR-α) in the epidermal development in utero was demonstrated in experiments with homozygous PPAR-α knockout mice [68]. PPAR-α −/− animals displayed delayed formation of the SC, decreased SC cell layers, decreased β-Gluc-Cer’ase activity, delayed processing of extracellular lamellar bilayer membranes, and lower expression of CE proteins [68].

Activation of PPAR-α stimulates keratinocyte differentiation and inhibits proliferation. Pharmacological PPAR-α activators caused in vivo decrease in the epidermal thickness and increase in the markers of differentiation, i.e. involucrin, loricrin, and profilaggrin/filaggrin [69]. The application of PPAR-α agonists in experimental models of irritant and allergic contact dermatitis decreased the magnitude of the inflammatory infiltrate and the expression of proinflammatory cytokines (tumor necrosis factor alpha and interleukin-1-alpha) [70].

A similar anti-inflammatory effect was also shown by activating the liver X receptor (LXR), another member of the NHR family [71]. Moreover, LXR activators stimulate keratinocyte differentiation, improve permeability barrier homeostasis, and accelerate the in utero development of the SC. In addition, findings from experiments with neonatal rats revealed that LXR activators accelerate postnatal SC acidification [72]. These studies suggest the possibility that LXR activators could be of clinical benefit in the prevention and/or treatment of cutaneous disorders during the neonatal period, as SC acidification is essential for formation of intact skin barrier.

The fact that liposensor NHRs are activated by lipids and their metabolites, and that the LB derive to the epidermis lipids and are then further processed, created the suggestion that these receptors could be the linking unit that regulates the bricks-and-mortar formation during

epidermal development and recovery of the impaired skin barrier [65].

1.4.4 Stratum Corneum pH as a Regulatory Mechanism

The acidic nature of skin surface is widely recognized and has been known for a long time [73]. Traditionally, exogenous (originating outside the epidermis) mechanisms have been invoked to explain the formation of the acidic surface pH. These exogenous mechanisms include the generation of (a) microbial metabolites (e.g. free fatty acids (FFA), generated by resident microorganisms lipases), (b) FFA of pilosebaceous origin [74], and (c) eccrine gland-derived products, such as lactic acid [75]. In addition to exogenous mechanisms, three endogenous pathways have been identified as potential contributors to SC acidity: generation of *cis*-urocanic acid by histidase-catalyzed degradation of histidine [76]; secretory phospholipase A2 (sPLA2) generation of free fatty acids from phospholipids [77]; and a nonenergy- dependent sodium proton exchanger [78]. A schematic overview of the present concept of the formation of SC pH is presented in Fig. 1.4.

The acidic pH of SC is essential for the formation of intact skin barrier. Although in rodent skin the basal permeability barrier function is competent at birth [78], skin surface pH is neutral at birth in both humans and in animal models [79–81]. Following acute barrier disruption either by tape stripping or by acetone treatment, barrier recovery was markedly delayed in the newborn rats [79]. Further animal studies excluded a variety of exogenous and endogenous mechanisms previously implicated in SC acidification after birth [82]. The results proved the roles for two endogenous mechanisms, the sPLA2 pathway and NHE1, in the generation of the postnatal acid mantle. It was also noted that neonatal epidermis, although morphologically similar to day 5–6 epidermis, is more hyperproliferative at birth than day 5–6 epidermis [82]. The functional consequences of neutral surface pH included abnormal permeability homeostasis and defects in SC integrity, attributed respectively to the reduced β-GlucCer'ase and increased serine proteases activity directly after birth [79]. Exogenous acidification of SC normalized barrier recovery kinetics and improved SC integrity [79].

An acidic surface pH develops within the first weeks to months of life in humans [81]. A prospective study in a cohort of 202 healthy neonates demonstrated decreased surface pH and an increase in desquamation in the first

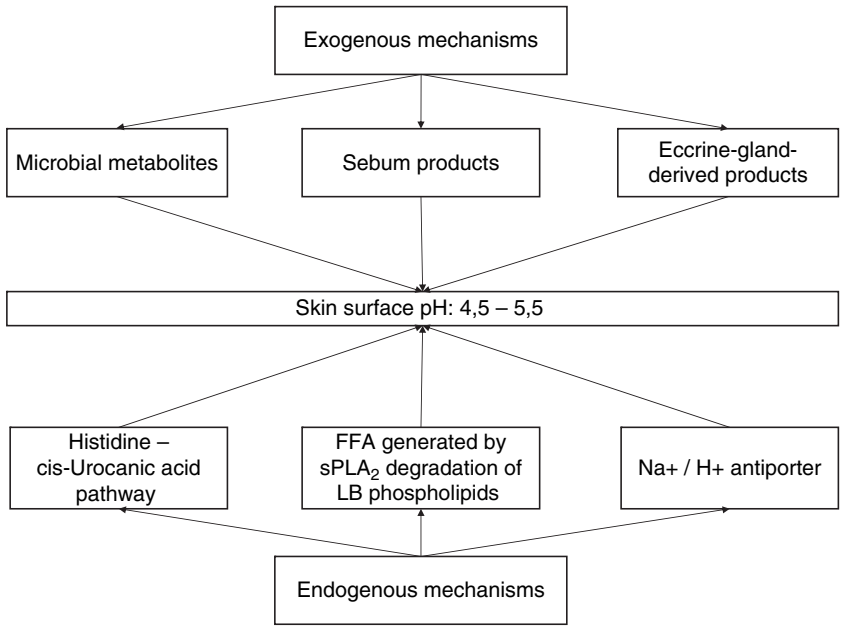

Fig. 1.4 An overview of the current concept of skin surface pH formation

12 weeks after birth (reviewed in [73)]. Moreover, the absence of an acidic SC at birth has been associated with an increased risk for bacterial and yeast infections in neonates [83]. The clinical importance of these findings is reflected in the pathophysiology of diaper dermatitis. The incomplete acidification of the SC, together with the ammonia-induced alkalization, activates stool enzymes (trypsin, lipase) causing irritation and further perturbation of the skin barrier.

SC acidity is essential for epidermal barrier recovery, the latter being delayed at a neutral pH, due to disturbance in processing of the secreted extracellular SC lipids, while lipid secretion remains unimpaired [84]. The abnormalities in barrier homeostasis have been attributed to the acidic pH optima of the key lipid-processing enzymes, i.e. β-Gluc-Cer'ase and aSMase. Rising of pH resulted in perturbations in the processing of the LB-derived lipid precursors. Later it was shown that prolonged increase of pH leads to degradation of these enzymes by sustained serine protease activity [85]. It was further demonstrated that prolonged increase of pH not only delays barrier recovery, but also increases the basal TEWL values [85]. It has been proposed that an acidic pH directly impacts lipid–lipid interactions in the SC extracellular lamellar bilayers [86].

The acidity of the skin surface is also involved in regulation of the corneocyte desquamation, respectively SC integrity and cohesion. The main enzymes proven to regulate integrity/cohesion, kallikrein 5 (previously known as SC trypsin-like enzyme, SCTE) and kallikrein 7 (previously known as SC chymotrypsin-like enzyme, SCCE), exhibit normal-to-alkaline pH optima [87, 88]. A superbase-induced elevation in SC pH resulted in reversible increase of the activity of these enzymes [31]. Moreover, these changes are followed by degradation of desmoglein 1 and reduction of the corneodesmosome density, thus stimulating the process of desquamation [31].

Finally, the acidic buffer system, or the so called acidic mantle of the skin, is essential for performing an unspecific antimicrobial protection. Elevation of the pH values is beneficial for growing pathogens on the skin surface, such as Staphylococcus aureus and Candida albicans, while normal flora predominantly grow best in an acidic environment [73, 89]. Hence, the alteration of a single regulatory mechanism, such as surface pH, leads to perturbations of multiple functions of skin barrier-permeability homeostasis, integrity/cohesion, and antimicrobial defence.

1.5 Barrier Disturbance and Skin Disorders

1.5.1 *Atopic Dermatitis as a Model of Impaired Barrier Function*

The assessment of the epidermal permeability barrier function routinely employs measurements of TEWL, which provides information about permeability barrier status under either normal, experimentally-perturbed, or diseased conditions [90]. Atopic dermatitis is one of the most important skin diseases not only for the patients but also for their treating physicians. Dermatologists, general practioners, and pediatricians feel the challenge of treating a rising number of patients with an increasing complexity with regard to their clinical picture and resistance to classical therapeutical approaches. Five to ten percent of children in western countries are affected by atopic eczema and epidemiological studies provide evidence that the prevalence of atopic dermatitis is increasing in wealthy populations [91, 92].

The physiology of atopic skin has been characterized over the last two decades. The low stratum corneum hydration [93, 94] is parallel to decreased water-binding capacity [94]. Both lesional and non-lesional skin suffers from an increased transepidermal water loss, indicative of a deficient epidermal permeability barrier function [95]. The assessment of atopic dermatitis activity is usually based on the so-called SCORAD (Score of atopic dermatitis) [96]. Recently, an objective activity score has been introduced based on the measurement of biophysical parameters (TEWL and SC hydration) [97, 98]. The observation of a defective barrier function was sustained by biochemical alterations in atopic skin, namely a decrease in ceramide 1 and 3 fractions [99–102]. Biochemical studies revealed the importance of alterations in the activity of sphingomyelin deacylase and glucosylceramide deacylase, resulting in decreased ceramide levels [103–106]. Furthermore, pathological extruding mechanisms of lamellar bodies are partly responsible for the biochemical alterations of epidermal lipids and for the impaired permeability barrier function in atopic dermatitis [107]. The vulnerability to bacterial colonization (S. aureus) of the skin of atopic patients might be associated with reduced levels of a natural antimicrobial agent, sphingosine, which results from decreased ceramide levels

as a substrate and from diminished activities of its metabolic enzyme, acid ceramidase [108]. The physiological regulation of the permeability barrier function, inflammation and SC integrity, cohesion, and desquamation, as well as anti-inflammatory activity and antimicrobial defense, have been attributed to acidity of the SC [10]. Atopic dermatitis, in contrast, is characterized by an increased stratum corneum pH. Recent studies have now revealed that the mutation in different genes (R510X, 2282del4, and others) encoding for filaggrin are associated with an increased risk of developing atopic dermatitis, asthma, and ichthyosis vulgaris [109]. This genetic defect leads to a premature termination of the filaggrin protein. An early exacerbation, as well as an increased risk of allergic contact sensitization, has been reported with this mutation [110]. In previous years, the main attention in the pathogenesis of atopic dermatitis was drawn to the importance of immunological factors. A key role for impaired epidermal barrier function can now be attributed to the development of atopic diseases [109].

1.5.2 Irritant Contact Dermatitis and the Skin Barrier

Irritant contact dermatitis, defined as the inflammatory response of the skin to an exogenous agent without requirement of prior sensitization, presents a major health problem with serious social and occupational impacts. The main pathological mechanism of irritancy include skin-barrier disruption, induction of a cytokine cascade, and involvement of the oxidative stress network, all of them resulting in a visible or subclinical inflammatory reaction.

The integrity of the epidermal barrier plays a pivotal role in the interaction and the response of human skin to irritating stimuli. Different mechanisms of barrier impairment are involved depending on the various irritating stimuli. Organic solvents, e.g. acetone and toluol, extract the SC lipids, thus disrupting the entity of the epidermal barrier [111]. On the other hand, the anionic surfactant sodium lauryl sulfate (SLS) damages protein structures such as keratins, which exposes new water-binding sites and causes hyperhydration of SC and disorganisation of the lipid bilayers [111, 112]. Regardless of the nature of the affecting agent, acute barrier disruption induces processes of restoration of the homeostasis. The triggering factor in the repair process is the increased water release through the impaired SC and the consequent reduction of Ca concentration in stratum granulosum, thus inducing lamellar body secretion and lipid restoration [113].

Chronic exposure to solvents, water and detergents, which is inevitable in many occupations, may lead to an impairment of the skin barrier, so that hazardous substances are allowed to reach the reservoir of the SC or even deeper layers of the skin [114]. Multiple strategies are known to prevent dermatitis. Improving skin-barrier function by use of barrier creams (BCs) is of a special interest not only in the field of occupational skin diseases. Skin BCs reduce or even prevent the penetration into the skin by building up a physical barrier, like a thin film, between the skin and the irritant. Barrier repair creams act on three different levels of the epidermis: (a) an immediate effect is provoked by adding a lipid mixture to the skin surface (occlusion), (b) an intermediate effect by adding a lipid mixture to the intercellular spaces, and (c) a delayed effect by providing lipids to the epidermal cells, which should restore the natural barrier function of the skin (reviewed in [114]). Despite the use of BCs in the prevention of irritant dermatitis, the best strategy remains the avoidance of the contact of the skin barrier to the irritant.

1.6 Epidermal Barrier and Life-Threatening Dermatoses

Skin-barrier properties could be seriously perturbed in a number of life-threatening skin diseases such as disorders of keratinization and cornification, toxic epidermal necrolysis (TEN), and staphylococcal scalded skin syndrome (SSSS) in particular. The loss of the epidermal barrier functions may result in excessive electrolyte and fluid loss, and/or massive invasion of pathogenic and opportunistic microorganisms [115]. Impaired epidermal barrier homeostasis is a well-known predisposing factor for the development of generalized cutaneous infections. A classical manifestation of the skin barrier abnormality and insufficient defensive mechanisms is the Kaposi's varicelliform eruption (KVE) in patients with atopic dermatitis. Erythroderma, characterized by impeded barrier homeostasis, has also been recognized as a cause for an increased susceptibility to KVE in psoriatic patients [116].

Studies in the past decade linked skin-barrier abnormalities and the SSSS on the molecular level. Virulent stains of Staphylococcus aureus produce exfoliative toxins (ET), which cause the loss of cell-to-cell adhesions in the upper layers of the epidermis [117–119]. Different isoforms of the ET (A, B, D) are capable of cleaving a single peptide bond in the extracellular region of desmoglein 1, responsible for formation of the desmosomes in the superficial part of the epidermis. ET are glutamate-specific serine proteases that do not possess enzymatic activity in their native state. However, the specific binding of desmoglein 1 to the ET promotes their enzymatic activity and leads to degradation of the cell-to-cell junctions in the superficial epidermis. It has been shown that this process was dependent on Ca ion concentration (reviewed in [120)]. Indeed, the alpha toxin of S. aureus exerts its proinflammatory and cytotoxic effects on the keratinocytes by forming a transmembrane pore, which represents an ionophore for ions such as Ca [121]. Thus, a mobilization of the intracellular Ca is stimulated. The changes in the Ca ion gradient, on the other hand, could influence the repair processes of the perturbed epidermal barrier as noted previously in this chapter. Furthermore, S. aureus induces the expression of tumor necrosis, factor-alpha in human keratinocytes [122]. Hence, this microbe–keratinocyte interaction could be the initial event in the S. aureus-induced inflammation and skin-barrier disruption in SSSS.

Skin-barrier abnormalities have been demonstrated in ichthyosiform erythrodermic syndromes such as Netherton syndrome (NS) and nonbullous congenital ichthyosiform erythroderma. NS is a life-threatening multisystemic congenital disorder characterized by ichthyosiform erythroderma, hair-shaft defect and atopic diathesis. Mutation in the gene encoding the lymphoepithelial-Kazal-type 5 inhibitor (LEKTI), a serine protease inhibitor with specific activity against epidermal kallikrein 5 and kallikrein 7, is the cause for the genodermatosis [123]. The increased activity of the epidermal serine proteases leads to enhanced loss of corneodesmosomes related to increased degradation of desmoglein 1 and desmocolin 1. Moreover, extracellular lipid processing was impeded in patients with NS due to decreased content of β-Gluc-Cer'ase and aSMase (key lipid processing enzymes). The skin-barrier abnormalities corresponded to the disturbed formation of the mature lipid lamellar bilayers [123, 124]. However, accelerated and premature LB secretion, together with the upregulation of the lipid processing enzymes in the nucleated epidermal layers, could compensate partly for the defective skin barrier in NS.

The role of skin-barrier impairment has been studied as a risk factor for the development of anaphylaxis and TEN after non-mucosal topical drug application [125]. Application of topical medication to wounds or to skin with compromised barrier function was revealed as a risk factor for anaphylaxis in 88% of the published cases. In the majority of these cases, the causative agent was an antibiotic or topical antiseptic agent. The role of perturbed barrier homeostasis in life-threatening dermatoses plays a key role in the systemic absorption of topical medications. An increased blood concentration of tacrolimus has been shown in patients with generalized leukaemic erythroderma treated with this topical medication [126]. Along with the large body surface area of treatment, perturbed skin-barrier function was disclosed as a cause for the excessive percutaneous absorption of the drug. In order to diminish the risk of the development of adverse events (e.g. nephrotoxicity), drug monitoring and decreasing the size of the application area are advisable in erythrodermic patients treated with tacrolimus.

Restoring the skin barrier is important in the therapy of potentially fatal diseases such as TEN. Wound coverage with glycerol-preserved donor allografts is recommended, in order to prevent fluid/protein loss and the development of infection [127]. Re-epithelization was completed for 8 days, and pain relief was achieved after the graft application. The efficacy and the limited costs of this treatment make it useful in the management of burns characterized by extensive skin loss. Understanding epidermal barrier and its diverse functions is important not only for the explanation of the pathology mechanisms of some deadly skin diseases but also for therapeutic considerations in connection with skin-barrier abnormalities.

1.7 Assessing Epidermal Functions

Transepidermal water loss (TEWL) is the most prominent parameter for evaluating the epidermal permeability barrier function of the skin. A low TEWL therefore is a characteristic feature of a healthy skin state.

TEWL measurements can be used to assess the inside–out barrier but also indirectly to predict the

influence of topically applied substances at the skin surface. Furthermore it might be an indicative parameter for the permeability of the barrier to externally applied compounds.

Measurement of TEWL is typically used to assess objectively skinbarrier function [128, 129]. Thus, the use of this parameter is reasonable in objective disease evaluation scores, such as in atopic dermatitis [97, 98]. There are different methods for TEWL measurement; the unventilated chamber (closed) method, the ventilated chamber method, and the method using an open chamber. To perform accurate and reliable measurements, variable factors related to the panellists, environment, and the instrument should be taken into account.

Basal skin barrier properties, evaluated by TEWL value, could be used as a predictor for susceptibility to irritating substances. Indeed, a number of studies have revealed good correlation between pre- and post-exposure TEWL in SLS irritation models, mainly after a single exposure [130, 131]. In terms of irritancy testing, TEWL measurement is the most appropriate non-invasive parameter for distinguishing skin changes over time in experimental irritation induced by SLS and tape stripping, compared to irritation models with dithranol and UV irritation [132]. Consequently, TEWL is useful in the evaluation of the irritants that interact primarily with the epidermal barrier.

Monitoring barrier function in clinical settings has revealed increased TEWL in diseases characterised by skin-barrier impairment, such as atopic and contact dermatitis, ichthyoses, and psoriasis.

Generally, one of the characteristics of healthy skin is the proportionality between TEWL and hydration [133]. Failure of the SC to retain water induces dryness, and thus leads to impairment of the skin-barrier function. Different techniques for evaluation of skin hydration have been introduced. Most commonly used methods are based on measuring the electrical conductance, capacitance, or impedance as an indirect indication for SC hydration. However, the classical electrical methods do not give the actual gradient distribution of water in SC. Novel techniques, e.g. confocal Raman microspectroscopy, are helpful in determination of the water gradient over the whole extent of SC [49]. The method is based on the inelastic light-scattering of different molecules. Beyond water gradient, it was also shown to be useful in detection and semi-quantitive measurement of skin components (lactate, urea, urocanic acid) and exogenously applied substances (dimethyl sulfoxide, trans-retinol) in the depth of the epidermis [134, 135].

Harvesting SC material is convenient ground for further research of skin-barrier components and functions. Different techniques for sampling skin surface material exist, e.g. scraping with a blade, use of quick-setting cements, and use of topical extracting solutions. Nonetheless, application of adhesive methods for harvesting SC is widely used in skin-barrier investigations. Collected material is then the object of further investigation with spectroscopic, cytological and qualitative/quantitative analysis. Skin-barrier disruption by adhesive tapes is influenced by different variables, such as pressure, time and anatomical site. The demand to gain reproducible and reliable data resulted in standardization of the D-Squame® adhesive tape method [136]. Sampled material with the D-Squame® method is processed further for studying the compounds and the regulation of biochemical processes in SC [137], oxidative stress [138], tracing of chemical substances [139], and the efficacy of cosmetic products [140].

Adhesive tape methods are applied in investigations of SC integrity and cohesion. The integrity of the SC is quantified as the number of tape strips required to induce a predefined degree of barrier disruption, e.g. to raise the TEWL to a certain level [136]. It reflects resistance to the dissociation of adjacent corneocytes. On the other hand, SC cohesion is evaluated by the amount of SC removed by sequential tape stripping. Thus, an increase in the mass removed by tape is a marker for a decrease in the cohesion of SC, and conversely, a lower amount of SC removed with increasing tape number is due to the increased cohesion between the cells in deeper layers.

In summary, skin as an integument organ plays an essential role in the survival of animals and humans. It accomplishes the protection of the human organism against the potentially hostile surrounding environment. The skin barrier is not just a fortuitous combination of biochemical compounds but a strictly organized and synchronized system acting as a unified entity. By performing simultaneously multiple protective functions, skin contributes to the sustaining of the homeostasis of the organism. The diverse defensive functions of the skin barrier are in intimate interrelation. The disturbance of one protective mechanism could lead to perturbation of other functions. Different regulatory mechanisms, such as surface pH, ion gradients, and hormonal regulation,

are required to sustain skin-barrier functions and homeostasis. Breakdown of the regulatory processes results in skin-barrier perturbation, which is clinically expressed as disease manifestation (e.g. atopic dermatitis, ichthyosis, psoriasis). Restoration of skin-barrier components and functions is the basis for the future perspectives of dermatological therapy.

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Skin Immune System

2

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Core Messages

- The epidermis has a powerful innate immune system.
- Keratinocytes are immunologically active cells, able to identify and kill invading microbes.
- Keratinocytes recognize highly conserved structures of the pathogens, called pathogen-associated molecular patterns (PAMPs), via pattern recognition receptors (PRRs), which results in the secretion of antimicrobial and proinflammatory mediators.
- Antimicrobial peptides and proinflammatory chemokines/cytokines, effector molecules of innate immunity, also act as regulators of acquired immune responses, inflammation and wound repair.
- Keratinocyte-derived effector molecules are critical in the recruitment of dendritic cells, T cells and neutrophils into sites of infection, linking innate and acquired immune responses in the skin.

2.1 Introduction

Daily contact with the environment exposes the skin to a large number of external microorganisms including pathogens. In healthy individuals, however, the deeper layers of the skin remain free of infection, suggesting that skin has the ability to fight against invading microbes. The outermost skin layer, the epidermis, provides the first line of defense against pathogens. Historically, keratinocytes, which form 95% of all epidermal cells, were believed to function in maintaining the structure of the epidermis via production of cytokeratins, and in constituting the physical barrier to a variety of exogenous microorganisms. In the last decade, after observations that keratinocytes express *pattern recognition receptors* (PRRs), are potent source of cytokines, chemokines, antimicrobial peptides, and are able to express the class II MHC antigens, it has become clear that keratinocytes play key roles in epidermal immune responses [1, 2]. This chapter will summarize recent findings concerning the role of PRRs, antimicrobial peptides and proinflammatory chemokines/cytokines in innate and acquired immune responses of the skin.

2.2 Ancient and Modern: Innate and Acquired Immunity

Innate immunity is the most ancient and common system for defense against microbial infections. It evolved a detection system, a limited set of receptors (e.g., toll-like receptors; TLRs) against microbial signatures that remain invariant inside a class of microbes [3]. Given that epithelial cells lie at the interface between the host and the environment, the expression of TLRs on these cells provides the first line of defense against invading pathogens through the recognition of microbial motifs. Although termed *pathogen-associated molecular patterns* (PAMPs), these motifs are not restricted to distinct pathogens, since they include structural molecules

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Table 2.1 Toll-like receptors (TLRs) expressed by keratinocytes and their ligands

Receptor	Ligand	Origin of ligand
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria
TLR2	Lipoproteins and lipopeptides	Various pathogens
	Phenol-soluble modulin	*Staphylococcus epidermidis*
	Lipoarabidomannan	Mycobacteria
	Lipoteichoic acid	Gram-positive bacteria
	Atypical lipopolysacharide	*Leptospira interrogans* and *Porphyromonas gingivalis*
	Zymosan	Fungi Host
	Heat-shock protein 70	
TLR3	Double stranded RNA	Viruses
TLR4	Lipopolysacharide	Gram-negative bacteria
	Heat-shock protein 70	Host
TLR5	Flagellin	Bacteria
TLR6	Lipoteichoic acid	Gram-positive bacteria
	Zymosan	Fungi
	Diacyl lipopeptides	*Mycoplasma*
TLR9	CpG-containing DNA	Bacteria and viruses

such as lipopolysacharide (LPS), lipoteichoic acid (LTA), peptidoglycan (PGN), lipoarabidomannan (LAM), flagellin, zymosan or double-stranded (ds) RNA (Table 2.1.), which are common to multiple species of bacteria, yeast or viruses. In addition, a number of endogenous ligands, such as heat-shock proteins or β-defensins, are also TLR ligands (Table 2.1). These endogenous molecules are also called 'danger signals', released from dying or dead cells in order to trigger an inflammatory response [3].

The innate immune network of the skin consists of a range of pre-existing, rapidly mobilized host defense components including keratinocytes, neutrophils, mast cells, eosinophils, macrophages, and sebocytes. The key cellular components of the pathophysiologic processes of the skin are the keratinocytes, cells that are in a unique position between the interface of the environment and the host organism [4]. The findings that keratinocytes, which form 95% of all epidermal cells, express PRRs and are potent source of antimicrobial peptides and chemokines/cytokines emphasize their key role in the innate immune responses of the skin [1, 2]. Epidermal keratinocytes express, in a constitutive or inducible manner, at least seven out of 11 known TLRs (TLR1-TLR6 and TLR9) [5–10], as well as nucleotide-binding oligomerization domain protein 2 (NOD2) [11]. Recognition of PAMPs by PRRs initiates quick innate immune responses such as phagocytosis, and the production of antimicrobial compounds and inflammatory mediators, resulting in the killing and elimination of microorganisms. In addition, these mediators link innate and acquired immunity, as they also function as chemoattractants for the effector cells of the acquired immune response [4].

A rapid innate immune response mediated by keratinocytes subsequently promotes acquired immunity [12]. Importantly, upon cutaneous inflammation, innate and acquired immunity operate simultaneously, leading to extravasation and homing of cutaneous lymphocyte-associated, antigen-expressing (CLA^+) memory T cells to the skin, permitting them to encounter and respond to appropriately presented antigen. The ability of not only T but also B cells to recombine antigen receptor genes during development provides an efficient and powerful acquired immune system with nearly unlimited specificity for antigen. Although a fundamental aspect of mammalian biology, immunologic memory is a relatively recent evolutionary event.

2.3 Molecular Mechanisms of Pathogen Recognition in the Skin

2.3.1 TLR/IL-1R Superfamily and Their Signaling Pathways

TLR/IL-1R superfamily members are characterized by the presence of a variable extracellular domain devoted to specific ligand-recognition, and a highly conserved intracellular toll-interleukin-1 (IL-1) receptor (TIR) domain that mediates the signal transduction (Fig. 2.1).

2.3.1.1 Members of the TLR Family Expressed by Keratinocytes

Since Gram-positive skin-infecting bacteria such as *Staphylococcus aureus* or *Borrelia burgdorferi* are known to be rich sources of LTA and lipoproteins that are well-known ligands of TLR2 homodimers (Table 2.1), the abundant and constitutive expression of TLR2 in the epidermis is not surprising [7–9]. TLR2 homodimers are also involved in the recognition of LAM of mycobacteria and atypical LPSs of *Leptospira* and

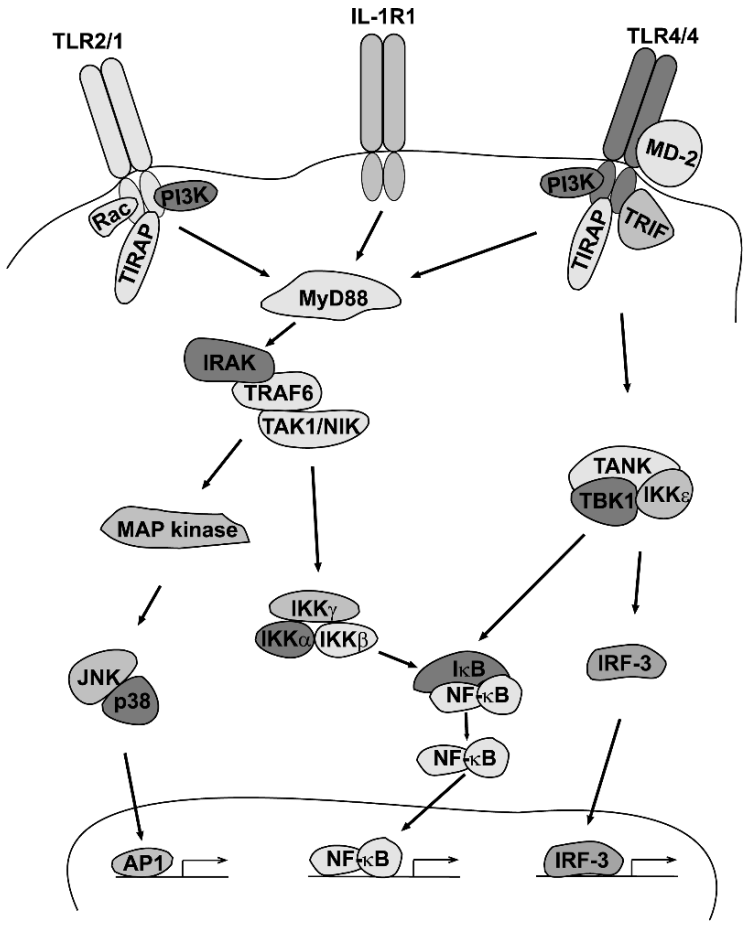

Fig. 2.1 *Signal transduction pathways via TLR/IL1R*. The TLR signaling pathway is highly homologous to that of the IL-1R family. After binding of an appropriate ligand, both TLRs and IL-1R interact with an adaptor protein, MyD88, through their TIR (Toll/IL-1R) domains. Upon signaling, MyD88 recruits a serine/threonine kinase, IRAK. IRAK is activated by phosphorylation and then associates with TRAF6, another adaptor protein, leading to activation of either the JNK pathway, through MAP kinase, or the NF-κB pathway, through the IKK complex. Signal transduction via TLRs and/or IL1Rs leads to the expression of antimicrobial and antiviral peptides, cytokines and chemokines. [*IKK* IκB kinase kinase, *IRAK* IL-1R-asssociated kinase, *JNK* c-Jun N-terminal kinase, *MyD88* myeloid differentiation primary-response protein, *NF-κB* nuclear factor kappa B, *TAK1* growth factor-β-activated kinase 1, *TIRAP* TIR- (TLR-IL1-R1-) associated protein, *TRAF6* TNF-receptor-associated factor (*TNF* tumor necrosis factor), *TRIF* Toll-receptor-associated activator of interferon]

Porphyromonas species [13]. TLR2 also forms heterodimer complexes with other members of the TLR family, namely with TLR1 and TLR6 [8]. These complexes are characterized by different ligand specificity, thus recognition of microorganisms through different complexes gives specificity to the immune response. The TLR2/TLR6 heterodimer is necessary for the recognition of diacyl lipopeptides, a common cell wall compound of all Gram-positive bacteria, but it is also involved in the recognition of PAMPs of fungal pathogens (Table 2.1). In contrast, TLR2/TLR1 heterodimers recognizes tripalmytoylated lipopeptides (Table 2.1) [14].

TLR3 has recently been demonstrated to provide a mechanism by which dsRNA species activate the innate immune response (Table 2.1.). Signaling through TLR3 leads to the expression of high levels of interferon (IFN)-γ and type-1 (Th1)-associated chemokines in a variety of cell types, suggesting that it has a key role in the innate immune responses against viral infections [6, 15].

The expression level of TLR4 by keratinocytes is anatomical location-dependent [8]. Moreover, the expression of TLR4 (together with that of TLR2) correlates with the differentiation state of keratinocytes [16]. Interestingly, the level of expression may also show interindividual differences or may be inducible by mechanical injury or inflammation [6, 9]. The recognition of Gram-negative bacteria-derived LPS requires at least two cofactor proteins in addition to TLR4. During LPS signaling, LPS first binds to CD14, which then interacts with TLR4 and initiates intracellular signal transduction. MD-2 is a protein that associates with the extracellular domain of TLR4, and enhances LPS responsiveness (Table 2.1, Fig. 2.1) [17].

TLR5 recognizes the bacterial motor protein flagellin (Table 2.1) [6] required for motility of microorganisms such as *B. burgdorferi*, which causes migratory erythema during the course of Lyme disease, or *Salmonella typhi* causing cutaneous ulceration [18].

Keratinocytes are able to upregulate their chemokine expression in response to *B. burgdorferi*, indicating that TLR5 is indeed functional on keratinocytes, enabling them to respond to invading flagellated bacteria [19].

During infection, TLR9 senses unmethylated bacterial CpG DNA derived from many classes of bacteria (Table 2.1.). Its expression in the epidermis is inducible, either by microbial compounds or by physical trauma [6, 20, 21]. Unlike TLR1-TLR6, TLR9 is not expressed on the cell surface but in the endoplasmic reticulum [22].

2.3.1.2 IL-1 Receptors in the Skin

IL-1 receptor type 1 (IL-1R1) can bind both IL-1α and IL-1β, resulting in the initialization of MyD88-dependent signaling (see below and Fig. 2.1). The receptor, expressed on the surface of a variety of cells, mediates all known biologic activities of IL-1 by initializing a cascade of events leading to recruitment and activation of macrophages and neutrophils, vascular dilation, fever and proinflammatory immune response. The central role of the IL-1 system is the protection against microbial colonization and infection [23].

The second receptor for IL-1, IL-1R2 also binds both IL-1α and IL-1β. By binding the functional ligands for the IL-1R1, IL-1R2 serves to inhibit IL-1 mediated inflammatory responses [23].

2.3.1.3 Signaling Pathways via TLR/IL-1R

Myd88-Dependent Signaling Pathway

Binding of specific ligand/s to TLRs initiates a signaling cascade mediated by the cytoplasmic TIR domain (Fig. 2.1). Due to the structural homology between the intracellular domains of TLRs and IL-1R, the TLR signaling pathway is highly homologous to that of the IL-1R family. Both TLRs and IL-1Rs interact with an adaptor protein MyD88, through their TIR domains (Fig. 2.1). Upon stimulation, MyD88 recruits the IL-1R-asssociated kinase (IRAK), that associates with TNF receptor associated factor 6 (TRAF6) leading to the activation of at least two distinct signaling pathways, JNK and NF-κB. TLR signaling through MyD88 leads to the phosphorylation and degradation of IκB, the regulator protein of NF-κB, allowing the nuclear translocation of NF-κB (Fig. 2.1). In the nucleus, NF-κB binds to the promoter region of genes of proinflammatory chemokines/cytokines, antimicrobial peptides, inducible enzymes and adhesion molecules, which are important effectors or mediators of innate and acquired immune responses [24, 25]. Keratinocytes respond to the challenge with *S. aureus* or *Candida albicans* with TLR2-MyD88-NF-κB-dependent induction of inducible nitric oxide synthase (iNOS), supporting the role of TLR-MyD88-NF-κB pathway in innate immune functions of the skin [8, 9].

Myd88-Independent Signaling Pathway

In addition to their common activation of the MyD88-IRAK-TRAF pathway, individual TLRs may activate different, alternative signaling pathways. These MyD88-independent pathways involve the activation of interferon-regulatory factor-3 (IRF-3) and are utilized by several TLRs such as TLR3 and TLR4/4 (Fig. 2.1). TLR signaling pathways are therefore not identical, and the specificity of some pathways may determine the pattern of gene expression, which accounts for the distinguishable biological responses following the activation of specific TLRs by different classes of pathogens [26]. These specific responses may be particularly important in the epidermis [27], which is constantly colonized by numerous microorganisms that do not induce immune response.

2.3.2 NOD2 and Downstream Signaling Events

While TLRs are mainly involved in recognition of pathogens in the extracellular compartment, the NBS–LRR (nucleotide-binding site and leucine-rich repeat) family of proteins (e.g., NOD2) is involved in intracellular sensing of microorganisms and their products; thus it may contribute to the innate immune defense against various pathogens [28, 29]. Indeed, keratinocytes express NOD2, a receptor responsible for the recognition of broad range of bacterial pathogens, as it recognizes muramyl dipeptide (MDP), the minimal bioactive structure of peptidoglycan [11, 28]. Induction

of the signaling cascade results in proinflammatory response through NF-κB and, to a lesser degree, AP-1 activation [11, 30]. Once activated, NOD2 promotes the release of antimicrobial peptides, such as hBD-2 in keratinocytes, thereby strengthening the cutaneous innate defense system [11].

2.4 Keratinocyte-Derived Effector Molecules

Human skin is exposed to a wide variety of pathogenic microorganisms. Despite these microbial threats, skin is highly resistant to infections. PRR-mediated signaling upon challenge with microbes and/or microbial-derived compounds induces a chemical cutaneous defense system based on the production of antimicrobial and proinflammatory proteins. These keratinocyte-derived soluble factors are fundamental in the elimination of invaders and recruitment of professional immune cells into the sites of skin infection.

2.4.1 Antimicrobial Peptides

Activation of PRRs, expressed by epidermal keratinocytes, is directly involved in the induction of antimicrobial peptides [11, 31, 32]. This diverse family of small, mostly cationic polypeptides exerts a broad spectrum of cytotoxic activity against bacteria, fungi, parasites and enveloped viruses. During the inflammatory processes of the skin, keratinocytes are the main cellular sources of antimicrobial peptides, and their expression levels correlate with the susceptibility of the skin to infections. The local accumulation of antimicrobial proteins offers a fast and very efficient way to prevent microbes from establishing an infection. Expression of antimicrobial peptides is induced upon encounter with pathogens as well as during wound healing [33–35]. Activation of antimicrobial genes by PAMPs can be further increased by proinflammatory cytokines produced at sites of inflammation [33–38]. Most keratinocyte-derived antimicrobial peptides belong to the defensin, cathelicidin, RNase or peptidoglycan recognition protein (PGRP) gene families that are able to kill or inactivate a wide spectrum of microorganisms.

2.4.1.1 β-Defensins

The expression of human β-defensin-1 (hBD-1) is constitutive in epidermal keratinocytes, and shows antimicrobial activity against predominantly Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* [39, 40]. The constitutive expression of hBD-1 in the suprabasal layers of the epidermis suggests that it contributes to the innate resistance of the skin to Gram-negative infections.

The second human β-defensin, hBD-2, was originally isolated from the desquamated scales of psoriatic skin [34]. Several data suggest a complex role for hBD-2 in cutaneous host defense. It has a microbicidal effect against various microorganisms, such as *E. coli*, *P. aeruginosa, S. aureus,* or *Streptococcus pyogenes* [37], but also acts as a chemoattractant for immature dendritic cells and neutrophils, and induces the migration of memory T cells. In vivo expression of hBD-2 is localized to the upper layer of the epidermis and the stratum corneum. hBD-2 was also found in the intercellular space indicating that the lipid 'permeability' barrier of the skin contains antimicrobial substances [41]. In correlation with the localization of hBD-2 in the more differentiated suprabasal layers of epidermis, the expression of hBD-2 is differentiation-regulated [35, 39]. Furthermore, the abundant expression of hBD-2 in inflamed and in infected skin goes in parallel with the finding that its expression is induced by Gram-positive (*E. coli*, *P. aeruginosa,* and *Propionibacterium acnes*) and Gram-negative (*S. aureus* or *S. pyogenes*) bacteria and also by *C. albicans* in cultured keratinocytes and in reconstructed human epidermis [34, 38, 42–45]. In vivo, the secretion of hBD-2 by keratinocytes activates dendritic cells, inducing their migration from the skin into local lymphoid organs, leading to the generation of cellular immune response through the activation of antigen-specific T-cells [46]. Thus, hBD-2 plays multiple roles in cutaneous host defense: (a) it provides the first line of defense against infection by acting as a 'natural antibiotic' against sensitive pathogens, and (b) it plays a key role in the initiation of acquired immune responses against infections by directing the migration of dendritic and/or T cells and inducing the maturation of dendritic cells. Taken overall, hBD-2 provides a link between the innate and acquired immune responses during skin infections.

hBD-3 has been cloned from keratinocytes, and it shows a broad spectrum of antimicrobial activity against Gram-negative and Gram-positive bacteria, including multiresistant bacteria. Its expression in keratinocytes is induced by PAMPs, by inflammatory mediators such as TNF-α, IL-1β, IFN-γ, and by the state of differentiation [38, 47].

Similarly to hBD-2 and -3, the production of hBD-4 in keratinocytes is inducible by inflammatory stimuli, PAMPs or differentiation [38]. Synthetic hBD-4 revealed antimicrobial activity against *P. aeruginosa* and *Staphylococcus carnosus*, implying a role for this peptide in the innate epidermal defense against bacterial infections.

2.4.1.2 Cathelicidins

LL-37 (CAP18), the only human antimicrobial peptide that has been identified in the cathelicidin gene family, is produced by neutrophils but is also induced in keratinocytes of inflammatory skin disorders [33]. In vivo, LL-37 provides protection against necrotic skin infection caused by Group A Streptococci, and it also exerts antimicrobial activity against a wide variety of Gram-positive and Gram-negative bacteria [48]. Similarly to β-defensins, LL-37 plays multiple roles in the fight against pathogens: in addition to its antibiotic effect, it has potential to recruit mast cells, neutrophils, monocytes and T cells to inflammation foci, and is involved in the reepithelization of skin wounds [36, 49, 50].

2.4.1.3 RNase7

RNase7 exhibits high antimicrobial activity against several potentially pathogenic microorganisms such as *S. aureus*, *P. acnes*, *P. aeruginosa*, *E. coli,* and *C. albicans* [51]. Detection of RNase7 gene and protein expression in keratinocytes, together with its high abundance in stratum corneum as well as its broad antimicrobial activity, indeed stress the role RNase7 plays in cutaneous innate immunity.

2.4.1.4 Antileukoprotease (Alp)

ALP, a serine protease inhibitor isolated from stratum corneum, has antiprotease capability and exhibits high antimicrobial activity against a broad range of skin associated microorganisms such as *P. aeruginosa*, *S. aureus*, *Staphylococcus epidermidis*, and *C. albicans* [52]. Its constitutive expression in keratinocytes indicates that ALP actively participates in mechanisms allowing homeostasis of bacterial and yeast colonization on human skin.

2.4.1.5 Peptidoglycan Recognition Proteins (PGRPs)

PGRPs are a new class of bactericidal and bacteriostatic proteins that kill bacteria by interacting with their cell-wall peptidoglycan [53]. Although not expressed in healthy human skin, the expression of PGLYRP2 in keratinocytes is induced by bacteria and cytokines [54]. This induction, limited to epithelial cells, does not involve TLR2 or TLR4, and correlates with keratinocyte differentiation and stress responses that proceed through the activation of the p38 mitogen-activated protein kinase [54]. Two other members of the family, PGLYRP3 and PGLYRP4, are highly expressed in keratinocytes of the healthy skin, and are also induced upon exposure to bacteria [53].

2.4.2 Proinflammatory Chemokines

Chemokines, a superfamily of small chemotactic peptides, are key mediators of the immune system, playing pivotal role in the initiation, propagation and regulation of immunologic responses [55]. They are of utmost importance in the pathogenesis of numerous diseases including inflammatory and malignant skin diseases, also coordinating innate and acquired immune responses. Chemokine-regulated migration of leukocytes and neutrophils from peripheral blood vessels into inflamed skin occurs as a sequence of tightly controlled events involving the activation of vessel endothelium, transendothelial migration and chemotaxis. Once recruited into the skin, leukocytes play an essential role in the initiation and amplification of skin inflammation [56, 57].

Skin-pathogenic microorganisms such as *P. acnes*, *S. aureus*, *B. burgdorferi,* or *C. albicans*, together with several PAMPs (e.g., LPS or PGN), induce the abundant secretion of CXCL8 [a chemokine which

used to be referred to as interleukin-8 (IL-8)] from keratinocytes in a TLR-NF-κB-pathway-dependent manner [9, 33, 58, 59]. Pathogen-induced secretion of keratinocyte-derived CXCL8 initiates neutrophil chemoattraction and transendothelial migration. In addition, CXCL8 is selectively involved in the transendothelial migration of CLA^+ T cells, emphasizing the role of CXCL8 in the homing of specific T cells to inflamed skin. Similarly to CXCL8, pathogens and microbial products such as heat-killed *S. aureus* and staphy-lococcal PGN stimulate the expression of other chemokines in keratinocytes, such as CCL5/RANTES (regulated on activation, normal T expressed and secreted) or CCL2/MCP-1 (monocyte chemoattractant protein-1) [58]. Interestingly, CCL5-expressing keratinocytes were detected in the lesional skin of patients with atopic dermatitis and psoriasis, implying a role for CCL5 in skin inflammation, possibly through the recruitment of distinct leukocyte subsets [60].

Chemokines also exert in vitro antimicrobial properties against a wide variety of microorganisms [61]. Under physiological conditions, 20 out of 45 known human chemokines function as potent antimicrobial factors, providing evidence for the close functional and evolutionary relationships between chemokines and antimicrobial peptides [61–63]. After challenge with microbial constituents or inflammatory signals, many of these 'antimicrobial chemokines' are expressed by epidermal keratinocytes (e.g., CCL18, CCL19, CCL20, CCL25, CXCL1, CXCL10), suggesting that keratinocyte-derived chemokines are involved not only in the recruitment of professional immune cells to the sites of infection but in the direct killing of pathogens as well. Still, further functional studies are needed to elucidate the exact role chemokines play in the elimination of skin-infecting pathogens.

2.4.3 Proinflammatory Cytokines

Upon challenge with microbial compounds, keratinocytes express numerous cytokines acting as cytoprotective factors in the processes of the immune response.

In primary keratinocytes, *S. aureus*-derived PGN induces the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) [58], an essential cytokine for survival, differentiation and maturation of dendritic- and Langerhans cells. Effects of GM-CSF on the antigen-presenting cells shift the immune response to Th2-type.

Skin contains a reservoir of preformed IL-1α, leading to the concept that epidermis is a shield of sequestered IL-1 surrounding the host, waiting to be released upon injury. External stimuli such as wounding, burns and microbial infection, or internal stimuli such as local cytokine release from stimulated leukocytes, can induce the release of IL-1 for local or systemic delivery. Although high levels of the IL-1RA also coexist within keratinocytes, the amount of IL-1 is sufficient to overcome any potential for inhibition mediated by the IL-1RA.

Both heat-killed *S. aureus* and Staphylococcal PGN induce the expression of TNF-α, IL-1β and IL-6 of primary keratinocytes [58]. TNF-α enhances the bactericidal effect of neutrophils and promotes the adhesion of neutrophils to endothelial cells. Thus, keratinocyte-derived TNF-α plays a crucial role in the recruitment of phagocytic cells into the sites of infection. The contribution of IL-6 and TNF-α to the granulomatous skin conditions, such as cutaneous leishmaniasis, granuloma annulare or leprosy, is suggested by the occurrence of these cytokines in the granulomatous reactions. Upon contact with pathogens, TNF-α, IL-1α, IL-1β and IL-6 are also implicated in the autocrine induction of antimicrobial peptide (e.g., β-defensins and LL-37) expression of keratinocytes.

2.5 Skin Infections and Innate Immune Responses of the Epidermis

Normal human skin supports the growth of resident microbiota and is colonized by a wide variety of resident microorganisms. In addition to normal flora, the skin is constantly challenged by pathogens, most of which do not cause clinical symptoms. Beside microbial adherence and virulence, environmental and local factors, as well as the host immunity, are important components of cutaneous infections. In particular, skin becomes more susceptible to infections when the epidermal barrier function is damaged or when the keratinocyte-mediated innate immune functions are inhibited. A typical example is the

pilosebaceous unit, which is an important place of skin infections such as inflammatory acne, folliculitis, furunculosis and carbunculosis. A common pathogen associated with infections in the pilosebaceous unit is *P. acnes*. It is proposed that hypercornification of the outer root sheath and the pilosebaceous duct, increased sebum production, abnormalities of the normal microbial flora and inflammation are the major factors in the pathogenesis of acne. Although inflammatory acne is not an infectious disease, the role of *P. acnes* in the pathogenesis of acne is well documented [64]. Recent results describing the expression of TLRs in the pilosebaceous unit, together with the increased amount of bacteria in inflammatory acne, suggests that inflammation found in acne is at least partially mediated by the TLR signaling pathways [45, 65, 66].

2.6 Conclusions

Increasing evidence suggests that keratinocytes not only participate in cutaneous immune responses against pathogens but may play key initiation roles. Keratinocytes are able to recognize a wide variety of microorganisms through their PRRs, and have evolved mechanisms to distinguish between skin commensals and pathogens. Signaling through specific PRR combinations provides selectivity and specificity to keratinocyte immune responses. As a result, keratinocytes produce a wide range of antimicrobial peptides and/or proinflammatory cytokines/chemokines. The secretion of antimicrobial peptides is indeed crucial, as skin lesions characterized by low levels of such host-defense peptides are more susceptible to infections. By exhibiting chemoattractant activity, keratinocyte-derived cytokines/chemokines and antimicrobial peptides can recruit T cells, neutrophils and dendritic cells into sites of infection, thus providing an improved immune response against pathogens. These findings indicate a close interdependence of keratinocytes and inflammatory infiltrate, as well as a balance between the innate and acquired immune systems. Any perturbation in this system, for example deregulation and abnormal expression of inflammatory mediators or their receptors in keratinocytes, can lead to the pathogenesis of chronic inflammatory skin diseases.

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Bacteriology of the Skin

3

Cristina Oprica

Core Messages

- Normal human skin is colonized by a large variety of organisms that exist as commensals on its surface. Some bacteria are normally present on the skin and represent the resident flora, while other bacteria occur occasionally and correspond to the transient flora.
- The major groups of microorganisms from the skin are various genera of bacteria and yeasts.
- Various factors may influence the normal microflora of the skin, e.g. climate, body location, gender, race, occupation and various antiseptics or drugs.
- There are host factors that prevent colonization and invasion of pathogenic organisms. Many organisms may also produce protein or protein-complex antibiotics that have antagonistic effect on other organisms, but not on the producer bacterium.
- The skin colonisation may lead to various infections that respond to treatment but may relapse. These infections may occasionally be severe in immunocompromised patients.

3.1 Introduction

Normal human skin is colonized by a large variety of organisms that exist as commensals on its surface. There are quantitative differences in different regions of the skin, related to temperature difference, moisture content, pH, oxygen concentration, ultraviolet radiation, interactions with other microbes and the presence of various concentrations in skin lipids. All these factors may influence microbial survival and growth on the skin. The skin is not a favourable place for the bacteria to live, due to its dryness and because the fluids on its surface have a relatively high osmotic pressure that will favour the survival of Gram-positive bacteria and will tend to exclude the Gram-negative species [1].

Some bacteria are normally present on the skin and represent the resident flora, while other bacteria occur occasionally and correspond to the transient flora [2].

The skin microflora resides on the surface of the stratum corneum, in the ducts of hair follicles and in the sebaceous glands. There are no bacterial inhabitants of the sweat ducts or glands [3].

3.2 Classification of Microorganisms

The major groups of microorganisms from the skin are various genera of bacteria and yeasts (Table 3.1) [3, 4].

3.2.1 Micrococcaceae: Staphylococci and Micrococci

Micrococci and staphylococci are Gram-positive, catalase-positive cocci in the family Micrococcaceae.

Staphylococcus spp. are able to produce acid aerobically from glycerol in the presence of erythromycin (0.4 µg ml^{-1}), and they are sensitive to lysostaphin and nitrofuran at defined concentrations, whereas

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Table 3.1 The indigenous microbiota of the skin [3, 4]

Genus	Characteristics
Staphylococcus	Facultative anaerobic, Gram-positive cocci
Micrococcus	Aerobic, Gram-positive cocci
Corynebacterium	Aerobic/facultative anaerobic, Gram-positive pleomorphic rods
Propionibacterium	Anaerobic Gram-positive rods
Acinetobacter	Aerobic, Gram-negative coccobacilli
Brevibacterium	Aerobic, Gram-positive rods
Dermabacter	Gram-positive rods
Malassezia	Lipophilic yeast

Micrococcus spp. are not. Staphylococci are divided into coagulase-positive *Staphylococcus aureus* and coagulase-negative species. Ten different species of the genus *Staphylococcus* have usually been isolated from the normal skin.

S. aureus should not be considered as a resident of the normal skin, and humans have a natural resistance to skin colonization by *S. aureus*. Despite the classification as a transient pathogen, it is estimated that 86.9 million people (32.4% of the population) are colonized with *S. aureus* [5]. This bacterium may be found as a part of the transient flora of normal skin or the nasopharynx [6]. Persistent nasal carriage occurs in 20–40% of normal individuals [7] and can lead to recurrent infections. *S. aureus* may be also found in the perineum of 20% of the population. Hospital workers [8], diabetics, patients on hemodialysis and intravenous drug abusers [9] are more susceptible to bacterial colonization.

- *S. aureus* clinical infections range from minor skin infections to life-threatening diseases. It is responsible for impetigo, folliculitis, furuncles, carbuncles, mastitis, hidradenitis suppurativa, subcutaneous abscesses and (through the production of exfoliative toxins) staphylococcal scalded skin syndrome [6, 10]. *S. aureus* may cause invasive infections such as septic arthritis, osteomyelitis, pneumonia, meningitis, septicaemia and endocarditis. Production of superantigen toxins can induce staphylococcal toxic shock syndrome [10]. Unfortunately, there has been a dramatic increase in antibiotic resistant strains: methicillin-resistant *S. aureus* (MRSA) and vancomycin-intermediate and vancomycin-resistant *S. aureus* strains (VISA and VRSA) [11, 12].

In patients with skin diseases such as psoriasis [13] or atopic dermatitis [14], *S. aureus* may be found widely over both diseased and normal skin and may produce infections, being the most common superinfecting agent [10]. The presence of *S. aureus* may both aggravate the eczema and prevent its resolution [6].

- Colonization by *S. aureus*. can not be considered synonymous with infection. Healthy persons seldom contact invasive infections due to this bacterium [15], and *S. aureus* found on healthy human skin and in nasal mucosa are acting as a commensal, rather than a pathogen [10].

Various coagulase-negative staphylococci are the organisms of the normal flora most frequently found on the skin. *Staphylococcus epidermidis* and *Staphylococcus hominis* are the most important numerically [3]. *S. epidermidis* colonizes the upper part of the body preferentially [16], and represents more than 50% of the resident staphylococci [17]. *Staphylococcus haemolyticus, Staphylococcus capitis, Staphylococcus cohnii, Staphylococcus saprophyticus,* and *Staphylococcus warneri* [18] have also been isolated from many individuals.

Some have predilection for particular areas, for example *S. hominis* and *S. haemolyticus* are found principally in areas where there are numerous apocrine glands, such as axillae and the pubic region [4, 19] and *S. saprophyticus* is often found in the perineum [6].

- *S. epidermidis* has emerged as a common cause of nosocomial infections. There are extrinsic factors that promote the conversion from a member of the resident microflora to an aggressive agent. This bacterium infects drug abusers, patients with acquired immune deficiency syndrome, premature neonates and patients with an indwelling foreign device [10]. Once systemic, *S. epidermidis* may produce sepsis or native valve endocarditis, and biofilm production reduces the access of antibiotics to the bacteria and may require the removal of implanted devices [20]. Patients with ulcerated tumours (squamous cell carcinoma, breast carcinoma or sarcoma) have a tendency for infection by *S. epidermidis* [10]. The specific skin infections caused by this bacterium require a predisposed host, and do not reflect bacterial–host interaction [10].

Peptococcus saccharolyticus is a strict anaerobic staphylococcus, and a member of the normal flora in 20% of individuals. It may be present in large numbers on the forehead and antecubital fossa [21].

Micrococci are found on the skin, especially in women and children [22], and *Micrococcus luteus* and

Micrococcus varians are the prevailing species. *Micrococcus kristinae* and *Micrococcus sedentarius* are also accepted as residents [23]. *Micrococcus lylae* is more frequently seen in cold months [18], and may have significance in infancy [23].

- *Micrococcus* species are generally considered contaminant when isolated from clinical specimens. *M. luteus* has occasionally been implicated in bacteremia, pneumonia, septic arthritis, and meningitis [6].

3.2.2 Coryneforms (Diphteroids)

Coryneform organisms are non-acid-fast, non-branching, non-sporing, pleomorphic Gram-positive rods, whether aerobic or anaerobic [1], that were initially all thought to be *Corynebacterium* species. Classical *Corynebacterium* species compose an important part of the normal flora from the intertriginous areas. These organisms were poorly classified in the past into two groups: lipophilic organisms that require lipid supplements for growth in artificial media, and non-lipophilic organisms [6].

A simple scheme divides aerobic coryneforms into four *Corynebacterium* spp. complexes (*Corynebacterium bovis*, *Corynebacterium minutissimum*, *Corynebacterium xerosis*, and *Corynebacterium hofmani*), together with *Brevibacterium epidermis*, *Dermabacter* and an apparently aerobic *Propionibacterium* spp. [1, 23]. *Corynebacterium minutissimum* appears to be a complex of as many as eight different species [24].

- *Corynebacterium minutissimum* causes erythrasma and *Corynebacterium xerosis* is associated with axillary odour [1]. Coryneforms are also involved in pitted keratolysis and trichomycosis [6].

Brevibacterium spp. are separable from the genus *Corynebacterium* by cell-wall composition studies, nutritional requirements and by the production of methane thiol [3]. They are obligate aerobic, produce proteolytic enzymes, are penicillin-resistant, and are the most rapidly growing of the coryneforms [25]. They are particularly associated with moist sites [3].

- *Brevibacterium mcbrellneri* is implicated in the superficial fungal infection of hair shaft, white piedra [26]. Brevibacteria are frequently isolated from the toe webs of patients with tinea pedis and are implicated in foot odour [27]. *Brevibacteria* are occasionally responsible for severe infections in humans.

3.2.3 Propionibacteria

Propionic acid-producing bacteria were first described by von Freudenreich and Orla-Jensen in 1906, and were originally isolated from cheese [28]. Propionibacteria have been classified over the years as *Bacillus* spp, *Corynebacterium* spp, anaerobic diphteroids and *Propionibacterium* spp.

Propionibacterium genera are composed of Gram-positive anaerobic non-motile non-spore forming rods. These rods can grow in oxygen, but at reduced rates because they possess oxygen de-toxifying enzymes. Propionibacteria have preference for hair follicles, and they grow at varying depths beneath the skin surface where oxygen levels are optimal. They also survive on skin surface in situations where oxygen utilization by aerobes and facultative anaerobes will help to offer an oxygen-depleted environment [1].

The cutaneous propionibacteria are *Propionibacterium acnes* and *Propionibacterium granulosum*, which are isolated mainly from sebum-rich areas (head, chest, back), *Propionibacterium avidum* (mainly in moist areas such as axillae, inguina, and the perianal area), *Propionibacterium propionicum* (on the eyelids and mouth) and *Propionibacterium lymphophilum* (it is not known if this should be regarded as a part of the normal flora). A sixth commensal strain previously known as *Propionibacterium innocuum* has been reclassified as *Propioniferax innocua* [29].

P. acnes is the most predominant specie in both prevalence and population among propionibacteria, while *P. granulosum* density is significantly lower [30]. *P. acnes* earned its name because it was first isolated from the skin of acne patients [31]. The name is improper, because *P. acnes* is present in nearly 100% of healthy persons [32].

- *P. acnes* is the causative agent of severe infections including endocarditis, endophtalmitis, osteomyelitis, and infections of implanted devices and wounds. *P. granulosum* may cause the same type of infections as *P. acnes*, while *P. propionicum* cause canaliculitis and dacryocystitis [1].

3.2.4 Acinetobacter

Acinetobacter spp. are non-fermentative aerobic Gram-negative coccobacilli that are widely dispersed in nature and are found in up to 25% of individuals as normal flora [33]. They include species that were previously referred to as members of the genera *Mima* and *Herellea. Mima polymorpha* has become *Acinetobacter calcoaceticus* var. *lwoffi* and *Herellea vaginicola* is *Acinetobacter calcoaceticus* var. *anitratus*.

Males are more frequent colonized than females, and there is a significant increase in colonization during the summer. The explanation would be that high moisture content is necessary for survival of these bacteria [18].

- Infections with *A. calcoaceticus* occur commonly in hospitals and immunosuppressed patients. *Acinetobacter* can cause bacteremia, endocarditis, meningitis, and infections of the genitourinary and respiratory tract [6]. *A. calcoaceticus* var. *lwoffi* has occasionally been isolated from the blood of patients with catheter-associated infections [1].

3.2.5 Dermabacter

Dermabacter hominis is the single member of the genus *Dermabacter*. This is a non-motile, Gram-positive bacillus, and until now there have been no reports of its involvement in any infectious diseases [1].

3.2.6 Malassezia

In the normal microflora, fungi are commonly present. Yeast organisms predominate both in temperate [34] and tropical [35] environments. At least seven species of lipophilic yeasts exist on the human skin: *Malassezia restricta, Malassezia globosa, Malassezia sympodialis, Malassezia slooffiae, Malassezia furfur, Malassezia obtusa* [36] and the recently described *Malassezia dermatis* [37]. *Malassezia pachydermatis* is often seen on animal skin, and *M. furfur* includes a complex of species.

These isolates are found in the scalp, upper trunk and flexures [38]. *M. globosa* is frequently associated with pityriasis versicolor, and *M. sympodialis* is often found on normal skin [39].

- A number of lipases, a lipoxygenase and a phospholipase are secreted by these organisms, and the latter may be considered as a virulence factor. This finding may explain why these organisms are involved in a number of inflammatory skin diseases: atopic dermatitis, seborrhoeic dermatitis, and folliculitis [1].

3.2.7 Transient Flora

Any microorganism that is found in nature or that belongs to the resident flora in non-cutaneous areas may be transiently found on the skin.

Transient Gram-negative organisms are frequently found as contaminants from the gastrointestinal system. Sporadically these may become resident flora in intertriginous areas and mucosal surfaces [23].

Pseudomonas aeruginosa is commonly found in non-sterile areas on healthy individuals.

- This bacterium may infect any tissue with which it comes into contact. Infections occur generally in compromised patients (individuals with AIDS, cystic fibrosis, bronchiectasia, neutropenia, different malignant diseases) and in association with hospital stays. *P. aeruginosa* may cause dermatitis on the skin or deeper soft-tissue infections. Dermatitis occurs after skin contact with infected water, and is usually mild. Into the blood, this bacterium may cause severe bone, joint, gastrointestinal, respiratory and systemic infections [10].

Group A streptococcus (*Streptococcus pyogenes*) rarely colonize the skin because they die rapidly on normal skin [40]. However, streptococci have been recovered from clinically normal skin in children for up to 10 days prior to the development of impetigo [41].

- *S. pyogenes* may cause both superficial and invasive disease. These infections are generally associated with diabetes, alcoholism, immune deficiency, skin ulcers and trauma**.** Superficial infections differ with age and cutaneous morphology. Pyoderma (non-bullos impetigo) occurs frequently in infants and children [10]; *S. pyogenes* is associated with deeper-seated cutaneous infections such as cellulites and erysipelas, especially in the elderly and in densely populated areas [42]. The ‘flesh-eating disease’ or

invasive necrotizing fasciitis is associated with a high degree of morbidity and mortality, and may be followed by streptococcal toxic shock syndrome. Group A streptococcus may cause infections in lung, bone and joint, muscle or heart valve [10].

Rheumatic fever is a complication of *S. pyogenes* pharyngitis, but occurs after pyoderma rarely if at all. The serotype of the organism is not relevant. Acute glomerulonephritis follows both throat and skin infections with certain nephritogenic serotypes of *S. pyogenes* [3]. Erythema nodosum, psoriasis and scleredema of Buschke have been linked with streptococcal infections of the throat [3].

3.3 Factors Modifying the Normal Flora

3.3.1 Climate

Increased temperature and humidity increase the bacterial density. In a study by Aly in 1982, after 24 h of occlusion on forearm skin, bacterial counts increased 10,000-fold, and the relative numbers of Gram-negative rods and coryneform bacteria had increased over coccal forms [43].

3.3.2 Body Location

The face, neck, and hands are exposed areas and have a higher bacterial density. The upper arms and legs are dry environments, and have lower bacterial counts. The axilla, perineum and toe webs are partially occluded and thus are heavily colonized with all microorganisms, particularly with Gram-negative and coryneforms [6].

3.3.3 Age

The flora is most varied in young children, who also carry a higher proportion of pathogens or potential pathogens on their skin. *Pityrosporum* and *Propionibacterium* species are present at lower levels before puberty, due to reduced levels of skin lipids [6]. In elderly persons streptococci may become skin residents, and enteric organisms start to colonize moist areas [3].

3.3.4 Gender

Males carry higher absolute numbers of microorganisms as well as more biotypes, probably due to higher sweat production, as well as to the tendency to wear occlusive clothing [6]. It was shown that males are more likely to be disseminators of *S. aureus,* if they are perineal carriers, than are women [44].

3.3.5 Race

White individuals are more likely to carry nasal *S. aureus* than black individuals [45]. Black individuals have fewer cutaneous streptococcal infections than whites [46]. Differences may be due to differences in HLA antigen expression [47], adhesion, or environmental conditions [6].

3.3.6 Occupation

Hospital workers carry more pathogenic organisms on their skin as transient organisms. They may become permanently colonized with these bacteria if they are consistently exposed [48].

3.3.7 Antiseptics

Antiseptics applied on the skin will remove the transient flora, and generally will reduce the resident organisms [49]. Various skin hygiene products may have incorporated antimicrobial agents such as clorhexidine or triclosan which will result in a reduction in the number of organisms on the skin. There is, in any case, concern about the development of resistance to such agents. Alcohol-based hand rinses are effective and safe formulations: they have a broad-spectrum antimicrobial activity, there is no risk for resistance development and their use is less damaging to the skin than washing with water and soap [1].

3.3.8 Medication

Antibiotics may suppress the normal flora and increase colonization by other bacteria. Antibiotics may also impair bacterial adherence to epithelial cells [50] and allow for the natural selection of Gram-negative rods [51].

Oral retinoids, such as 13-*cis*-retinoic acid, cause a decrease of *P. acnes* due to a significant decrease in sebum production. This decrease will persist even after treatment is discontinued [52]. The number of Gram-negative rods of the mucous membranes decrease significantly, while the *S. aureus* from the anterior nares increase [6, 51].

Oral steroids can increase susceptibility to infections [6].

Patterns of colonization by cutaneous microbiota related to the local environmental conditions are presented in Table 3.2.

3.3.9 Natural Resistance of the Skin against Bacterial Infections

There are host factors that prevent colonization and invasion of pathogenic organisms. Intact stratum corneum will offer defence, and dryness of the skin will limit the growth of species that require moisture. Skin appendages may represent routes of infection with *S. aureus* [6]. Skin breaches represent an absolute condition for inducing a streptococcal infection [53]. Rapid cell turnover, the lipid layer and the humoral and cellular immune systems of the skin may also influence the composition of the skin bacteria [6].

Many organisms produce protein or protein-complex antibiotics that have an antagonistic effect on other organisms, but not on the producer bacterium. Substances produced by Gram-negative bacteria have a wide range of antibacterial activity, while those produced by Gram-positive bacteria are effective against strains of closely related species. The latter substances are called bacteriocins [6]. A resident bacterium will prevent colonization by other strains by competitive inhibition on binding sites. Certain resident bacteria may exercise antagonistic inhibition over other residents that are of dissimilar species. The large numbers of *S. aureus* in atopic dermatitis will eliminate the lipophilic coryneform bacteria from the skin [54].

Table 3.2 Patterns of colonization by cutaneous microbiota related to the local environmental conditions [1]

Body region	Environmental conditions	Microbiota
Head	Many sebaceous and sudoriferous glands	High bacterial density; Propionibacteria and few Corynebacteria
Arms/legs	Relative dry regions; few sebaceous glands; no sudoriferous glands	Staphylococci and Micrococci; very few fungi
Axillae	Many sebaceous and sudoriferous glands	High microbial density; Corynebacteria, fungi and *Acinetobacter* spp.
Perineum	Occluded; increased moisture and temperature	High microbial density; Corynebacteria, fungi and *Acinetobacter* spp.
Toe webs	Occluded; increased moisture and temperature	High microbial density; Corynebacteria, fungi, Brevibacteria, and *Acinetobacter* spp.
Hands	No sebaceous glands	Staphylococci; few fungi, Corynebacteria, and Propionibacteria

3.4 Conclusions

The resident bacteria and the human skin form a complex ecosystem in which bacteria tend to adapt to the changes of the environment and to the action of the other bacteria.

There is an unexpected stability of the normal microflora in response to changes in environment, suggesting close co-evolution of the skin microflora and the skin environment [29]. Occasionally, skin colonisation may lead to various infections that respond to treatment but may relapse. These infections may on rare occasions be severe in immunocompromised patients [6].

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Acute Skin Failure

4

Laurence Valeyrie-Allanore, Saskia Oro, and Jean-Claude Roujeau

Core Messages

- Widespread skin diseases can be life-threatening.
- Skin is much more than an inert barrier.
- Skin contributes to important functions including thermoregulation, metabolism, innate, and acquired immune defense.
- Skin failure can result from several dermatological diseases.
- A few easy symptomatic measures can improve rapidly the systemic consequences from skin failure.

The skin has many more functions than the mechanical barrier it had been considered only to be for decades. To emphasize this complex role and the danger to life that may result from widespread skin diseases, we proposed 20 years ago the concept of 'acute skin failure' (ASF) [1]. In this chapter, we will briefly review the principal functions of the skin, the known consequences of their disturbance, and some symptomatic measures to correct these effects, whatever the cause of acute skin failure may be.

4.1 Functions of the Skin

4.1.1 Barrier Function

As detailed in another chapter (page 3) this function is principally devoted to the stratum corneum (corneal layer). This upper part of the epidermis is very thin (20–80 µm) and constituted of a few dozen layers of corneocytes, cells that are the finally differentiated form of keratinocytes after they have lost their nuclei, accumulated resistant proteins in their cytoplasm and acquired very thick lipid membranes. The frequent comparison with the bricks and cement of a wall provides a good image of an efficient barrier, but underscores the fact that corneocytes are still living and especially capable of transmitting biochemical messages of danger to the proliferating and differentiating keratinocytes of the lower layers of the epidermis. Keratinocytes will respond by accelerating or downgrading their multiplication and differentiation rates. For example, removal of a few layers of corneocytes by an adhesive tape will result in activation of keratinocyte proliferation and prompt restoration of the barrier. The quality of the barrier also depends on a correct balance between the variety of lipids (sterols, sphingolipids and free fatty acids) that constitute the intercellular cement. This is in turn dependent on nutrition, endocrine and metabolic factors, and also on systemic medications acting on lipids.

A normal barrier function is essential to the conservation of the 'milieu interieur'. It prevents the loss of electrolytes and water. In conditions that block sweating, the trans-epidermal water loss (TEWL) varies between body sites, with an average value of 5 ml m^{-2} h^{-1}, i.e., 100–250 ml per day.

The barrier also mechanically prevents the penetration of xenobiotics, including most bacteria and hydrophilic chemicals.

4.1.2 Thermoregulation

The skin provides a major contribution to the control of body temperature through interaction between sweat and cutaneous blood flow. Blood flow to the skin is

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0.5–1 l per min in basal situations, i.e., 15–20% of cardiac output. That is much higher than what would be needed for local metabolism only, but is a key factor of temperature homeostasis. Regulation of cutaneous blood flow depends on arterial baroreceptors but also on skin thermoreceptors, and is mediated by vasoconstrictor nerves and by many pharmacological substances released in inflammatory conditions. It is highly variable between extreme values of 0.3–4,000 ml m^{-2} min^{-1}. These variations are accompanied by modifications of skin color, temperature and production of sweat. Eccrine sweat glands excrete basically 200–300 ml per day of water with low electrolyte concentration. In extreme conditions of exercise and heat, the volume of sweat can increase to over 1 l per hour. The evaporation of 1 ml of water, either from sweat or trans-epidermal losses, dissipates 0.6 Kcal, i.e., 600 Kcal per liter.

4.1.3 Innate and Acquired Immunity

In addition to being a mechanical barrier to most microorganisms, the skin shares with other interface epitheliums a dynamic role in the defense against infections. That occurs through both the non-specific weapons of innate immunity and the specific tools of acquired immunity. Dendritic cells in the dermis and keratinocytes in the epidermis can express toll-like receptors (TLR), activated by molecular patterns that are conserved among a variety of microorganisms. This activation promotes the synthesis and release by keratinocytes and eccrine duct cells of two families of wide-spectrum 'natural antibiotics' — cathelicidins and beta-defensins [2]. Another role of these antimicrobial peptides is to attract immature dendritic cells and T cells, and so to promote acquired immunity. Examples of the potential pathogenetic relevance of skin innate immunity is exemplified by the relative resistance to infection of psoriasis lesions (in which the expression of several beta-defensins is increased), in contrast to frequent viral or bacterial infections of atopic dermatitis lesions that underexpress beta-defensins.

Activation of keratinocytes by TLRs also triggers their synthesis and release of cytokines and chemokines that will contribute to local inflammation and initiation of specific immune response.

More generally, keratinocytes can be activated by a variety of triggers, including type 1 and 2 Interferons, TNF-alpha, traumatism, and alteration to the stratum corneum. Activation manifests as phenotype changes: expression of HLA class II molecules, Fas-Ligand and ICAM 1, overexpression of HLA Class I molecules, Fas and other death receptors. Activation also induces synthesis and release of various cytokines including interleukins (IL) 1, 3, 4, 6, 7, 8, 10, 12, 13, 15, 18, IFN-alpha and beta, TNF-alpha, growth factors, colony-stimulating factors (CSF) and chemokines [3]. The results include attraction and activation of immature dendritic cells, monocytes, granulocytes and lymphocytes, inflammation and initiation of adaptive immunity. Widespread lesions will lead to systemic manifestations of inflammation (fever, synthesis of acute phase proteins, metabolic alterations …).

Langerhans cells, representing about 3–5% of epidermal cells, are 'professional' differentiated antigen-presenting cells. They are distinct from two other sub-lineages of dendritic cells: dermal dendritic cells and plasmacytoid dendritic cells. At variance with prior knowledge, dermal DC may be more important than Langerhans cells for initiating an immune response to contact sensitizers after moving to the draining lymph nodes [4]. Plasmacytoid dendritic cells in the dermis have important immuno-regulatory functions.

4.1.4 Cutaneous Metabolism

Keratinocytes express constitutively, or can be induced to express many of the enzymes needed for the metabolism of foreign substances. Epidermal cells have been shown to transform many drugs, and for example to oxidize sulfamethoxazole in reactive metabolites [5]. This metabolic capacity is much weaker than that of the liver anyhow, and its relevance to the physiology and pathology of the skin is unclear.

Synthesis of vitamin D and of its active derivatives is the best-studied metabolic function of the skin. The skin is the sole source of vitamin D3 (cholecalciferol) synthesis. After ultraviolet light irradiation of the blood precursor 7-dehydrocholesterol, keratinocytes transform it to Vitamin D3. After D3 has been hydroxylated to 25 OH-D3 in the liver, it is transformed to the

most active form 1,25 (OH)2-D3 in the kidney and many other organs including the epidermis. In turn, 1,25 (OH)2-D3 decreases the proliferation and increases the differentiation of keratinocytes. Beyond this regulatory effect on proliferation/differentiation, Vit D3 derivatives also modulate the production of cytokines and growth factors by keratinocytes. This decreases the production of the inflammatory cytokines IL1, IL6 and IL8, but increases TNF-alpha.

4.1.5 Neuro-Endocrine Functions

Within the epidermis, Langerhans cells are in close anatomical contact with terminal fibers of sensory nerves. LC have receptors for several neuro-mediators including calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), and substance P (SP) neurotensin [6]. On the other hand, many of the cytokines that are released by keratinocytes and immune cells during inflammation can activate or modulate the activation of sensory nerves. Many experimental models have demonstrated that contact hypersensitivity is modulated by neuro-mediators. The cross-talk between the skin immune system and the neuro-endocrine system is certainly profoundly affected in situations of skin failure, but the evaluation of the real impact of such changes needs further investigation.

4.2 Main Features of Skin Failure

Most pieces of knowledge about acute skin failure have been acquired from physiological investigations of animals or humans with extensive burns. Few of these findings have been checked and confirmed in patients with toxic epidermal necrolysis (TEN). Because of lack of studies, most analogies are likely but unproven. In addition, if the skin barrier is destroyed in all burns whatever the deepness, deep burns are characterized in addition by necrosis of blood vessels within the hypodermis and/or dermis. These vascular lesions are usually absent in most dermatological diseases that may induce skin failure. That is an important difference that probably explains that the constitution of a 'third sector' of edema is not a feature of TEN, and also that the immediate fluid requirements are lower in patients with TEN than in burn patients for the same extent of lesions.

4.2.1 Loss of Water, Electrolytes, and Proteins

The total removal of the stratum corneum, by tape stripping in experimental conditions or as the result of disease, raises the trans-epidermal water loss from 5 to 60–100 ml m^{-2} h^{-1}. That is a well-known consequence from burns or toxic epidermal necrolysis, but it is frequently overlooked that an abnormal stratum corneum associated with a phenotype of scaly and 'dry' skin also results in increased water losses. TEWL reaches 10–30 ml m^{-2} h^{-1} in skin areas affected by atopic dermatitis or psoriasis. In cases of exfoliative dermatitis, TEWL rates of 60 ml m^{-2} h^{-1} were measured, corresponding to daily water losses of 2,000–3,000 ml per day.

In contrast with trans-epidermal water, exudates from blisters and erosions contain concentrations of electrolytes and proteins that are close to those in plasma, i.e., 140 mEq/l sodium and 20–50 g/l proteins.

Electrolyte and fluid losses combined with hypo-albuminemia lead to the reduction of intravascular volumes. The first consequence is a reduction in urinary output, with hyper-osmolar urines showing a pattern of secondary hyper-aldosteronism (low sodium, high potassium and urea concentrations). Serum levels of urea and creatinin are elevated, indicating functional renal failure. If not corrected, hypo-volemia may lead to haemodynamic changes, organic renal failure and shock.

4.2.2 Altered Thermoregulation

Many disorders of the skin are characterized by a massive release by keratinocytes and other inflammatory cells of a variety of cytokines. Even in lesions with moderate extension, blood concentrations of pyrogenic cytokines, including interleukins 1 and 6 and TNF-alpha, are elevated and contribute to fever, through deregulation of the hypothalamus 'thermostat'.

In common feverish illnesses, such as flu, the central temperature is raised by a simultaneous increase

in the endogenous production of calories by the muscles (shivering) and a decrease of thermal losses through the skin (vasoconstriction, reduction of blood flow and sweat). Remission of fever will be obtained by vasodilatation of skin vessels and sweating.

In skin diseases leading to ASF, the thalamus orders to raise the body temperature are antagonized by the vasodilatation of skin blood vessels inherent to local inflammation and redness and by the increased losses of water (with dissipation of heat physically linked to evaporation).

This situation can be compared to an attempt to raise the temperature of a room up to 39°C with large open windows; the lower the external temperature, the larger the amounts of energy which will be needed.

In human skin diseases, dependence of caloric expenditures on external temperature has been perfectly demonstrated in patients with extensive burns. The metabolic rate increased with extent of burns up to 100% at 22°C. For burns of similar severity the metabolic rate increased by 50% and 30% only when room temperature was set at 28°C and 32°C respectively [7]. Even though this effect of environmental temperature has not been formally demonstrated in patients with TEN, it is very likely to be similar for extended autoimmune blistering diseases or exfoliative dermatitis.

4.2.3 Increased Cardiac Output

From normal values of 0.5–1 l min^{-1}, the cutaneous blood flow cutaneous blood flow can increase to more than 5 l min^{-1} in patients with universal erythema. This remains dependent on body temperature, as demonstrated in exfoliative dermatitis, with values of 3–5 and 5–10 l min^{-1} for temperatures of 37°C and 38.5°C respectively [1]. Immediate consequences on haemodynamics include increase in the overall cardiac output from 6 to >10 l min^{-1}, tachycardia and a decrease in the blood flow in other territories, especially gut. That may result in impaired intestinal functions, renal failure, hyper-aldosteronism with low urinary output and sodium retention. Oedemas are frequent, whether related to kidney or cardiac failure. They often initially mask the profound muscular wastage induced by the hyper-catabolic state and a negative caloric balance. Sepsis and cardiac failure have been reported as the leading causes of deaths in patients with prolonged exfoliative dermatitis.

4.2.4 Altered Immune Functions and Infection

There is accumulated clinical evidence that extensive burns result in immuno-suppression, with decreased Th1 responses to stimulation by polyclonal or specific antigens. The depression of immune functions begins 1 week after the burn, and can last for months. Increased activity of regulatory T cells has been suggested as one mechanism of this depression [8]. Since similar alterations also occur after major stress and trauma other than thermal injury to the skin, the skin immune system can't be the sole cause of immunosuppression in burns.

In cases of severe skin diseases, there are a few studies suggesting that immune response is altered [9, 10].

Local infection and sepsis are major threats for all patients with skin failure. Severe infections are an important cause of death in severe burns, auto-immune blistering diseases [11, 12], exfoliative dermatitis [13], and TEN [14]. The increased prevalence of infections depends for a large part on mechanical disruption of the stratum corneum, enhanced bacterial proliferation within protein-rich exudates, and selection of resistant rods in ICU wards. Several studies in burns have also pointed to a probable role of defective innate skin immunity. The expression of beta defensin-2 has been shown to be dramatically decreased in burn wounds [15], and remarkably the most frequent pathogens in patients with compromised skin (i.e., *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans*) are sensitive to antibacterial peptides originating from keratinocytes. A variant allele of the toll-like receptor 4 (TLR4) was associated with an increased risk of sepsis in burned patients [12]. In a murine model of burns, it was also demonstrated that the enhanced Treg activity was restricted to the lymph nodes of the burned area, suggesting local cross-talk rather than a systemic effect of stress [8].

4.2.5 Other Consequences from 'Stress'

Hyper-metabolism and prolonged catabolism are a normal response to the increased loss of heat through diseased skin and to systemic inflammation. Endogenous catecholamines are primary mediators of

hyper-metabolism in severe burns, but many other contributing factors are directly induced by 'inflammatory cytokines', heat-shock proteins or neuro-endocrine pathways.

The consequences of the hyper-metabolic status include the following:

- Hyper-glycaemia may result in overt diabetes, glycosuria, polyuria, hyper-osmolarity and worsening of water losses. In TEN patients, hyper-glycemia above 14 mmol l^{-1} affects about 15% of patients, and is one of the factors that most adversely affects the prognosis [16].
- Hypo-albuminemia, from decreased albumin synthesis, may contribute to oedemas.
- Lipolysis provides energy in the first days of skin failure, with a resultant elevation of blood free fatty acids.
- Proteolysis follows to supply elements for hepatic neo-glucogenesis. Protein balance is negative and after a couple of weeks muscle wastage will become clinically patent from muscle weakness, even though weight loss can be masked by oedemas. In chronic situations such as exfoliative dermatitis, bone demineralisation can be marked.
- Inhibition of bone-marrow function, mainly by inflammatory cytokines, will block the maturation of blood cells and contribute to anaemia and neutropenia.

Hypo-phosphoremia is often a part of this hyper-metabolic status. It is present in about one half of patients with SJS or TEN [16]. It should not be overlooked, since it contributes to insulin resistance and can impair ventilation through muscle dysfunction.

4.2.6 Patients at Risk for Skin Failure

As expected from the physiologic considerations developed above, patients at risk for skin failure are those with a combination of alteration of barrier functions and skin inflammation. In diseases with very active inflammation (e.g., thermal or caustic burns, severe dermatitis, blistering diseases, pustular psoriasis), ASF should be suspected when more than 10% of the body surface area is involved, especially in newborns and the elderly. Conditions with milder inflammation (e.g., keratinization disorders, atopic dermatitis, plaque psoriasis) are at risk when larger skin surfaces are altered (at least 30% of BSA) (Table 4.1).

Table 4.1 Percentage of BSA of various parts of body depending on age (Lund and Browder Table)

Age	*0*	*1*	*5*	*10*	*15*	*Adult*
Head	19	17	13	11	9	7
Neck	2	2	2	2	2	2
Anterior trunk	13	13	13	13	13	13
Posterior trunk	13	13	13	13	13	13
Genitals and buttocks	6	6	6	6	6	6
Thighs	11	13	16	17	18	19
Legs	10	10	11	12	13	14
Feet	7	7	7	7	7	7
Upper arms	8	8	8	8	8	8
Lower arms	6	6	6	6	6	6
Hands	5	5	5	5	5	5

Depending on the nature of the dermatological disease, the relative weights of components of ASF are different. Destruction of the epidermis (blisters), with mild or absent erythema, creates exposure to fluid losses and infection but not to the skin blood flow being increased to a point compromising heart function. On the other hand, patients with exfoliative dermatitis are more prone to cardiac failure than to severe infection, as long as they do not have venous lines inserted through diseased skin.

4.3 Main Principles of Symptomatic Treatment

For many of the diseases that are complicated by skin failure, 'specific' treatments, when existing, are not of very rapid effectiveness. It is therefore of key importance for the management to (1) closely monitor patients for clinical and biological manifestations of skin failure, and (2) take some simple measures that will reduce the risk.

4.3.1 Patient Monitoring

Key clinical parameters:

Extension and inflammation of skin lesions, measurement of the percent of body surface area

(BSA) involved
Intensity of pain (visual analogue scale)
Fever
Weight
Heart and respiratory rates, blood pressure
Urinary output

Key biological parameters:
Blood saturation in oxygen (pulse oxymetry)
Glycemia
Bacterial colonisation of the skin, especially around venous lines

4.3.2 Simple Symptomatic Measures

- Decrease the part of stress that results from pain and anxiety, with a liberal use of pain drugs including morphine at doses needed for adequate control of pain.
- Reduce caloric losses by warming environment temperature and reducing patient fever (antipyretics).
- Decrease the cutaneous blood flow. Decreasing fever will substantially reduce the cardiac output. Potent topical corticosteroids will also contribute to improve rapidly the cardiac function through vasoconstriction of skin vessels.
- Reduce and compensate water losses. Intravenous lines are most often needed. When possible they must be inserted in normal skin, avoiding central catheters with a tight attention to prevention of local infection.
- Control the metabolic response to stress. Several measures should be associated. The first is to treat hyper-glycemia. Several oral medications have been shown in burn patients to decrease insulin resistance, but insulin is the most important treatment. A strict control of glycemia with intensive insulin therapy has been proven to decrease morbidity and mortality of critically ill patients, as compared with a more conservative attitude using insulin only when glycemia was ≥12 mol l^{-1} [17]. The second measure is to provide a high caloric and protein enriched nutrition. When possible oral or continuous gastro-enteric nutrition should be preferred, since it has been shown to decrease the incidence of stress ulcers and bacterial translocation from the gut.

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Part II

Life Threatening Dermatoses

Purpura Fulminans

5

Saul N. Faust and Simon Nadel

Core Messages

- Purpura fulminans has many causes, both infectious and non-infectious.
- It is a common clinical and histological manifestation of a number of distinct disease processes.
- The term was first used in the nineteenth century to describe a rapidly progressive skin condition that is most commonly associated with serious systemic infection.
- Recent years have seen an explosion in our understanding of the pathophysiological processes which occur both in the skin and elsewhere.
- This has led to advances in management of both the skin condition and underlying disease.
- We now understand that abnormalities in both the coagulation and fibrinolytic pathways can lead to purpura fulminans.
- In addition, endothelial cell dysfunction may play a major role in the pathophysiology.
- Treatments are designed to correct the underlying abnormalities in the coagulation or fibrinolytic pathway, and correct the underlying cause of these abnormalities.
- Understanding pathophysiology will lead to improvements in therapeutic modalities and outcome.
- The prognosis of purpura fulminans has improved in recent years, but is mainly associated with that of the underlying condition.

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5.1 Aetiology and Pathology

Purpura fulminans is not a single disease, but a common clinical and histological manifestation of a number of distinct disease processes. We have previously proposed a classification of purpura fulminans categorizing patients with purpura fulminans into one of eight groups, on the basis of clinical and epidemiological criteria, and laboratory findings (Table 5.1) [1].

Infections reported to cause purpura fulminans include *Neisseria meningitidis, Streptococcus pneumoniae*, *Haemophilus influenzae*, *H. aegyptius*, *Staphylococcus aureus*, Group A and other beta-haemolytic streptococci, *Pseudomonas aeruginosa*, Rickettsiae and *Candida albicans*.

The pathophysiology of purpura fulminans due to meningococcal infection will be discussed in detail below.

Children with homozygous congenital protein C and S deficiency often present in the neonatal period with thrombosis of major vessels, leading to tissue and organ infarction, with or without the cutaneous manifestations of purpura fulminans [2].

Post-infectious purpura fulminans usually occurs 1–3 weeks after an acute infectious process [3], most commonly following varicella or streptococcal infection. Post-infectious purpura fulminans may be caused by an acquired deficiency of protein S. A consistent feature of this condition is development of auto-antibodies against protein S [4]. The underlying mechanism remains unclear, as proteins associated with the varicella zoster virus that have structural homology to protein S have not been described. It is also possible that auto-antibodies directed against protein C may cause a similar clinical picture.

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Table 5.1 Classification, clinical features and suggested therapy for purpura fulminans [1]

Clinical subgroup	Aetiology	Clinical features	Laboratory features	Pathophysiology	Medical therapy	Outcome
Acute infectious purpura fulminans	*Neisseria meningitides; Streptococcus pneumoniae; Haemophilus influenzae; Staphylococcus aureus; b*-haemolytic streptococci; Other bacteria; Rickettsiae; *Candida albicans*	Any age; Acute febrile illness; Hypotension; Multiorgan failure	Coagulopathy; Positive blood culture; Other evidence of specific infection	Circulatory insufficiency; Endothelial dysfunction; Coagulation activation; Platelet activation; Anticoagulant dysfunction; Fibrinolytic dysfunction	*General*: Antimicrobial therapy; Treatment of shock; Support of multiorgan failure *Specific* Consider fasciotomy	Mortality rate 20–40%; May require skin grafting, amputation of digits or limbs; Long-term orthopaedic problems including disrupted bone
Post-infectious purpura fulminans	Varicella; Group A b-haemolytic streptococci; Other viruses, e.g. rubella	Usually young children; Biphasic illness; Sudden onset of PF; Haemodynamically stable	Coagulopathy; Specific factor deficiency	Acquired protein S or C deficiency; Autoantibody-mediated; Other mechanisms?	FFP; Heparin; fibrinolytics	Self-limiting; Mortality rate 15–20%; Surgical intervention may be necessary
Congenital protein C or S deficiency	Homozygous or Compound heterozygous genetic defects	Usually early neonatal period; Spontaneous onset of PF; Haemodynamically stable; Family history of thromboembolism	Coagulopathy; Specific factor depletion; Specific deficiency in family members	Inherited protein C or S deficiency	*Immediate*: FFP or factor concentrate; Heparin *Prophylaxis:* Anticoagulation: warfarin; protein C concentrate	Lifelong deficiency; Fatal if untreated; Neurological and ophthalmic sequelae are common; Continuous risk of recurrence; Surgical intervention may be necessary
Acquired protein C or S deficiency associated with drugs or disease	Coumarin drugs; Cholestasis; Renal dialysis; Nephrotic syndrome; Bone marrow transplantation	Any age; Predisposing factors: drugs, interventions, hepatic or renal disease	Coagulopathy; Specific factor depletion	Acquired protein C or S dysfunction or depletion	FFP or protein C concentrate; Heparin; Address underlying cause	Usually self-limiting; Surgical intervention may be necessary
Antiphospholipid antibody syndrome	Autoimmunity	Usually older children and adults; underlying SLE	Prolonged APTT slightly prolonged PT; Lupus anticoagulant; Antiphospholipid antibodies	Haemostatic dysregulation: multiple autoantibody mediated mechanisms identified	*Immediate:* Anticoagulation; Fibrinolytics; Immunosuppression; Plasmapheresis; *Prophylaxis:* Anticoagulation: warfarin; antiplatelet therapy	Fulminant variant is frequently fatal; Long-term prophylaxis is required to prevent recurrences; Surgical intervention may be necessary

Vasculitic disorders	Polyarteritis; Henoch–Schönlein purpura; Other systemic vasculitides	Fever; Multiorgan involvement; Vasculitic rash; Arthritis	Acute phase response; Leucocytosis; Organ dysfunction	Vasculitic damage to blood vessel wall	Immunosuppression: Steroids; Cyclophosphamide anticoagulation; Antiplatelet agents	Significant mortality; Prognosis depends on response to underlying disease
Platelet-mediated purpura fulminans	Heparin therapy	Usually subcutaneous heparin PF at injection site	Thrombocytopenia	Antibody-mediated platelet aggregation	Discontinue heparin therapy; cyclo-oxenge-nase inhibitors	Self-limiting; Surgical intervention may be necessary
Toxins/poisons	Spider bites; Snake bites	History of envenoma-tion; Purpura maximum at site of bite	Coagulopathy	Toxic damage to blood vessels; Activation of coagulation	Specific antitoxins; Supportive treatment	Self-limiting; Surgical intervention may be required

PF purpura fulminans; *APTT* activated partial thromboplastin time; *AT* antithrombin; *PT* plasma thromboplastin; *SLE* systemic lupus erythematosus; *FFP* fresh-frozen plasma

Acquired protein C or S deficiency may also occur due to drugs or specific non-infectious diseases. Coumarin derivatives suppress protein C and S production; and acquired protein C and S deficiency may also occur in patients with cholestatic disease, nephrotic syndrome, and in patients being treated with peritoneal dialysis, or bone marrow transplantation [5]

Purpura fulminans may occur both as part of the anti-phospholipid antibody syndrome and in patients with systemic autoimmune disease such as systemic lupus erythematosus (SLE), polyarteritis nodosa or Henoch–Schönlein purpura. The mechanisms by which anti-phospholipid auto-antibodies cause thrombosis or purpura fulminans are not completely understood. Different theories have been proposed, including the effect of anti-phospholipid auto-antibodies on endothelial cells, monocytes, and platelets. Other mechanisms include inhibition of protein C activation by thrombomodulin, inhibition of the anticoagulant action of activated protein C, and interference with anti-thrombin 3 binding to endothelial glycosaminoglycans. Non-antibody-mediated vasculitic damage to the vessel wall may contribute to the pathophysiology, mediated by neutrophils and lymphocytes or other inflammatory cells [6].

Platelet-mediated purpura fulminans may occur at the injection site during subcutaneous heparin therapy, and is caused by antibody-mediated platelet aggregation.

Finally, more localised purpura fulminans may occur following snake or spider bites due to activation of coagulation, and endothelial injury appears to be the underlying mechanism.

Whatever the cause, the major histopathological finding in purpura fulminans is thrombotic occlusion of dermal vessels [7]. This thrombotic occlusion may occur only in the dermal capillaries and venules, or may extend to thrombosis of the large vessels of deep tissues. Thrombotic occlusion of the major veins draining entire limbs may occur. In meningococcal infection, there may be evidence of vasculitis surrounding areas of venous thrombosis, although this is not always the case. In post-infectious purpura fulminans, the intravascular thrombosis usually occurs without any evidence of underlying vasculitis or inflammatory cell-induced disruption of the vessel wall.

5.2 Clinical Features

The specific clinical features occurring in patients with purpura fulminans *depend on the cause*. The first purplish skin lesions are most commonly on the extremities but may occur anywhere on the body. Within hours, progression to sharply defined ecchymoses may occur. Lesions vary in size between small (a few millimeters in diameter) and large confluent areas which affect entire limbs. Over days the lesions become black and necrotic, indicating infarction of the affected area of skin. Rarely, haemorrhagic bullae or vesicles may occur. Where circumferential lesions of limbs, or major venous thrombosis develop, there may be evidence of peripheral ischaemia of whole or multiple limbs or digits, reflected in the loss of arterial pulses in the affected areas. Critical ischaemia of entire limbs may occur within a few hours of disease onset.

Later in the course of disease, areas of purpura become sharply demarcated from the surrounding normal tissues, which may be warm and well-perfused. Where the thrombotic process has extended into the deep tissues, necrosis of the overlying skin will occur. Over weeks, the thrombosed and necrotic skin sloughs off, revealing healthy underlying granulation tissue. In superficial lesions viable skin may regrow without the need for skin grafting, even when there have been extensive areas of apparent skin necrosis, and patients may recover fully without extensive scarring. However, where lesions are deep and extensive, skin grafting may be required, or in the most severe cases amputation may be necessary.

The effective treatment of individual patients with purpura fulminans depends on the aetiology and specific treatment of that underlying condition (Fig. 1).

5.3 Purpura Fulminans due to Meningococcal Infection

Acute infectious purpura fulminans is best illustrated by the example of purpura fulminans seen in meningococcal disease, where a greater understanding of the pathophysiology has been elucidated.

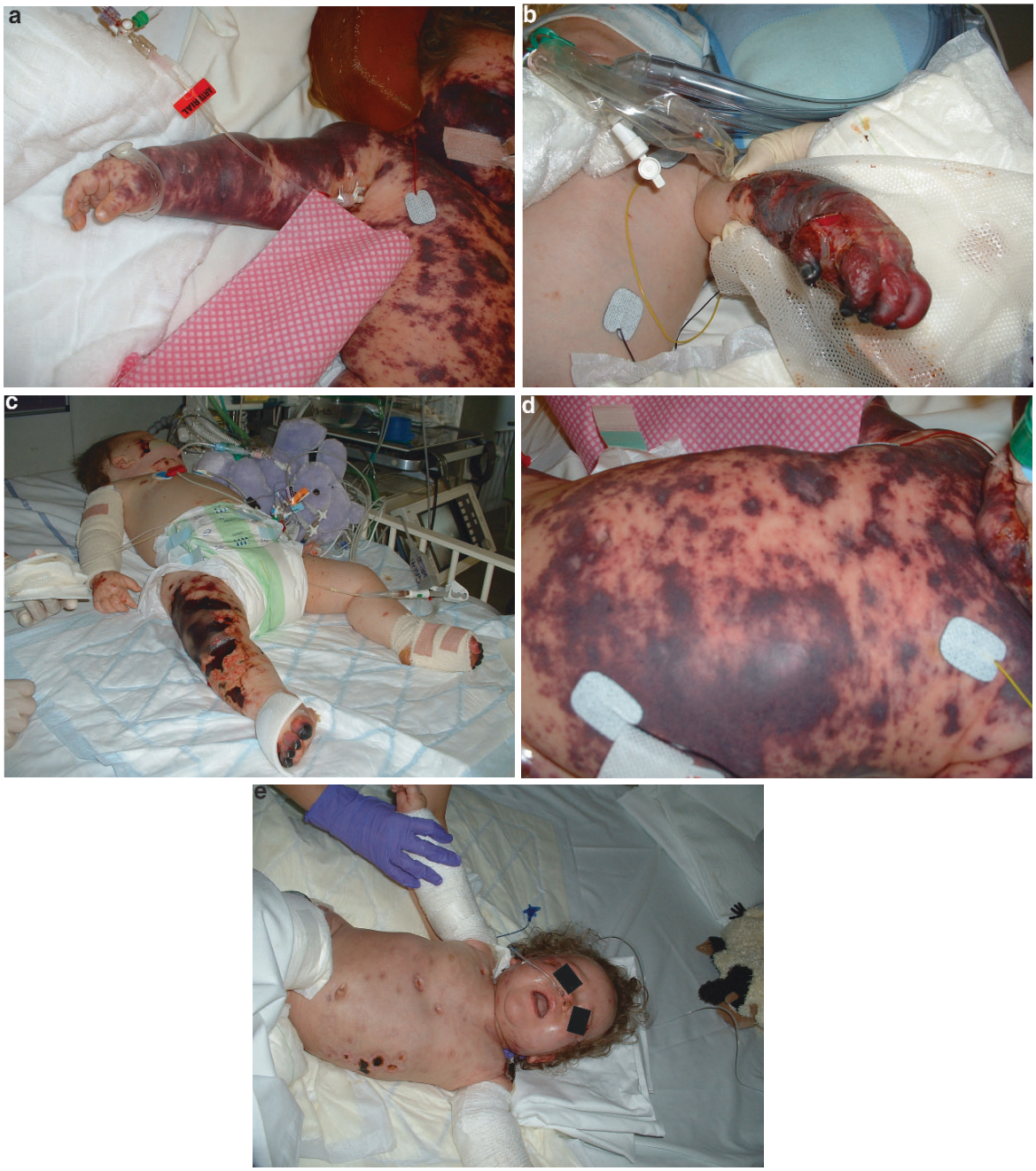

Fig. 5.1 **a** Meningococcal septicaemia and purpura fulminans, severe necrotic lesions over all skin without digital gangrene. **b** Meningococcal septicaemia and purpura fulminans, peripheral ischaemia and digital gangrene. Note virtual absence of purpuric lesions on trunk and face. **c** Meningococcal septicaemia and purpura fulminans, extensive tissue necrosis over right lower limb and bilateral digital gangrene. Note purpuric lesions on face. **d** Meningococcal septicaemia and purpura fulminans, extensive tissue necrosis over trunk. **e** Meningococcal septicaemia and purpura fulminans, convalescence (same patient as **d**). Note extensive healing with scarring of the extensive purpura over trunk

5.3.1 Pathophysiology

Most commonly, but not exclusively, seen in children, purpura fulminans associated with meningococcal infection usually presents with the clinical features of severe sepsis [8, 9]. With recent advances in the early recognition and aggressive treatment of the disease, childhood mortality rates of 20–40% have been reduced to around 5–10% in countries with modern paediatric intensive care facilities [10].

The intravascular thrombosis of meningococcal purpura fulminans is due to a combination of circulatory failure and poor perfusion due to clinical shock, platelet activation and degranulation leading to local vasoconstriction, upregulation of procoagulant pathways, and downregulation of anticoagulation and fibrinolytic regulatory pathways due to endothelial cell dysfunction [11, 12].

The inflammatory and coagulation cascades triggered by meningococcal infection result from the presence of bacterial endotoxin derived from proliferating meningococci in the circulation. Endotoxaemia triggers a complex inflammatory pathway, leading to release of pro- and anti-inflammatory mediators, upregulation of the procoagulant pathways, and downregulation of the anticoagulant and fibrinolytic pathways. The pathophysiology of the coagulopathy is complex (Fig. 5.2) [11], with endothelial cell dysfunction playing a central role [13]. While coagulation

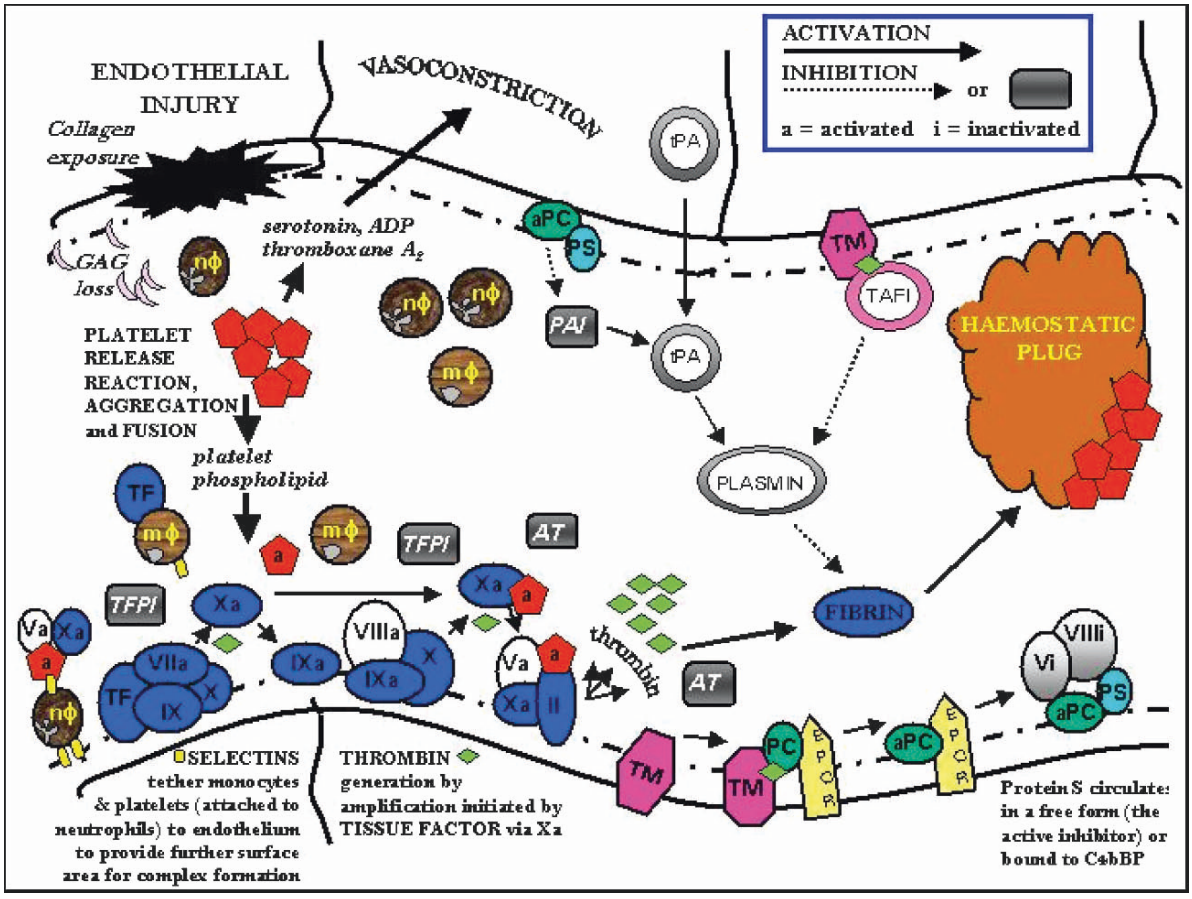

Fig. 5.2 The pathophysiology of disseminated intravascular coagulation in bacterial infection-related purpura fulminans. Abbreviations: *GAG*, Glycosaminoglycans; a*PC*, activated protein C; *PS*, protein S; t*PA*, tissue plasminogen activator; *TM*, thrombomodulin; ADP, adenosine diphosphate; *TAFI*, thrombin-activated fibrinolysis inhibitor; *PAI*, plasminogen activator inhibitor-1; *TF*, tissue factor; *TFPI*, tissue factor pathway inhibitor; *ATIII*, antithrombin 3; *PC*, protein C; *EPCR*, endothelial protein C receptor; *Roman numerals*, clotting factor; *nØ*, neutrophil; *mØØ:* macrophage

pathways are activated, the self-regulatory functions of the blood vessel wall are disrupted (Table 5.2), leading to uncontrolled local thrombosis (Fig. 5.3).

Endothelial injury mediated either by bacterial toxins directly, or secondary to host inflammatory factors such as tumour necrosis factor (TNF), interleukin 1 (IL-1), reactive oxygen intermediates or proteolytic enzymes, results in endothelial cell dysfunction and loss of anti-thrombotic mechanisms. Endotoxin induces upregulation of adhesion molecules on the endothelial surface which facilitate neutrophil adhesion to the endothelial surface. Upregulation of endothelial procoagulant mechanisms, including tissue factor, occurs. Activated neutrophils induce loss of the anticoagulant glycosaminoglycans, heparin sulphate and chondroitin sulphate from the endothelial surface, downregulation of prostacyclin production, and a defect in the activation of anti-thrombin by the endothelium [8].

The normal regulatory systems which prevent uncontrolled coagulation on the endothelial surface are similarly disturbed. Acquired deficiencies of tissue factor pathway inhibitor, anti-thrombin and proteins C and S are caused by the development of abnormal capillary permeability, leading to leakage of these proteins and others out of the intravascular compartment, together with consumption of these factors by the thrombotic processes. Reduced thrombomodulin and endothelial protein C receptor (EPCR) expression on the endothelial surface cause depression of protein C activation in the dermal vessels [13].

The fibrinolytic system is also impaired, due in part to increased production of plasminogen activator inhibitor 1 (PAI-1), the physiological inhibitor of tissue plasminogen activator (t-PA). In sepsis, elevated PAI-1 has been correlated with the development of shock, renal impairment, and mortality [23]. In meningococcal infection, a genetically determined increase in PAI-1 has been associated with mortality [24].

The dysfunction of the coagulation and fibrinolytic pathways described above leads to the development of disseminated intravascular coagulation (DIC) and to purpura fulminans in many patients with meningococcal infection. Some individuals have more severe purpura than others, and some patients show little correlation between the degree of cardiovascular compromise and the extent of purpura.

It is now clear that individual susceptibility to invasive meningococcal disease is determined by both genetic predisposition and bacterial virulence. Genetic factors also appear to play an important role in determining severity of disease and complications. For example, the factor V Leiden mutation confers a genetic predisposition to thrombotic disease in the population, and has been shown to be associated with an increased risk of thrombotic complications such as amputation and skin grafting in individuals who develop meningococcal infection [25]. In addition, those individuals who are genetically determined to secrete higher levels of PAI-1 in response to TNF-alpha, due to a polymorphism in the PAI-1 gene, have an increased likelihood of dying if they suffer meningococcal infection [24].

Table 5.2 Endothelial regulatory dysfunction in meningococcal sepsis

Endothelial prostacyclin production reduced [14]
Expression of anticoagulant glycosaminoglycans impaired [15]
Increased monocyte tissue factor activity [16]
Decreased tissue factor pathway inhibitor [17]
Deficiency of antithrombin, protein C and protein S [18, 19, 20, 23]
Dysfunction of endothelial protein C activation pathway [13]
Disruption of the fibrinolytic pathway [21, 22]

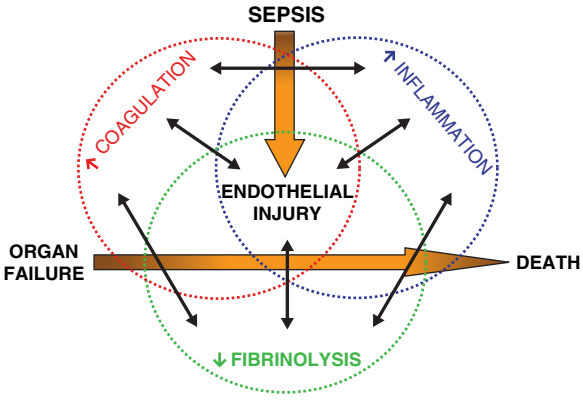

Fig. 5.3 Pathophysiology of sepsis

5.3.2 Treatment

The initial management of patients with purpura fulminans due to meningococcal infection is directed at treatment of the infection and the main complication, which is the presence of circulatory failure and shock [9, 26]. Patients with severe disease should be initially treated with broad spectrum antibiotics, and resusci-

tated with fluid to correct circulatory failure. These patients will often need tracheal intubation and mechanical ventilation, together with inotropic support to improve multiple organ dysfunction.

There have been few controlled trials in the treatment of purpura fulminans due to infection. Many of the commonly used therapies have no evidence to support their use. Fresh frozen plasma (FFP) or cryoprecipitate infusions are often used in an attempt to correct the coagulopathy and to reduce the risk of haemorrhage associated with hypofibrinogenaemia [27]. There have been anecdotal reports of the use of prostacyclin (a vasodilator and platelet inhibitor) to treat vasoconstriction where impending peripheral gangrene is developing, but this agent may exacerbate hypotension and lead to worsening of circulatory failure. Heparin therapy has also been suggested in the past, but limited clinical trials have not shown any benefit for its routine use in sepsis [28].

Many adjunctive therapeutic agents to modulate inflammation and the coagulation pathways have been suggested for the treatment of severe sepsis. Despite many clinical trials, none has proven to be beneficial in the overall management of patients with severe sepsis, despite a rational basis for these therapies being suggested in experimental models.

One of the reasons why most controlled clinical trials of adjunctive therapies have not shown benefit is that many of the experimental therapies have only acted on replacement or modulation of one component of an extremely complex sequence of pathway interactions.

However, one of the more promising areas for clinical intervention has been the protein C anticoagulant pathway. Following reports of uncontrolled case series and a small clinical trial, some authorities have suggested that administration of protein C concentrate [29] may be beneficial. However, there are concerns that even if plasma protein C level is normalised by the use of protein C concentrate, it is not possible to predict which patients will be able to activate protein C on the endothelial surface, due to defective thrombomodulin and EPCR function. There is a theoretical risk that excess unactivated protein C may displace any activated protein C at the endothelial protein C receptor, and thus potentially exacerbate dermal vessel thrombosis.

A large phase 3 randomised controlled study of recombinant activated protein C in critically ill adults with sepsis has shown a significant reduction in mortality in those patients treated with activated protein C compared with placebo [30], and this has now become a standard of care for adults with severe sepsis and septic shock. However, a phase 3 randomised placebo-controlled study of activated protein C in children with severe sepsis showed no overall benefit in terms of mortality. It did, however, suggest an increased, though statistically non-significant, mortality benefit in those children with DIC [31].

Although the use of anti-thrombin to restore circulating levels was suggested by animal data and some human series, a large placebo-controlled trial of this agent in adult sepsis showed no survival benefit of using the drug, together with an increased risk of bleeding where administered with heparin [32].

There have been a number of case reports of the use of tissue plasminogen activator (tPA) in patients with critical limb ischaemia, and the use of tPA to treat severe meningococcal infection has a sound theoretical basis. However, in a retrospective European study of 62 children with meningococcal disease treated with tPA, no obvious clinical benefit was seen, and 8% of those children treated suffered serious intracerebral bleeding so that its use cannot now be recommended [33].

Many clinicians faced with a patient with a devastating illness such as meningococcal disease, and the prospect of limb loss and death in young previously healthy patients, feel justified in attempting to utilise experimental treatments in an uncontrolled way. The potential beneficial effects of anticoagulant or fibrinolytic agents must be balanced against the potential risk of causing severe haemorrhage. The experience in evaluating tPA in severe meningococcal disease highlights the need to avoid such strategies, and for clinicians to participate in multicentre controlled trials to evaluate experimental therapies properly.

5.3.3 Surgical Treatment and Multidisciplinary Care

Patients with extensive purpura fulminans and peripheral ischaemia of the limbs or digits require multidisciplinary treatment involving physicians together with vascular, orthopaedic and/or plastic surgeons, nurses, physiotherapists and occupational therapists. Nutritional support and the avoidance of nosocomial wound infection are essential in the overall care package.

In severe meningococcal infection, marked swelling of the limbs and other tissues may occur extremely rapidly. In the acute phase of severe meningococcal infection complicated by peripheral gangrene, our unit and others have advised fasciotomy (following compartment pressure measurement) to relieve the potential compartment syndrome that may develop in severely affected limbs. However, there has not been any formal evaluation of the utility of this therapy. Fasciotomy may lead to uncontrolled bleeding, but rapid improvement in deep tissue perfusion is sometimes seen. In addition, there is a possibility of increased risk of infection in the open dead tissue, and there may be difficulties with skin coverage around the amputation site once amputation has occurred, due to the fasciotomy incision [34].

Amputation, debridement and skin grafting of large purpuric areas should be delayed until complete demarcation of the infarcted areas from the surrounding tissues has occurred. There are two main reasons for a delay in surgery. Firstly, the risk of bleeding and cardiovascular compromise during major surgical procedures in patients with septic shock is higher than the potential benefit of surgical invention. More importantly, the extent of potential recovery is impossible to assess in the early stages of disease, and significantly more spontaneous recovery may occur than may have been predicted at the start.

When demarcation has occurred, surgery including skin grafting, microvascular flaps or amputations may be required. Multiple grafting procedures and scar revision are likely to be necessary, often for many years after the acute event. Decisions regarding timing of any surgical procedure require careful multidisciplinary discussion.

5.3.4 Post-Infectious Purpura Fulminans

With the recognition that the pathophysiology of post-infectious purpura fulminans involves acquired deficiency of protein S and that the disorder is primarily a disorder of venous thrombosis, treatment has become much clearer [4]. Immediate heparinisation should be undertaken in any patient presenting with purpura fulminans in the convalescent phase of varicella infection. Clinicians must be aware of the risk of superinfection with Group A streptococcus or Staphylococcus aureus in patients with varicella. Either of these infections may lead to development of systemic sepsis and shock, necrotizing fasciitis and DIC, with or without purpura. Recognition of these complications and appropriate antimicrobial and surgical therapy is mandatory before deciding that post-infectious purpura fulminans is present and embarking on the therapies described below.

Patients with post-infectious purpura fulminans do not usually present with signs of circulatory dysfunction and ongoing sepsis. The presence of these should raise the possibility of infection-related purpura fulminans or bacterial superinfection.

In those patients where post-infectious purpura fulminans is diagnosed, heparinisation should be started concurrently with infusion of FFP. Correction of hypofibrinogenaemia, and replacement of clotting factors, will usually enable full heparinisation to be achieved without major risk of haemorrhage. Heparinisation is achieved by immediate administration of 100 units per kg of heparin, followed by a constant infusion of 25 units kg/h. Patients with purpura fulminans are frequently heparin-resistant, and much larger doses may be required to achieve anticoagulation. In most patients heparin alone will be adequate to prevent progression of the purpura. Our most frequent regime would be to administer FFP on a daily basis (10–20 mL/kg) and to administer heparin continually, initially by the intravenous route and then switche to low molecular weight heparin to complete therapy [35]. Heparinisation is generally indicated until levels of protein S return to normal 2–6 weeks after the onset of the disease.

Although immunosuppression, or plasmapheresis, would theoretically hasten the reduction in plasma levels of anti-protein S antibodies, these treatments are generally not indicated. Anti-protein S antibody levels decline spontaneously over a few weeks, and it is doubtful whether immunosuppression with steroids or plasmapheresis would result in a decline of the levels much more rapidly. In addition, there are significant complications of both of these therapeutic options; in the presence of purpura fulminans and protein S deficiency, major vessel thrombosis including intracardiac thrombosis formation may occur, and central venous cannulation should be avoided if at all possible. In addition, large areas of skin necrosis are a high risk for superinfection, which may be made more likely by immunosuppression.

5.4 Prognosis

Purpura fulminans remains a devastating condition which may cause considerable long-term disability as well as significant mortality. For patients presenting with purpura fulminans as a complication of meningococcal or other infection, the prognosis is largely that of the underlying disorder. With earlier disease recognition and modern intensive care, a higher proportion of patients with septic shock are now surviving. However, with improvements in the survival rates for patients with severe sepsis, many patients who previously may have died of shock and multiorgan failure are now surviving, but being left with the consequences of severe purpura fulminans, including potential loss of whole limbs or digits, and of extensive areas of skin [36].

For the other forms of purpura fulminans including post-infectious purpura fulminans, the prognosis has improved as a result of a better understanding of the disease. Reports in the literature of patients with post-infectious purpura fulminans suggested mortality rates of 20–30%. With early anticoagulation, and judicious use of clotting factor replacement or fibrinolytic therapy for large-vessel occlusion, the prognosis has undoubtedly improved, and the majority of patients in whom the diagnosis is made and appropriate treatment administered should now survive. Those patients in whom the true nature of the illness is not appreciated, and in whom appropriate treatment is therefore not instituted, continue to have a poor prognosis.

Improved understanding of the pathophysiology of infection-related purpura fulminans and DIC, and the link with systemic inflammation, has led to development of adjunctive therapies for patients with severe sepsis and DIC. The next few years should see the translation of these theoretical treatments into clinical use, with the potential for further improvements in outcome.

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Severe Infections of Soft Tissues (Including Fasciitis and Diabetic Foot Infections)

6

Philippe Bernard

Core Messages

- Erysipelas and other non-necrotizing dermal–hypodermal infections are mainly caused by streptococci, though other bacteria can cause such infections, which often occur in specific circumstances.
- There is an increasing prevalence of soft-tissue infections (STIs) caused by community-acquired MRSA which are responsible for about half of the cases of cellulitis with purulent exudates in involved geographic areas. Contrary to erysipelas, the best therapeutic option will be an antibiotic that is effective both against streptococci and *S. aureus*.
- Treatment of necrotizing fasciitis, a rare, life-threatening infection, primarily affecting the superficial muscular fascia and adjacent hypodermis, is surgical excision of all necrotic tissue; it must be considered as an emergency once the diagnosis is suspected.
- Diagnosis of purulent diabetic foot infections within soft tissues or localized osteomyelitis generally requires imaging investigations. The initial empirical antibacterial regimen may be tailored based on the results of bacteriological cultures.

6.1 Introduction

Soft-tissue infections (STIs) can be defined as infections of any of the layers within the soft-tissue compartment: dermis, subcutaneous tissue (i.e. hypodermis), superficial and deep fascia, or even muscle. STIs are generally severe infections, and require hospitalisation in a majority of cases. They include non-necrotizing dermal–hypodermal infections (erysipelas), forms of intermediate severity with abscess and/or exudate and necrotizing STIs (necrotizing fasciitis), the latter being infrequent but life-threatening. In diabetic patients, severe STIs of the lower extremity represent a frequent and difficult problem; these diabetic foot infections frequently expand to bones and joints, and are associated with a poor prognosis of limb salvage. Except diabetic foot infections, STIs are frequently due to streptococci though staphylococci, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), play a growing role in dermal–hypodermal infections evolving into abscesses. However, numerous other bacteria (*Pseudomonas aeroginusa*, *Entero-bacteriaceae*, anaerobes) may also be responsible for severe STIs with local necrosis and/or abscess formation.

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6.2 Erysipelas

6.2.1 Definition

Erysipelas is an acute, superficial, non-necrotizing dermal–hypodermal infection which is mainly caused by streptococci [1–3]. The definitive diagnosis is based on clinical findings which usually include a sharply demarcated shiny erythematous plaque of sudden onset associated with pain, swelling and fever. Erysipelas differs clinically from other non-necrotizing cellulitis by a more defined margin, its acute course and a more elevated fever.

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6.2.2 Bacteriology

Erysipelas is most commonly caused by β-haemolytic streptococci of group A, less so by group B, C or G streptococci [1, 4, 5] and rarely by staphylococci [2].

6.2.3 Epidemiology

A recent study in the Netherlands showed an incidence of about 2 per 1,000 per year when both erysipelas and cellulitis affecting the leg were considered [6]. Predisposing factors for erysipelas of the leg mainly include local factors, i.e., disruption of the cutaneous barrier (leg ulcer, wound, fissured toe-web intertrigo, pressure ulcer) and lymphedema, whereas general factors such as obesity are less important [7]. Chronic foot dermatomycosis increases the risk of leg erysipelas [8].

6.2.4 Clinical Features

Erysipelas affects predominantly adult patients in the sixth or seventh decade, and is located to the lower limb in more than 80% of cases, particularly the leg [9]. A female predominance exists, except in young patients. The onset is typically abrupt with high fever, chills and malaise, and within 24 h the erythematous, indurated, hot, painful plaque develops unilaterally, which is clearly demarcated from surrounding uninvolved skin (Fig. 6.1, 6.2). It may also affect less frequently other sites such as face, arms, hip or trunk [2, 10]. Regional lymphadenopathy is frequently present, with or without lymphatic streaking. A portal of entry exists in two-thirds of cases (toe-web intertrigo, ulcer or wound). Without treatment, erysipelas spreads within 24–48 h without central healing or deep necrosis, though bullae, vesicles or pustules may form sometimes, resulting in small areas of superficial necrosis.

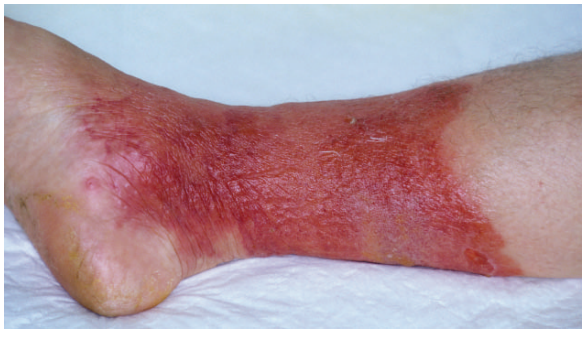

Fig. 6.1 Typical erysipelas involving the leg; note the translucide, superficial blisters

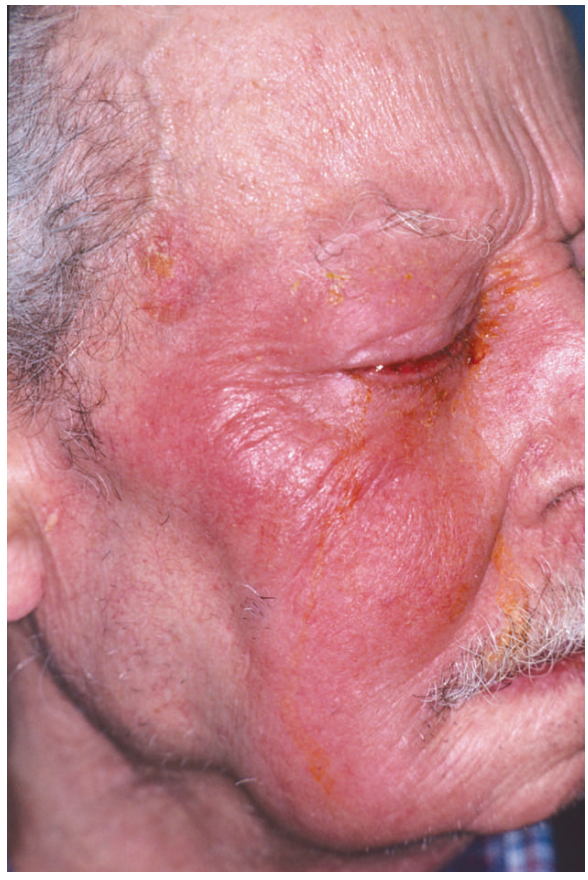

Fig. 6.2 Erysipelas involving the face; note the well-demarcated margin

6.2.5 Diagnosis

It is based primarily on clinical findings. Routine laboratory investigations will show elevated blood leukocytosis and CRP. Blood cultures are very rarely positive (2–5% of cases). Bacteriologic cultures from needle aspirates or skin biopsy are useless, since they yield poor results. Swabs from suspected portal of entry or nose may be useful in populations with a high prevalence of MRSA carriage. Anti-DNAse B and ASLO titers are only retrospective indicators of group A *Streptococcus* infections [1, 5].

Dermatoses sometimes associated with fever that may resemble erysipelas include staphylococcal cellulitis secondary to furuncle, abscess or osteomyelitis, erysipeloid, Wells' syndrome, Sweet's syndrome, acute lipodermatosclerosis of the leg or systemic lupus erythematosus (facial involvement). Necrotizing fasciitis (early stage) may also resemble erysipelas, but general and local signs and symptoms are more severe (see below).

6.2.6 Course and Treatment

Erysipelas can be a severe disease, but it is seldom life-threatening. The clinical evolution is favourable in over 80% of the cases with an appropriate antibiotic treatment [2, 10]; fever disappears within 36–48 h, whereas local signs resolve more slowly (8–12 days). Recurrence is the main complication [11]; it occurs in about 20% of cases. Systemic complications are very rare, including anecdotal cases of endocarditis, or acute glomerulonephritis. Local complications are more frequent, occurring in up to 10% of the cases, and include dermal abscesses, superficial skin necrosis or deep gangrene (necrotizing fasciitis) with potential limb-threatening. Later, severe or repeated episodes of erysipelas may lead to lymphedema, sometimes substantial enough to cause elephantiasis [12]. Osteoarticular complications of erysipelas are infrequent, and include non-septic (mainly bursitis) and septic complications (osteitis, arthritis, tendinitis) [13]. Most patients with erysipelas are not hospitalized but treated at home by oral antibiotics [6, 14]. The main reasons for hospitalization are the severity of general or local signs, old age, the existence of an associated disease (diabetes, mellitus, arteriosclerosis obliterans) possibly responsible for further complications [15], and the necessity to eliminate deep venous thrombosis [3]. Therapy for erysipelas should include an antibiotic active against streptococci. Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice for erysipelas [10, 17, 18]. Patients with erysipelas without local or general severity signs can be treated orally by amoxicillin (3–4.5 g daily) for 2 weeks [cc 2000]. Pristinamycin (1 g three times per day) [19] or clindamycin (300 mg three times per day) may be used in penicillin-allergic patients. In hospitalized patients, parenteral penicillin G (12–20 MU daily) or amoxicillin (3–6 g daily) can be used initially in severe cases until apyrexia, followed by oral amoxicillin.

Measures to reduce recurrences of erysipelas include treatment of any predisposing factor such as toe-web intertrigo or wound, such as reducing any underlying oedema by compressive stockings or pneumatic pressure pumps [2, 3]. If frequent infections occur despite such measures, prophylactic antibiotics appear reasonable. Options include intramuscular benzathine penicillin injections (1.2–2.4 MU monthly or every 3 weeks) or oral therapy with twice-daily doses of either 250 mg of erythromycin, 1 g of pristinamycin or 1 g of penicillin V [3, 11, 17].

6.3 Other Non-necrotizing Bacterial Dermal–Hypodermal Infections (Cellulitis):

Very often named "cellulitis" in the literature, they are acute spreading infections of the skin, extending more deeply than erysipelas to involve the subcutaneous tissues. They therefore lack a clear line of demarcation between involved and uninvolved tissue typical for erysipelas. Associated regional lymphadenopathy and lymphatic streaking are inconstant, and local complications (abscesses, necrosis) more frequent than in erysipelas. Petechiae and ecchymoses with frequent bullae may develop in inflamed skin, resulting in haemorrhagic cellulitis which requires both antibiotics and systemic corticosteroids for complete resolution [20, 21] (Fig. 6.3); however, if these are widespread and associated with systemic toxicity, a deeper infection such as necrotizing fasciitis should be considered.

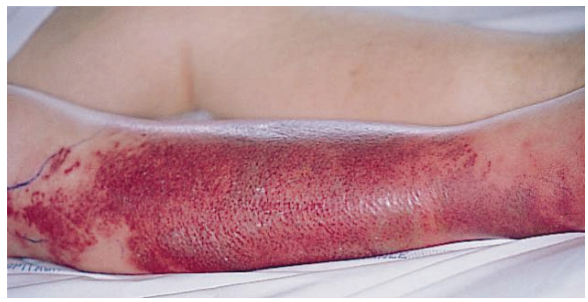

Fig. 6.3 Haemorrhagic cellulitis of the leg with prominent purpura and superficial blistering

Although most cases are caused by β-haemolytic streptococci, many other bacteria can produce such infections, which often occur in particular circumstances. Following cat or dog bites, the organism responsible is typically *Pasteurella multocida. A. hydrophila* may cause cellulitis following immersion in fresh water, whereas infection after saltwater exposure is generally due to *Vibrio* species, particularly *Vibrio vulnificus* in warm climates. Periorbital cellulitis due to *Haemophilus influenzae* may occur in children. In neutropenic hosts, infection may be due to *P. aeruginosa* or other Gram-negative bacilli, and in patients infected with HIV, the responsible organism may be *Helicobacter cinaedi*. Occasionally, *Cryptococcus neoformans* causes cellulitis in patients with deficient cell-mediated immunity. An emerging problem is the increasing prevalence of STIs caused by community-acquired MRSA, which are responsible for about half of the cases of cellulitis with purulent exudates in involved geographic areas [22]. Those community strains cause infections in patients lacking typical risk factors (hospital admission, long-term care facility residence); they are often susceptible to non-β-lactam antibiotics, including doxycycline, clindamycin,trimethoprim–sulfamethoxazole,fluoroquinolones, or rifampicin.

As in erysipelas, needle aspirations and skin biopsies are unnecessary in typical cases, which should respond to antibiotic therapy directed against streptococci and staphylococci. In cellulitis with collections or exudates, needle aspiration and blood cultures are more fruitful, and allow identification of one or several bacterial organisms in more than two-thirds of cases. These procedures should be considered for patients with diabetes mellitus, malignancy, or specific predisposing factors, such as immersion injury, animal bites, neutropenia or immunodeficiency [17, 23].

Contrary to erysipelas, the best therapeutic option will be an antibiotic that is effective both against streptococci and *S. aureus,* although this organism rarely causes cellulitis unless associated with an underlying abscess or penetrating trauma. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci resistant to these agents are common in the community [17]. Cephalexin is the most cost-effective choice over most of the modeled range of probabilities, with clindamycin becoming more cost-effective at high likelihoods of MRSA infection [24].

6.4 Necrotising Fasciitis

6.4.1 Definition

Necrotizing fasciitis is a rare, life-threatening infection, primarily affecting the superficial muscular fascia (which is comprised of all of the tissue between the skin and underlying muscles) and adjacent hypodermis, that tracks along fascial planes and extends well beyond the superficial signs of infection [2, 3, 17, 25]. It can affect any part of the body, and results in an extensive gangrene of the surrounding tissues.

6.4.2 Bacteriology

Necrotizing fasciitis is predominantly polymicrobial (type 1) and, less frequently, monomicrobial (type 2) [2, 26]. Monomicrobial forms are mainly caused by *S. pyogenes*, especially after varicella or minor injuries; those streptococcal forms are frequently associated with toxic shock syndrome, with most cases caused by M types 1 and 3, producing exotoxin A and streptolysin O. They may be also caused by *V. vulnificus, Klebsiella pneumoniae*, *Aeromonas hydrophila,* or anaerobic streptococci. Recently, necrotizing fasciitis has been described in patients with MRSA infection [27]. In polymicrobial necrotizing fasciitis, most cultures yield a mixture of aerobic (*S pyogenes, S aureus, Enterobacteriaceae*) and anaerobic organisms (*Peptostreptoccus*, *Bacteroides fragilis*, *Clostridium*, *Fusobacterium*).

6.4.3 Epidemiology

It is a rare condition, with an estimated annual incidence of 1–4 per million individuals in Canada [28]. Risk factors for necrotizing fasciitis are not well-established. The role of comorbidities, i.e. diabetes mellitus and alcoholic liver diseases in adults and varicella in children, has been suggested from retrospective cohort studies [26, 28, 29]. The role of non-steroidal anti-inflammatory drugs as a predisposing or a severity factor of necrotizing fasciitis is no longer considered [30].

6.4.4 Clinical Features

Necrotising fasciitis may occur at any age and can affect any part of the body, but the lower extremities, the perineum (syn.: Fournier's gangrene) and the trunk are most commonly involved. The initial presentation is that of cellulitis, which can advance more or less rapidly. As the infection progresses, there is systemic toxicity with high fever. The patient may be disoriented and lethargic. The following clinical features are suggestive of a necrotizing fasciitis, especially when a number of them are present [3, 17]: severe pain, haemorrhagic bullae, skin necrosis, ecchymosis, crepitus of the affected area, oedema that extends beyond the margin of erythema, cutaneous anesthesia, systemic toxicity (fever, delirium, renal failure), and rapid spread despite antibiotic therapy (Fig. 6.4).

6.4.5 Diagnosis

Establishing the diagnosis of necrotising fasciitis is difficult, and often results in delay of an appropriate surgical treatment. Clinical characteristics (see above) help to raise the degree of suspicion, but the sensitivity of these typical findings is low (10–40%). Whenever there is doubt and likelihood for necrotising fasciitis, a surgical exploration of the involved area must be performed [3, 17]. The most important diagnostic feature of necrotizing fasciitis is the appearance of the subcutaneous tissues or fascial planes at operation: the fascia is swollen and gray necrotic, whereas there is typically no true pus nor bleeding emerging from the wound; extensive undermining of surrounding tissues is present, and the tissue planes can be easily dissected with a gloved finger. The finding of soft-tissue air on plain radiographs is inconstant. Although CT scan or magnetic resonance imaging may show oedema extending along the fascial plane [31, 32], in practice clinical judgment remains the most important element in diagnosis. Routine laboratory investigations typically show elevated blood leukocytosis, CRP, serum glucose, creatinine, and muscular enzymes (CPK). A definitive bacteriologic diagnosis is best established by culture of tissue specimens obtained during operation or by blood cultures, which yield positive results in a majority of cases [2, 26]. The diagnosis therefore remains a clinical one, and the clinician should not rely on individual tests [25].

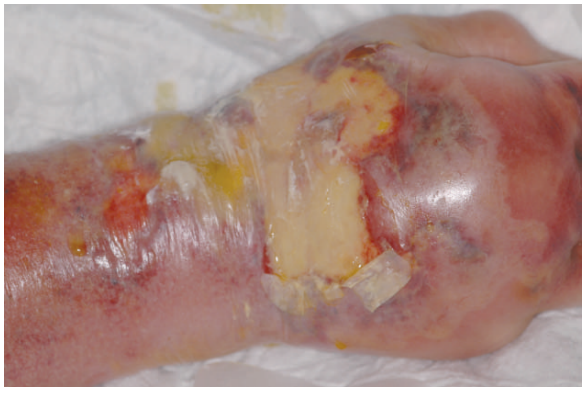

Fig. 6.4 Late-stage necrotizing fasciitis of the dorsa of the hand

6.4.6 Course and Treatment

Necrotising fasciitis is a life-threatening condition, with a high associated mortality and morbidity. Recent mortality rates vary from 15 to 35% [33] but may be higher, approaching 50–70%, in patients with organ failure or in post-operative forms. The risk of death is significantly associated with co-morbidities, delay superior to 24 h from onset to surgery and age greater than 60 years [26, 33]. Morbidity is mainly represented by post-surgical sequelae, including amputation.

Surgical intervention is the major therapeutic modality of necrotizing fasciitis [2, 3, 17, 25, 34]; it must be considered once the diagnosis is suspected. If necrotizing fasciitis is recognized early and treated aggressively, mutilating surgical procedures may be avoided and mortility rate decreased. All non-viable skin and subcutaneous tissue, including fascia, should be excised. Further surgical exploration 24–48 h later is recommended to ensure that the necrotic process has not extended, and repeated debridements may be necessary depending on the state of the wound and the general status of the patient [17, 25]. On occasion, amputation is necessary. Aggressive fluid rescuscitation and blood component therapy is often required in the preoperative period, and management in an intensive care unit is recommended.

Treatment of polymicrobial necrotizing fasciitis must also include agents effective against both aerobes

and anaerobes, such as a combination of ampicillin/sulbactam plus clindamycin plus ciprofloxacin [17]. Necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by *S. pyogenes* should be treated with clindamycin and penicillin [17].

Hyperbaric oxygen therapy and intravenous γ-globulin (especially if concurrent streptococcal toxic schock syndrome) remain controversial, and cannot be recommended with certainty [3, 17, 23, 25]. Reconstructive surgery should be considered only once the infection has been fully eradicated. Vacuum-assisted closure therapy may be employed to help in reducing the size of larger defects before grafting.

6.5 Diabetic Foot Infections

6.5.1 Definition

Diabetic foot infection (DFI) is defined by invasion of the tissues with proliferation of micro-organisms, causing tissue damage with or without an associated inflammatory response by the patient [35]. DFIs are generally secondary to a skin wound, which typically follows trauma to a neuropathic foot. The diagnosis of DFI is clinical, and must be distinguished from bacterial colonization. Two types of DFIs have to be separated: (1) superficial infections, which involve tissue layers above the superficial fascia and present as acute bacterial hypodermal infections (cellulitis), and (2) deep infections, which involve superficial fascia (necrotizing fasciitis, wet gangrene), muscles or bones (including osteomyelitis) and joints. Deep infections are more frequent than clinically suspected, and must be looked for as a key marker of severity and frequent need for additional surgery. The diagnosis of infection is based on the presence of at least two of the following signs: swelling, induration, erythema around the lesion, local tenderness or pain, local warmth or presence of pus [35]. The severity of infection is assessed according to the International Consensus on the Diabetic Foot Classification System [36, 37] (Table 6.1).

6.5.2 Bacteriology

To obtain isolation and identification of the micro-organisms responsible for the infection from a specimen, it is mandatory to avoid contamination by the commensal flora that colonizes the skin. Before taking

Table 6.1 International Consensus on the Diabetic Foot classification of foot wound infection from [36]

Grade 1	No symptoms, no signs of infection
Grade 2	Lesion only involving the skin (without involvement of deeper tissues nor systemic signs) with at least two of the following signs: • Local warmth • Erythema > 0.5–2 cm around the ulcer • Local tenderness or pain • Local swelling or induration • Purulent discharge (thick, opaque to white or sanguineous secretion) Other causes of inflammation of the skin must be eliminated (for example: trauma, gout, acute Charcot foot, fracture, thrombosis, venous stasis)
Grade 3	• Erythema > 2 cm and one of the findings described above or • Infection involving structures deeper than skin and subcutaneous tissue, such as deep abscess, osteomyelitis, septic arthritis or fasciitis There must not be any systemic inflammatory response *(see grade 4)*
Grade 4	Any foot infection, in the presence of a systemic inflammatory response manifested by at least two of the following characteristics: - Temperature > 38°C or < 36°C - Pulse > 90 bpm - Respiratory rate > 20 per min - $PaCO_2$ < 32 mmHg - Leukocytes > 12,000 or < 4,000 per mm^3 - 10% of immature (band) forms

any specimen, debridement with a sterile curette or scalpel is essential, while the wound must be cleaned with sterile physiological saline. Repeated specimens should be taken in the event of an unfavourable course or severe sepsis. Curetting or swabbing are sufficient for superficial DFIs, while fine-needle aspiration of abscess/phlegmon, or bone biopsy in case of rough bone contact, are necessary in deep DFIs [35]. Gram-positive aerobic bacteria are the most frequent micro-organisms, and the sole causative pathogens in mild and moderate infections; among these, *S. aureus* is most often isolated, either alone or in association with other bacteria, both in superficial and in deep DFIs [38]. Gram-negative aerobic bacteria, mainly *Enterobacteriaceae*, (*Proteus mirabilis*, *Escherichia coli*, *Klebsiella* spp) are commonly isolated in chronic or previously treated infections [39]. Though *Pseudomonas aeruginosa* is frequently isolated, particularly after a long hospital stay, its pathogenic role has to be considered. Strict anaerobic bacteria are also often isolated in association with aerobic bacteria. Multiresistant bacteria, especially MRSA or *P. aeruginosa*, must be taken into account, and represent a serious and increasing problem [40].

6.5.3 Epidemiology

Diabetic patients are at greater risk than the general population of developing severe foot infections. Fifteen to 25% of diabetic patients develop a foot ulcer at some time during their disease [41], and approximately half of these ulcers become infected. Risk factors for DFIs include wounds that penetrated to bone, recurrent or chronic (>30 days) wounds and presence of peripheral vascular disease [42].

6.5.4 Clinical Features

Superficial infections present in the form of non-necrotizing acute dermal–hypodermal infections (cellulitis) [3]. Deep infections include necrotizing fasciitis, muscles or bone and joint involvement (Fig. 6.5). Abscesses or phlegmon in the soft tissue of the foot, eventually extending to the leg, are frequently observed. They may be either evident (pus discharge) or difficult to demonstrate clinically, requiring the use of imaging investigations (see next paragraph). Bone infection is present in 30–80% of DFIs, depending on the severity of the infection. It may consist of isolated osteomyelitis, affecting particularly the toes and calcaneum, or more frequently bone and joint infection, while isolated septic arthritis is rare [3, 37]. Bone and joint infection generally occur by contiguous spread from a skin wound. In acute DFIs, ostemomyelitis must be particularly suspected in the case of infection localized over a bony prominence, rough bone contact, or of edematous, erythematous sausage appearance of a toe with abnormal motility.

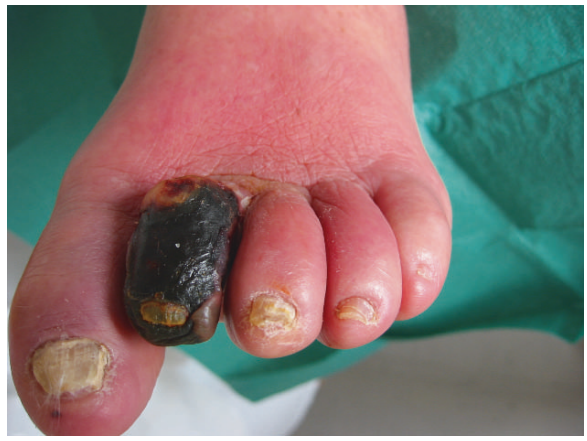

Fig. 6.5 Acute diabetic foot infection with distal cellulitis and toe-web necrosis

6.5.5 Diagnosis

Diagnosis of superficial DFIs and necrotizing fasciitis is clinical (see definition), and no laboratory marker is sufficiently sensitive and specific to confirm diagnosis of infection or colonization of a diabetic foot wound [35]. The diagnosis of purulent collections within soft tissues (abscess, phlegmon) or localized osteomyelitis generally requires imaging investigations, including standard radiographs (plain X-rays), magnetic resonance imaging or isotope studies [43–46].

6.5.6 Course and Treatment

Several wound classifications have been proposed to guide the management of DFIs, among which the University of Texas classification is the reference

(Table 6.2). According to the complementary classification of the International Consensus on the Diabetic Foot (Table 6.1), DFIs may be classified as mild (grade 2), moderate (grade 3) or severe (grade 4), which largely determines the approach to therapy [48]. Clinical failure rates for DFIs are between 20 and 30%, leading to a lower-extremity amputation [36]. Elevated white blood cell count and severe DFIs (grade 4) are clinical predictors of treatment failure [49]. DFIs solely due to Gram-positive bacteria can usually be treated with culture-based narrow-spectrum antibacterials, along with appropriate surgical debridement, in an outpatient setting. In contrast, severe DFIs are often polymicrobial, requiring treatment with broad-spectrum antibacterials, along with appropriate medical and surgical interventions and therefore hospitalisation [48]. Once infection has been confirmed clinically, bacteriological specimens are taken, and empirical

Table 6.2 Classification of foot wounds in diabetic patients: University of Texas Wound Classification combining grade and stage (1996). The amputation rate according to the wound category is shown in parentheses from Armstrong et al. [47]

	Grade 0:	Grade 1:	Grade 2:	Grade 3:
	Completely epithelialized lesion (%)	Superficial wound (%)	Wound penetrating to tendon or capsule (%)	Wound penetrating to bone or joint (%)
Stage A Not infected Not ischemic	0A (0)	1A (0)	2A (0)	3A (0)
Stage B Infected	0B (12.5)	1B (8.5)	2B (28.6)	3B (92)
Stage C Ischemic	0C (25)	1C (20)	2C (25)	3C (100)
Stage D Infected Ischemic	0D (50)	1D (50)	2D (100)	3D (100)

Table 6.3 First-line antibiotics in diabetic foot infections (excluding osteomyelitis) from French Consensus Conference [35]

Type of infection	Suspected pathogens	Antibiotic therapy
Recent infection of a superficial wound (<1 month)	MSSA[b] *S. pyogenes* MRSA[c]	Cloxacillin or cephalexin or (amoxicillin + clavulanate) or clindamycin Pristinamycin or linezolide or vancomycin or teicoplanin
Extensive cellulitis	MSSA[b] S. pyogenes MRSA[c]	Oxacillin AG[a] Vancomycin or teicoplanin or linezolide
Deep and/or chronic lesion with or without sepsis	MSSA[b] *S. pyogenes,* GNB[d], anaerobes MRSA[c]	(Amoxicillin + clavulanate) AG[a] +vancomycin or teicoplanin or linezolide
Severe sepsis	MSSA[b] *S. pyogenes,* GNB[d], anaerobes	(Piperacillin + tazobactam) or (ticarcillin + clavulanate) + AG[a]
Septic shock	MRSA[c], GNB[d], anaerobes	Imipenem or ertapenem + (vancomycin or teicoplanin or linezolide) + AG[a]

Shaded zone: oral outpatient treatment; for the other cases, treatment is initially parenteral, followed by oral therapy when possible, depending on the course and the susceptibility profile of the bacteria isolated

[a]*AG* aminoglycosides (gentamicin or netilmicin);

[b]*MSSA* methicillin-susceptible *Staphylococcus aureus;*

[c]*MRSA* methicillin-resistant *Staphylococcus aureus*;

[d]*GNB* Gram-negative bacilli

therapy is immediately started [35]. The initial empirical antibacterial regimen may be tailored based on the results of bacteriological cultures. Several antibacterial regimens have demonstrated effectiveness in randomized controlled trials, though the evidence is too weak to recommend any particular antimicrobial agent as first-line treatment [48, 50, 51]. Proposals from the recent French Consensus Conference [35] are shown in Table 6.3. No consensus has been reached about the type of daily dressing to be used in DFIs, while adhesive or occlusive dressings must not be used in those situations [35]. Adjunctive growth factors treatment (G-CSF) does not appear to hasten the clinical resolution of diabetic foot infection or ulceration [52] and is not recommended; nor is hyperbaric oxygen therapy [35]. However, a recent meta-analysis suggested that although it does not accelerate cicatrisation or decrease hospital stay, it decreases the risk of amputation [52]. In every case, it is essential to evaluate the patient's arterial status to assess the need for a revascularization procedure, which could reduce healing time. Treating diabetic foot osteomyelitis requires reliable cultures to select an appropriate antibiotic regimen. Surgical resection of the infected and necrotic bone favours a good outcome in chronic osteomyelitis. The recommended duration of antibacterial therapy ranges from 1 to 4 weeks for soft-tissue infection, to >6 weeks for unresected osteomyelitis. The increasing incidence of MRSA infection in both the hospital and the community should be considered when selecting antibiotic therapy. Certain other organisms, such as *P. aeruginosa* and *Enterococcus spp*., while potentially pathogenic, are often colonisers that do not require targeted therapy.

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Severe Staphylococcal Cutaneous Infections and Toxic Shock Syndrome

7

Isabel C. Valencia and Francisco A. Kerdel

Core Messages

- Community-acquired *Staphylococcus aureus* (CA-MRSA) infections have become epidemic in the United States and elsewhere, and represent a threat to the community and to persons without risk factors.
- MRSA infection should be suspected in certain patient populations, and in patients not responding to standard β-lactam therapy.
- Cultures of wounds should be obtained, and proper antibiotic guidelines should be followed.
- Because there are epidemiological and microbiological differences between community-associated and health care-associated MRSA infections, strategies to prevent and treat these infections likely differ as well.

Abbreviations: HA-MRSA Hospital-acquired methicillin-resistant *Staphylococcus aureus,* CA-MRSA Community-acquired methicillin-resistant *Staphylococcus aureus*

7.1 Introduction

In recent years, many infectious diseases have either been newly described, or have re-emerged after decades of relative quiescence. Toxin-mediated streptococcal and staphylococcal diseases and community-acquired *S. aureus* (CA-MRSA) are only some of these entities with prominent mucocutaneous manifestations, and thus of great relevance to the dermatologist.

7.2 Staphylococcal Cutaneous Infections

7.2.1 Epidemiology and Pathogenesis

S. aureus is a Gram-positive cocci of the Micrococcaceae family. It is one of the most common pathogens in skin and soft-tissue infections, and can cause potentially serious nosocomial infections when acquired in the hospital setting. *S. aureus* has a diverse arsenal of components and products that contribute to the pathogenesis of infection. The virulence of *S. aureus* infection is remarkable, given that the organism is a commensal that colonizes the nares, axillae, vagina, pharynx or damaged skin surfaces. Infections are initiated when a breach of the skin or mucosal barrier allows staphylococci access to adjoining tissues or the bloodstream (Fig. 7.1). Whether an infection is contained or spreads depends on a complex interplay between *S. aureus* virulence determinants and host defense mechanisms [1–3].

Penicillin was introduced in the 1940s as an effective treatment against *S.aureus*. Methicillin, a semisynthetic penicillin was introduced in 1959 to overcome the resistance to penicillin that developed shortly after its introduction [4]. However, within a year, methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a hospital-acquired infection, and was first detected in the United Kingdom and later in the United States

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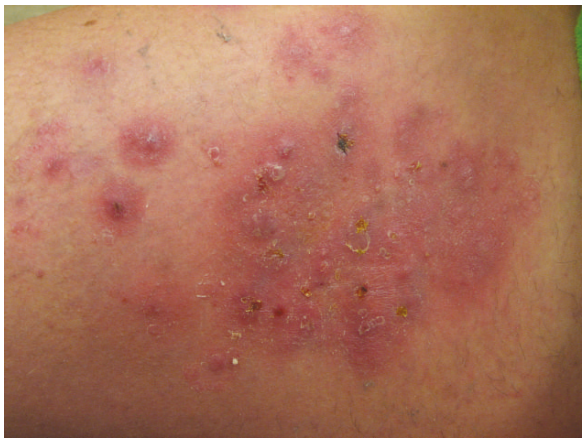

Fig. 7.1 Cutaneous community-acquired MRSA infection presenting as red, follicular papules, pustules and nodules on the thigh of a young man

[5, 6]. Worldwide emergence of MRSA was established by the 1980s [7]. Since that time, MRSA has become widespread in hospitals and long-term facilities around the world, accounting for numerous nosocomial infections [8]. In the United States, increasing MRSA rates have been reported with a prevalence of 2.4% in 1975, 29% in 1991, and 36% in 1999 [9]. Wide variations in prevalence have been described worldwide, not only between countries but also between hospitals, and even within different departments of the same hospital. In Europe, a north–south gradient is observed, MRSA strains being rare in Scandinavian hospitals (<2%) and far more prevalent in Mediterranean hospitals (>40%). Whether low or high, the prevalence of MRSA in European countries has remained approximately the same during the last decade [10]. Moreover, the bacteria continue to acquire resistance to antimicrobial agents, with some strains, fortunately rarely, demonstrating resistance to vancomycin [11].

MRSA is no longer solely a concern in the hospital setting, as there has been an alarming increase in the incidence of community-acquired MRSA (CA-MRSA). Sporadic reports of community-acquired MRSA infections have appeared since 1980 [12], but 1999 marked the beginning of the current epidemic in the United States, with a series of fatal cases of CA-MRSA infections in Native American children living in the Midwest [13]. Even though most of the reports originate in the continental US, CA-MRSA occurs throughout the world [14–17].

7.2.2 Antimicrobial Resistance and Toxin Genes

Interestingly, molecular analysis has shown that CA-MRSA differs from HA-MRSA both genotypically and phenotypically [18].

The insertion of a mobile staphylococcus cassette chromosome (SCC *mec A*) has led to methicillin resistance in *S. aureus*. In MRSA isolates, the *mecA* gene encodes a protein designated "penicillin-binding protein 2" that has transpeptidase activity necessary for peptidoglycan synthesis in *S. aureus*. Despite its designation, it actually has decreased binding affinity of β-lactam antibiotics, and allows peptidoglycan synthesis even in the presence of β-lactam antibiotics. *mecA* is carried on a mobile genetic element called "staphylococcal cassette chromosome *mec*" (SCC*mec*). The sequenced prototype CA-MRSA strain MW2 was isolated from a pediatric case of fatal septicemia in North Dakota in 1998, and was shown to harbor the SCCmec type IV. No definition of CA-MRSA is universally accepted, but several authors consider the insertion of the SCCmec IV as characteristic, while HA-MRSA carries the mecA gene types I–III [19]. Type I lacks genes conferring resistance to other drugs, whereas types II and III are associated with multiple drug resistance.

Among CA-MRSA strains, Panton–Valentine leukocidin, which codes for the production of a cytotoxin that causes leukocyte destruction and tissue necrosis, has been identified as the most important virulence factor [20, 21]. In the United States, two clones, designated as USA 300 and USA 400 by the Centers for Disease Control and Prevention (CDC), have been identified as the primary types that cause CA-MRSA infections [22, 23]. USA 400 was first described in Native American children living in the Midwest, while USA 300 was recovered in 99% of 384 patients living in Atlanta, Georgia. Both of these clones have subsequently caused infections throughout the country [13, 23].

7.2.3 Populations at Risk and Risk Factors

Risk factors for infection with MRSA in health-care settings (HA-MRSA) include prolonged hospital stay, exposure to multiple or prolonged broad-spectrum

antimicrobial therapy, stay in an intensive care or burn unit, proximity to patients colonized or infected with MRSA, use of invasive devices, surgical procedures, underlying illnesses, and MRSA nasal carriage [24]. Typically, CA-MRSA infection occurs in patients without traditional risk factors. CA-MRSA outbreaks have occurred among young children, prisoners, intravenous drug-users, athletes, military trainees, and homosexual men [25–27]. However, the number of populations at risk for CA-MRSA is steadily expanding [23]. Although factors associated with CA-MRSA are poorly characterized, some transmission factors that have been associated with outbreaks include crowding, frequent skin-to-skin contact, compromised skin, contaminated surfaces, shared items, uncleanliness, and antimicrobial use. Our knowledge of CA-MRSA epidemiology is incomplete, which adds to the challenge of controlling CA-MRSA infection. For example, whereas nasal colonization commonly precedes serious infection with methicillin-susceptible *S. aureus* (MSSA), nasal colonization may not precede CA-MRSA infections. In fact, several studies suggest that the nasal carriage rate for MRSA in the community is considerably lower than that for MSSA, which can approach 30% or more. Graham et al. found a surprisingly low prevalence (0.84%) of nasal carriage of CA-MRSA strains, suggesting that nasal carriage is not the prime predictor of subsequent infection, as is believed to be the case for hospital-acquired MRSA (HA-MRSA) and MSSA. Persons 65 years of age or older, women, persons with diabetes, and those who were in long-term care in the past year were more likely to have MRSA colonization [28].

Less is known about skin and soft-tissue infections in a non-outbreak setting. In a recent study at a large hospital and its affiliated clinics in urban Atlanta, Georgia, CA-MRSA was responsible for 72% of skin and soft-tissue infections. Factors independently associated with CA-MRSA were black race, female sex and hospitalization within the previous 12 months. Inadequate initial antibiotic therapy was statistically significant, more common among those with CA-MRSA than among those with methicillin susceptible *S. aureus* skin and soft-tissue infections [23]. In another recent report by Cook et al, the authors encountered three households in which heterosexual transmission was responsible for new CA-MRSA infection. The vaginal and inguinal isolates obtained from the sexual partners were USA 300. This potential means of transmission might help to explain the ability of these new strains to become established in what would otherwise be considered low-risk communities [29]. Recent studies also suggest that household pets may be additional reservoirs for CA-MRSA [30]. Contamination of our food supply is also a potential mode of CA-MRSA spread. In Japan, mecA positive MRSA has been isolated from retail raw chicken meat [31].

7.2.4 Crossover Between Community and Health Care Settings

Overall, patients with health-care-associated MRSA (HA-MRSA) are significantly older, and have different distributions of clinical infections compared with CA-MRSA. CA-MRSA causes the same spectrum of disease as HA-MRSA, but the community-acquired strains more often cause skin and soft-tissue infections (75% vs 37%) [18]. However, certain CA-MRSA cases can progress to invasive tissue infections, bacteremia and death [32]. Some of these patients may require hospital therapy, making the distinction between hospital-acquired and community-acquired blurred. Moreover, CA-MRSA is now being introduced into hospitals, thus blurring the borders between CA-MRSA and hospital-acquired strains [33]. Hospital transmission of CA-MRSA has been described in postpartum women with skin and soft-tissue infections, including mastitis with abscess, postoperative wound infection, cellulitis and pustulosis (Fig. 7.2). It has also been reported in a neonatal intensive care unit [34, 35]. Although reservoirs of CA-MRSA are becoming more

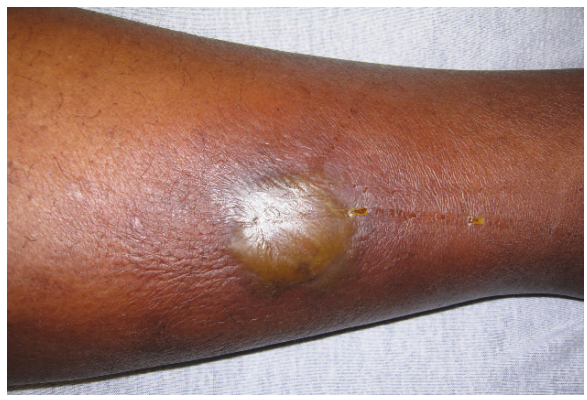

Fig. 7.2 CA-MRSA infection presenting as bullous cellulitis on the lower leg of a 49-year-old man

Table 7.1 Comparison of hospital-acquired vs community-acquired MRSA infection

	Hospital-acquired MRSA	Community-acquired MRSA
Molecular genetics	SCCmec I–III	SCCmec IV
Population affected	Elderly, sick	Immunocompetent: young children, prisoners, IV drug abusers, athletes, military trainees, homosexual men
Colonization of nares in general population	High	Low (< than 1%)
Skin and soft-tissue infection	Less common	More common
Risk factors	• Multiple, prolonged exposure to antibiotics • Stay in ICU/ burn unit • Proximity to patients infected with MRSA • Invasive devices • Inderlying illnesses • MRSA nasal carriage	• Less characterized: • Crowding • Frequent skin-to-skin contact • Compromised skin • Contaminated surfaces • Shared items • Uncleanliness • Previous antimicrobial use
Treatment of choice	IV vancomycin	Trimethoprim-sulfamethoxazole, tetracycline

common, patients colonized with MRSA at the time of hospital admission are still likely to have acquired the organism during previous encounters with health care facilities. As the epidemiology of strains changes, the definitions for hospital-acquired and community-acquired MRSA may have to be altered [36].

Please see Table 7.1 for summary of comparison of hospital acquired vs community acquired MRSA.

7.2.5 Diseases Caused by S.aureus

S. aureus infection is a major cause of skin, soft-tissue, respiratory, bone, joint and endovascular disorders. Infections caused by CA-MRSA range from minor skin infections to rapidly fatal, overwhelming pneumonia [37] and sepsis which can be accompanied by the Waterhouse–Friderichsen syndrome [38]. Because skin infections caused by these organisms often have necrotic centers, physicians may misdiagnose them as "spider bites" [39]. The discussion below is limited to severe or life-threatening community-acquired staphylococcal infections relevant to the dermatologist.

7.3 Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly progressive, life-threatening infection involving the skin, soft tissue and deep fascia. These infections are typically caused by group A streptococcus, *Clostridium perfringens*, or a mixture of aerobic and anaerobic organisms including group A streptococcus, the Enterobacteriaceae, anaerobes, and *S. aureus* [40–42]. Owing to the frequently polymicrobial nature of necrotizing fasciitis, most authorities recommend the use of broad-spectrum empirical antimicrobial therapy for suspected cases. However, therapy directed against MRSA, such as vancomycin, is not recommended in current standard guidelines, presumably because of the rarity of this pathogen as a cause of the disease [42]. To date, MRSA has been related with necrotizing fasciitis in rare cases such as that of a subacute, polymicrobial infection [43], and as a monomicrobial infection in a patient in a hospital setting, 1 week after knee-replacement surgery [44]. *S. aureus* has been a very uncommon cause of necrotizing fasciitis until recently, when an alarming number of these infections caused by CA-MRSA was

noted [42]. In a recent report by Miller et al., 14 patients out of 843 patients with MRSA infection presented from the community with clinical and intraoperative findings of necrotizing fasciitis, necrotizing myositis or both. Coexisting conditions or risk factors for these patients included current or past injection-drug use, previous MRSA infection, diabetes, chronic hepatitis C, cancer and human immunodeficiency virus infection. Four patients had no serious conditions or risk factors. All patients received combined medical and surgical therapy and surprisingly none died, given that the mortality rate of necrotizing fasciitis historically has been reported to be about 33%. The absence of deaths in this series suggests that necrotizing fasciitis caused by CA-MRSA may be less virulent than similar infections caused by other organisms. However, serious complications were common, including prolonged stay in the intensive care unit, the need for mechanical ventilation and reconstructive surgery, septic shock, nosocomial infections and endophtalmitis. Although the onset of disease in this series was often subacute, in some patients the infection progressed rapidly over a period of several hours; making the disease clinically indistinguishable from necrotizing fasciitis caused by other pathogens. The authors conclude that in areas in which CA-MRSA is endemic, empirical treatment of suspected necrotizing fasciitis should include antibiotics that are reliably active against this pathogen [42] (Fig. 7.5. see p. 76).

7.4 Pyomyositis and Myositis

Pyomyositis, an acute bacterial infection of skeletal muscle with localized abscess formation, is endemic in tropical countries, and much less common in temperate climates. *S. aureus* accounts for 75–90% of these infections, which are frequently seen in children. Acute bacterial myositis is an infection within the muscle, but inflammation extends diffusely through more than one muscle group without distinct abscess formation. Acute bacterial myositis is much less commonly reported than pyomyositis, and more frequently involves adult patients. Most cases have been due to *Streptococcus pyogenes*, although cases secondary to *S. aureus* have also been reported [45–47]. Muscle infections are postulated to occur when transient bacteremia seeds a site of local muscle injury. MRI is the optimal imaging modality to demonstrate muscle inflammation and/or presence of a muscle abscess. Drainage of the abscess expedites healing, and is helpful in isolating the causative pathogen [45]. Empirical antimicrobial therapy for myositis and pyomyositis will depend upon local epidemiologic and susceptibility patterns. The duration of therapy depends on clinical improvement. In cases of primary muscle infection without bone or joint involvement, treatment with an intravenous agent followed by an oral agent (when clinical improvement has occurred) for a total of 3 weeks seems to be appropriate [45].

In a recent report from Pannaraj et al., the authors found CA-MRSA to be an increasing cause of pyomyositis and myositis in children hospitalized at Texas Children's Hospital. Children with CA-MRSA infection had a shorter duration of bacteremia than did those with community-acquired methicillin-sensitive *Staphylococcus aureus* (CA-MSSA) infection. Nevertheless, CA-MRSA infections were associated with larger abscesses and required more drainage procedures than did CA-MSSA infections, suggesting that CA-MRSA can attack muscle and form abscesses more readily than CA-MSSA. Also CA-MRSA affected patients at a younger age, but other clinical parameters were similar. Almost 70% of the *S. aureus* isolates recovered from myositis and pyomyositis patients in this study were USA 300.

7.5 Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a rare syndrome defined by the following; erythema and desquamation of the skin with a positive Nikolsky sign, isolation from the patient of *S. aureus* which produces an exfoliating toxin, and superficial intra-epidermal cleavage at the level of the *stratum granulosum* on histology. This syndrome was originally described by von Rittershain in infants and children, and is rarely seen in adults [48, 49]. The superficial epidermal blister formation is caused by exfoliative toxin A or B produced by *S. aureus*, which targets desmoglein 1, a desmosomal adhesion molecule, that when inactivated results in blisters [50]. The same toxins that are responsible for causing SSSS also cause bullous impetigo. Adult cases of SSSS are uncommon, and this is thought to be due to the increased ability of adults to metabolize

and excrete the toxin through the kidneys. Most reports of adult cases concern patients with renal failure, although underlying immuno-suppression is also associated [51–53].

SSSS presents with a prodrome of malaise, sore throat or conjunctivitis. SSSS starts as erythema most often of the head, involving all the body within few hours. Within 48 h, flaccid bullae develop, which commonly affect the flexures. The bullae may be absent, but a Nikolsky sign is present: dislodging of the epidermis with lateral finger pressure. Rupture of the bullae or slipping of epidermis after the Nikolsky maneuver reveal a moist erythematous base, which gives rise to the scalded appearance. This base, however, is quite different from the raw oozing deep red dermis revealed in toxic epidermal necrolysis: it is more pink and less moist. Scaling and desquamation occur over the next days, leading to complete healing without scarring in 10–14 days. Mucous membranes are spared. An emergency biopsy shows the intra-epidermal cleavage at the level of the *stratum granulosum*. There are no inflammatory cells in the bullae.

The diagnosis of SSSS is mainly clinical. Its diagnosis can easily be differentiated from bullous auto-immune diseases by histology. The absence of pseudococard, sparing of mucous membranes and the predominance at flexural areas make it possible to discriminate it from toxic epidermal necrolysis.

SSSS in adults is a rare disorder, though there are over 50 documented cases. While mortality in childhood SSSS is approximately 4%, the mortality rate in adults is reported to be much greater. There appears to be a spectrum of disease extent, as there is a relationship between the disease extent, the amount of toxin produced and whether the toxin is released locally or systemically. Treatment is usually straightforward when there is no coexistent morbidity and the presentation is mild, but can be challenging if the patient is systemically compromised [54].

The first report of SSSS in an adult due to MRSA was described in 1999 [48]. This case was particularly unusual, as the MRSA produced toxic shock syndrome toxin 1 and enterotoxin, but not exfoliatoxin. There are several reports of clinical SSSS in which the infecting staphylococcus produces either toxic shock syndrome toxin 1 or enterotoxin, but exfoliatins are not demonstrable. Isolated reports of SSSS due to MRSA in adults [55] and infants have also been described [56, 57].

7.6 Management of Cutaneous MRSA Infection

Because there are epidemiological and microbiological differences between community associated and health-care-associated MRSA infections, strategies to prevent and treat these infections likely differ as well.

7.6.1 Treatment of HA-MRSA

Vancomycin remains the drug of choice; however, cyclic lipopeptides such as daptomycin has been effectively used to treat MRSA infections. Unfortunately, resistance has already been reported, and in-disk diffusion testing may not be predictive of clinical outcome [58, 59].

Quinupristin–dalfopristin, a parental streptogramin, has been used in critically ill patients with severe MRSA infections that are unresponsive to vancomycin, and demonstrates synergy when used with rifampin. Unfortunately, resistance is emerging and side-effects limit its use [58, 60].

Newer-generation carbapenems such as meropenem, panipenem and ertapenem have shown activity against MRSA and synergism with vancomycin [58, 61, 62].

Linezolid, an oxazolidinone, is useful for severe, refractory MRSA infections, and in some groups of severely ill patients has proved to be more effective than vancomycin [63]. Despite its cost, it might be an alternative to vancomycin in patients with impaired renal function, poor venous access, or inability to tolerate glycopeptides. Overall the drug is well-tolerated, but gastrointestinal side-effects and more rarely peripheral neuropathy, thrombocytopenia and myelosuppression may occur [58].

Tigecycline is a glycylcycline related to minocycline that shows efficacy against MRSA isolates resistant to other tetracyclines and may be particularly useful for infections that involve both MRSA and gut organisms [64].

A new cephalosporin, Ceftobiprole medocaril, is being studied for MRSA infections [65]. Early data suggest that it may be comparable in efficacy to vancomycin [66].

7.6.2 Treatment of CA-MRSA

Incision and drainage with or without adjunctive narrow-spectrum antimicrobial therapy has been used abscesses with successful outcomes as a primary treatment method for skin, and this may be applicable for some community-acquired MRSA abscesses [23]. Indeed, CA-MRSA skin infection may persist, even when the patient is being treated with appropriate systemic antimicrobial therapy, if the contents of the infectious abscess are not released either by surgical intervention or spontaneous rupture [67]. As CA-MRSA infection is contagious and often associated with infection, appearing within other family members and close contacts, antibiotic therapy, in addition to appropriate surgical intervention, may be helpful to limit the spread of infection [68].

The variability in antibiotic susceptibility among some reported CA-MRSA infections highlights the need for all patients with skin and soft-tissue infections to undergo wound culture, in order to guide treatment after empiric antibiotic therapy. Subsequently, the patient's systemic therapy can be altered on the basis of the reported antibiotic sensitivity if the culture reveals MRSA.

Because most CA-MRSA isolates were susceptible to several already available antimicrobial agents, and because most patients had noninvasive infections, the treatment of CA-MRSA infections should not routinely require the use of vancomycin. Most CA-MRSA cases isolated in the United States are susceptible to several non-beta-lactam drug classes including tetracyclines and trimethoprim–sulfamethoxazole. They are both inexpensive and an effective choice for the majority of patients [18]. Clindamycin presents an additional challenge because some strains are susceptible to clindamycin in vitro, but contain genes encoding inducible resistance to macrolides, lincosamides, and streptogramin that confer potential to develop resistance to clindamycin during therapy [69]. Rates of inducible lincosamide resistance vary widely among staphylococci that are resistant to erythromycin. They have been low in Houston (2–8%), while they have been much higher in Chicago (94%) [69, 70]. However, although concern about clindamycin resistance is legitimate, the drug has been used effectively to treat invasive infections caused by CA-MRSA isolates [71]. Even though many CA-MRSA strains remain sensitive to fluoroquinolones, resistance is emerging, and overuse of fluoroquinolones in a population favors the emergence of CA-MRSA. It appears to also favor the emergence of fluoroquinolone-resistant *Pseudomonas* and uropathogens [72, 73]. Rifampin has been used in combination with other antibiotics, but should never be used alone to treat a staphylococcal infection because of the rapid development of resistance. The combination of rifampin plus trimethoprim–sulfamethoxazole has been shown to eradicate MRSA colonization, and has been suggested for the treatment of MRSA in the community [74].

Multidrug-resistant CA-MRSA has emerged in Taiwan. In a Taiwanese children's hospital, 198 episodes of *S aureus* infection were identified among 191 children between July 2000 and June 2001. MRSA accounted for 47% of 114 community-acquired infections and 62% of 84 hospital-acquired infections. CA-MRSA isolates showed a high rate of resistance to clindamycin (93%) and erythromycin (94%). Fortunately, 91% remained susceptible to trimethoprim–sulfamethoxazole, and all children recovered without sequelae. Six different genotypes were identified, and type IV staphylococcal chromosomal cassette mec was carried by only 25% of the CA-MRSA isolates [75]. In contrast, recent testing of strains of CA-MRSA in Hong Kong indicates that the strains were methicillin-resistant only [76].

7.7 Prevention

Because of the epidemiological and microbiological differences between CA-MRSA and HA-MRSA infections, strategies to prevent and treat these infections also differ. To prevent clinical complications from CA-MRSA infections, clinicians working in emergency rooms or outpatient settings should consider practice modalities in areas where such infections are known to be prevalent. These modifications could include more frequent culturing and susceptibility testing of *S. aureus* isolates, surgical drainage of infections when appropriate, and careful selection of empirical

antibiotic therapy when suspecting staphylococcal infections. The treatment of non-invasive CA-MRSA infections should not routinely require the use of vancomycin [18]. In a prospective study, the authors were able to reduce nosocomial transmission of MRSA in a highly endemic setting by using an aggressive infection control program that included using alcohol handrub, early detection, isolation and a decolonization strategy [77]. Proper hygiene, use of barriers when touching patient's wounds and bandages, limiting direct skin–skin contact, proper disinfection and disposal of waste should be standard precautions in any out- or in-patient setting.

7.8 Conclusion

The epidemic of CA-MRSA in the United States and elsewhere raises basic questions for which we have no answers. We know little about the epidemiology of this organism, and even less about the pathogenesis of the severe and overwhelming infections that it can cause. The role of host factors in determining severity of infection, the optimal antimicrobial therapy, as well as the cellular mechanisms that have allowed certain clones such as the USA 300 or USA 400 to become dominant in the community, are still unknown.

7.9 Toxic Shock Syndrome

Toxic shock syndrome (TSS) is caused by coagulase-positive staphylococci (*S. aureus*) and group A beta-hemolytic streptococcus (*S. pyogenes*). Staphylococcal toxic shock syndrome (TSS) was first described by Todd in 1978; however, it came to prominence in 1980–1981, when numerous cases were associated with the introduction of superabsorbent tampons for use during menstruation. In 1983, toxins similar to the ones in *S. aureus* were described in β-hemolytic Streptococcus, and in 1987 streptococcal toxic shock syndrome was described in two patients with cellulitis (Fig. 7.3). Since then, multiple case reports and series have described the clinical spectrum of Streptococcal TSS, particularly in association with soft-tissue infections and pneumonia [78]. In the US, staphylococcal TSS had a highest incidence during the menstrual-related outbreak, with rates ranging from 2.4 to 16 cases per 100,000 population. Since then, staphylococcal TSS related to menstruation has persistently diminished, largely because of a decrease in the use of superabsorbent tampons and consumer education. A similar decline has not been demonstrated in non-menstrual cases of TSS. In fact, an increase in the incidence of Staphylococcal TSS was recently reported in the Minneapolis–St Paul area of the United States, from 0.8 per 100,000 in January 2000 to 3.4 per 100,000 in December 2003 [79]. The disease is now known to also affect neonates and non-menstruating women. The prevalence of streptococcal TSS is not well-known, but it is estimated to be 10–20 cases per 100,000 population. An increasing number of reports describing rapidly progressive invasive group A streptococcal infections have appeared in the medical literature, and have attracted a great deal of attention, given their ability to cause explosive, often life-threatening disease [80].

Staphylococcal TSS is caused by a strain of *S. aureus* that produces the toxins TSS-1 and enterotoxins A through E. TSS toxin-1 (TSST-1) suppresses neutrophil chemotaxis, induces T-suppressor function, and blocks the reticuloendothelial system. The toxins act together as superantigens that stimulate the release of various cytokines (including interleukin 1β, tumor necrosis factor- α and β, interferon γ and interleukin-2), prostaglandins, and leukotrienes, known to mediate fever, shock and tissue injury. TSST-1 produces an antibody response in vivo that is believed to be protective. By middle age, 90–95% of women have detectable anti-

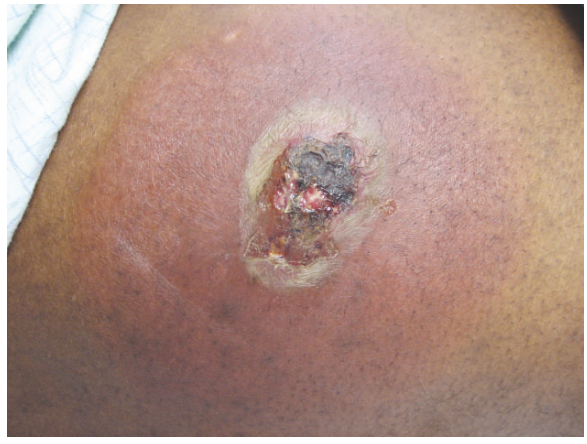

Fig. 7.3 CA-MRSA cellulitis with abscess formation and central necrosis

body titers [81–85]. Streptococcal TSS is caused by *S. pyogenes* exotoxins A, B, C as well as with combinations of toxins which, similar to the staphylococcal toxins, activate production of superantigens that release inflammatory mediators, resulting in widespread endothelial damage [80].

TSS has been linked to many bacterial infections, including osteomyelitis, sinusitis, and skin and gynecologic infections. The mortality rate varies with the bacteria involved: with staphylococcal TSS, the mortality rate is less than 3%, while mortality with streptococcal TSS is 30–70%. Causes of death of group A β-hemolytic streptococcus include bacteremia, associated aggressive soft-tissue infection, shock, adult respiratory distress syndrome and renal failure [86, 87]. Recurrences have been reported in 30–40% of cases. Most recurrences occur less than 2 months after the initial episode and are generally less severe than the initial episode. Women who have had TSS should avoid using tampons during menstruation, as re-infection may occur. The use of diaphragms and vaginal sponges may also increase the risk of TSS (Fig. 7.4).

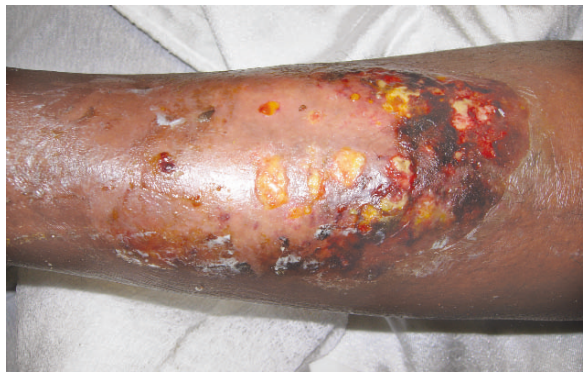

Fig. 7.4 CA-MRSA infection presenting initially as bullous cellulitis, later evolving into necrotizing cellulitis

TSS predominantly occurs in young, healthy individuals who do not have predisposing underlying disease. An absence of protective immunity is postulated to be a major risk factor for acquisition of TSS. Some of the risk factors that have been related to TSS include: use of super-absorbent tampons, postoperative wound infection, postpartum toxic shock, nasal packing, viral infection with *Influenza A* or varicella, diabetes mellitus, HIV infection, common bacterial infections, and chronic cardiac or pulmonary disease. Symptoms are similar for both staphylococcal and streptococcal diseases, but unlike staphylococcal TSS, in which blood culture results are typically negative, blood-culture results in patients with streptococcal disease are usually positive. Also, whereas group A streptococcal TSS is associated with extensive soft-tissue infection, bullae formation, and bacteriaemia, these findings are uncommon in staphylococcal toxic shock syndrome [88]. Nevertheless, because there is such clinical overlap between these two infections, presumptive antibiotic therapy in the setting of fulminant multi-system disease should include coverage for both streptococci and staphylococci [80].

The Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of streptococcal TSS include: a positive culture for group A streptococcus, hypotension and involvement of two or more organ systems (e.g., renal impairment, coagulopathy, liver involvement, acute respiratory distress syndrome, generalized rash with or without desquamation, and soft-tissue necrosis).

The CDC criteria for staphylococcal TSS include: fever, hypotension and rash, involvement of three or more organ systems and absence of serologic evidence of Rocky Mountain spotted fever, leptospirosis, measles, hepatitis B, antinuclear antibody, positive Venereal Disease Research Laboratory tests results and antibodies at Monospot testing.

Laboratory abnormalities that are found in more than 85% of the cases include immature pleocytosis, hypo-albuminemia, hypo-calcemia, elevated liver enzyme levels, and elevated creatine phosphokinase levels. Thrombocytopenia, pyuria, proteinuria and elevated blood urea nitrogen and creatinine levels can also occur [89].

The differential diagnosis of TSS is broad, but a few features should alert the provider. Although headache, myalgias, emesis, and fever can be symptoms of an acute viral syndrome or gastroenteritis, the severity of the patient's symptoms, along with a great amount of immature leukocytosis, suggests a more serious infection [85].

Patients with TSS require aggressive multimodality therapy similar to that of other patients with septic shock and multiple organ dysfunction, including the rapid institution of antibiotics and aggressive fluid resuscitation guided by invasive hemodynamic monitoring. Rapid and aggressive surgical debridement may be necessary for those with deep soft-tissue infections, particularly if there is evidence of necrosis or collections of pus.

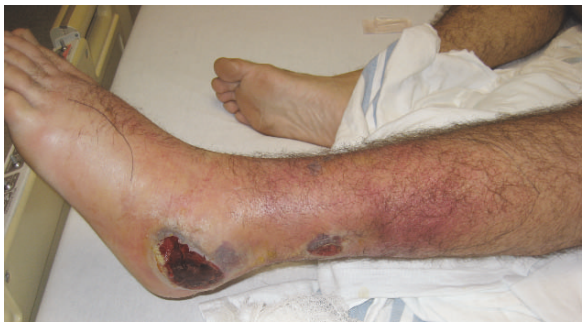

Fig. 7.5 CA-MRSA infection presenting as necrotizing fasciitis on the leg of a 56-year-old man

Intravenous immunoglobulin (IVIG) therapy has been proposed as an adjuvant treatment in severe streptococcal toxic shock, because of its ability to neutralize toxic superantigens toxins. A recent meta-analysis evaluated the effect of polyclonal intravenous immunoglobulin therapy on death in critically ill adult patients with sepsis, and found a survival effect for patients with sepsis who received polyclonal intravenous immunoglobulin therapy compared with those who received placebo or no intervention [90]. Some studies have demonstrated the efficacy of IVIG in decreasing morbidity and mortality in TSS in isolated reports.

Once the diagnosis is made, adequate antibiotic therapy with a penicillinase-resistant antibiotic and with coverage for both staphylococci and streptococci should be initiated until a definitive diagnosis is made. Antibiotics such as clindamycin may be particularly effective as part of the antibiotic regimen, because they inhibit bacterial protein synthesis and release and can overcome the *Eagle effect* (which is a manifestation of decreased bacterial replication, which can occur when local concentrations of bacteria are high) [78]. Under such circumstances, β-hemolytic *Streptococcus* may become relatively resistant to cell-wall inhibitors such as penicillin, but may succumb to protein synthesis inhbitors such as clindamycin. Close follow-up is recommended, as not infrequently patients can have sequelae.

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Erythroderma and Exfoliative Dermatitis

8

Michelle A. Thomson and John Berth-Jones

Core Messages

- Erythroderma is conventionally defined as inflammation of at least 90% of the skin surface, characterized by erythema and variable scaling. When the scaling is prominent it is often called exfoliative dermatitis.
- Erythroderma is a potentially life-threatening state of 'skin failure' in which patients are at risk from complications including hypothermia, fluid, and electrolyte imbalance, hypo-albuminaemia, cardiac failure and infection including septicaemia.
- There are a multitude of possible causes which encompass virtually all inflammatory skin diseases; a proportion develop without any apparent trigger and remain 'idiopathic'.
- The commonest causes of acute erythroderma are psoriasis, atopic and other varieties of eczema, cutaneous T-cell lymphoma and drug reactions.
- Management of erythroderma requires a combination of general supportive measures and treatment directed at the underlying cause. Acute cases need hospital management with intensive monitoring and support.
- The prognosis depends substantially on the aetiology and is best for drug-induced erythroderma, which often resolves promptly when the offending drug is withdrawn.

8.1 Introduction

Erythroderma (exfoliative dermatitis) is a persistent, severe, generalized inflammation of the skin. By convention, the term tends to be reserved for cases affecting at least 90% of the body surface. Erythema is a constant feature, but the scaling or exfoliation is highly variable. Erythroderma may develop extremely rapidly or quite gradually. In either event, it is an important dermatological emergency, as the systemic effects are potentially fatal.

8.2 Epidemiology

The prevalence and incidence of erythroderma are based on several large series [1]. A recent study from the Netherlands estimated the annual incidence at 0.9 per 100,000 population [2]. Males are more commonly affected (male-to-female ratio of approximately 2:1 to 4:1) and if the hereditary disorders and atopic dermatitis are excluded, most are over 45 years old.

8.3 Aetiology

Erythroderma arises as a 'reaction pattern' in a diverse range of circumstances (Table 8.1). In adults, the most common causes include atopic dermatitis, psoriasis, cutaneous T-cell lymphoma (CTCL) and drug reactions. Other rarer causes include bullous dermatoses, pityriasis rubra pilaris, Ofuji's papuloerythroderma, and connective tissue diseases [3, 4]. Graft-versus-host disease may progress to erythroderma in some cases. Erythroderma

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Table 8.1 Causes of erythroderma in adults

Common
Psoriasis
Atopic dermatitis
Drug reactions
Cutaneous T-cell lymphoma
Idiopathic erythroderma
Less Common
Other eczemas (contact allergic dermatitis, stasis with autosensitization)
Pityriasis rubra pilaris
Paraneoplastic
Bullous dermatoses (pemphigus foliaceous, bullous pemphigoid)
Rare
Lichen planus
Crusted (Norwegian) scabies
Dermatophytosis
Connective tissue disorders (dermatomyositis, cutaneous lupus erythematosus)
Ofuji's papuloerythroderma
Graft-versus-host disease
Congenital ichthyoses (usually present at birth)

has rarely been reported with seroconversion following HIV infection[5]. In established AIDS, erythroderma can arise from a variety of causes including severe seborrhoeic dermatitis or lymphoma [6].

The major causes of erythroderma in the newborn include genodermatoses, ichthyoses, immunodeficiencies, psoriasis, and infections (e.g., staphylococcal scalded-skin syndrome).

In addition, the possibility of drug-induced erythroderma needs to be considered.

Identification of the underlying disease process in erythrodermic patients is one of the most complex challenges in dermatology. Despite extensive investigations, a proportion of cases develop without any apparent trigger and remain 'idiopathic'.

8.4 Pathology

Histology of the skin is often non-specific, and varies depending upon the severity and duration of the inflammatory process. In the acute stage, spongiosis and parakeratosis are prominent, and there is a non-specific inflammatory infiltrate. In the chronic stage, acanthosis and elongation of the rete ridges becomes more apparent. Histopathological clues to the underlying disease are usually subtle, but may be identified in some cases [7]. Immuno-fluorescent staining for immunoglobulin deposition should be performed if an immunobullous disease is suspected [8].

In erythroderma resulting from CTCL, the infiltrate may become increasingly pleomorphic and may eventually acquire diagnostic features [9]. In other cases, it remains non-specific throughout the course. Patients with Sezary syndrome often show features of chronic dermatitis, and benign erythroderma may occasionally show features suggestive of lymphoma. Immunophenotyping of the lymphoid infiltrate may not solve the problem, as it generally shows features of mature T cells in both benign and malignant erythroderma [10]. A skin biopsy for T cell receptor analysis to demonstrate clonal proliferation of lymphocytes may have some diagnostic value [11, 12].

8.5 General Clinical Features

Some features are common to all patients with erythroderma, regardless of the cause. The condition often develops suddenly, particularly when associated with lymphoma or eczema. A patchy erythema may spread rapidly to be universal within 12–48 h and be accompanied by pyrexia, malaise, and shivering. Many patients feel cold, especially when the erythema is increasing. Scaling appears 2–6 days later and varies greatly in degree and character. The scales may be fine in atopic dermatitis or dermatophytosis, bran-like in seborrhoeic dermatitis, crusted in pemphigus foliaceous or exfoliative in drug reactions. At this stage the skin is bright red, hot, dry, and thickened. Irritation is sometimes severe, but a sensation of tightness is more characteristic. Severe pruritus is sometimes a clue to underlying lymphoma.

Scalp and body hair is lost when erythroderma has been present for some weeks. The nails become ridged and thickened and may also be shed. Mucous membranes are usually spared, although the peri-orbital skin is oedematous, which can result in ectropion with consequent epiphora. In very chronic cases, patients develop dyspigmentation, with hyperpigmentation observed more frequently than hypo- or depigmentation [13].

Lymphadenopathy occurs to some degree in most cases. The lymph nodes are usually slightly or moderately enlarged and of rubbery consistency, but in some cases may be prominent. The major differential diagnosis is between dermatopathic lymphadenopathy and lymphoma, and in difficult cases a lymph node biopsy is

recommended. However, the pathologist must be told that the patient is erythrodermic for a reliable histopathological interpretation to be made.

8.6 Specific Features of the Underlying Disease

In addition to the aforementioned general features, the clinical presentation is modified by the patient's age and general physical condition. There are also additional, sometimes specific, features suggesting the underlying aetiology.

8.6.1 Eczemas

Eczema of any variety may progress to erythroderma. Venous eczema is a common precedent in the sixth and seventh decades. However, atopic erythroderma (Fig. 8.1) may occur at any age. It is found most frequently in patients with a history of moderate to severe atopic dermatitis, where exacerbation of existing lesions usually precedes the generalization. The pruritus is intense, and secondary excoriations or prurigo-like lesions are observed. Some patients have increased serum IgE and lactic dehydrogenase levels with eosinophilia [14].

8.6.2 Psoriasis

Psoriatic erythroderma (Fig. 8.2) is usually preceded by typical psoriatic plaques but when the exfoliative stage is reached, these specific features are lost. In some cases, sterile pinhead-sized pustules develop, and the condition may progress to generalized pustular psoriasis. Due to the slow turnover rate, nail changes may still be visible and provide valuable clues to the diagnosis. Psoriatic erythroderma is most frequently precipitated by the withdrawal of potent topical or systemic steroids or methotrexate, and occasionally widespread flares follow irritant contact dermatitis, inter-current illness, photo-toxicity, and emotional stress.

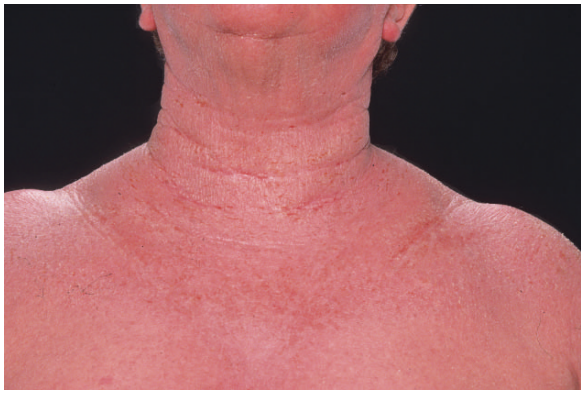

Fig. 8.1 Erythroderma in adult atopic dermatitis

8.6.3 Drug Reactions

A wide range of drugs can cause erythroderma [15] (Table 8.2). The eruption usually begins as a morbilliform or scalatiniform exanthem often associated with

Fig. 8.2 Psoriatic erythroderma

Table 8.2 Drugs that may cause erythroderma

Allopurinol*	Omeprazole*
Amiodarone	Phenytoin
Ampicillin/amoxicillin*	Penicillin G*
Antimalarials	Phenobarbital*
Aspirin	Phenothiazines*
Captopril	Quinidine
Carbmazepine*	Ranitidine
Cephalosporins	Sulfonamides*
Cimetidine	Sulphonylureas*
Dapsone*	Thiazides
Diltiazem	Trimethoprim
Epoprostenol	Vancomycin*
Gold	
Isoniazid	
Lithium	

"*" drugs commonly associated with erythroderma

some irritation (Fig. 8.3). Erythema may first appear in the flexures or over the whole skin, and lesions may become prupuric around the ankles and feet. The incidence of erythroderma may be higher in patients who use traditional remedies or self-medicate [16, 17]. St. John's wort may trigger erythroderma [18].

Drug-induced erythrodermas can have an excellent prognosis, especially if the erythroderma is the only manifestation of hypersensitivity [1, 19]. Once the causal agent is discontinued, a drug-induced erythroderma will often resolve in 2–6 weeks [20].

It is important to note, however, that the erythroderma may be accompanied by other manifestations of hypersensitivity. It is not uncommon for a drug-induced rash to be accompanied by haematological abnormalities, or evidence of hepatitis or nephritis.

An important example is the syndrome known as DRESS (drug reaction with eosinophilia and systemic symptoms) [21, 22]. The precise status of this syndrome as a single entity is not firmly established, but the term has been widely used and seems to have provided an 'umbrella diagnosis' for a group of severe, multi-system drug reactions characterized by later onset than most manifestations of drug hypersensitivity. Typically, exposure to the drug lasts for weeks or months before the reaction emerges. DRESS may also persist for a long time, and even worsen after withdrawal of the causative agent. The pathogenesis in many cases seems to involve reactivation of a range of herpes viruses (including EB virus, HHV-6, HHV-7, and cytomegalovirus). The rash is of variable severity and morphology. Erythroderma is a frequent manifestation, but others include erythema multiforme and Stevens–Johnson syndrome. Multisystem involvement may include fever, eosinophilia, lymphadenopathy, hepatitis, renal dysfunction and pneumonitis. Causative drugs have included allopurinol, various anticonvulsants, nevirapine, abacavir, minocycline, and recently efalizumab [23].

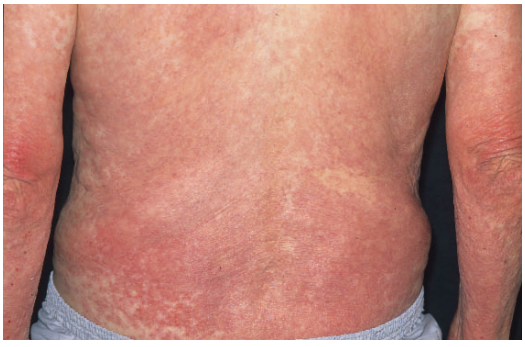

Fig. 8.3 Drug induced morbilliform exanthema

8.6.4 Cutaneous T-Cell Lymphoma

CTCL is the most common malignancy to cause erythroderma. Erythroderma due to CTCL is subdivided into Sezary Syndrome (Fig. 8.4) and erythrodermic mycoses fungoides [24]. Sezary syndrome is defined by the triad of erythroderma, lymphadenopathy, and abnormal circulating T lymphocytes. Additional features include palmoplantar keratoderma, alopecia, and leonine facies. Pruritus is often severe, and rubbing and scratching produces secondary lichenification. The manifestations of erythrodermic mycoses fungoides are identical, but leukaemic Sezary cells are absent. The possibility of CTCL persists in any patient with idiopathic erythroderma.

8.6.5 Paraneoplastic Erythroderma

Paraneoplastic erythroderma is most commonly associated with lymphoproliferative malignancies. As previously discussed, the commonest is CTCL, followed

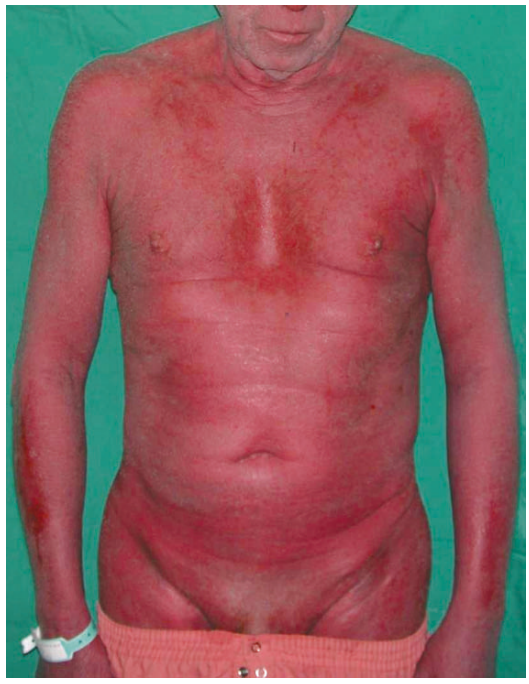

Fig. 8.4 Sezary syndrome. Courtesy of Dr Berty Dharma, University Hospitals Coventry and Warwickshire, U.K

by Hodgkin's disease and rarely Non-Hodgkin's lymphoma, leukaemias, and myelodysplasia. Associations with other internal malignancies have been observed less often [25, 26]. In the case of solid-organ malignancies, the erythroderma appears late in the course of the disease. Additional signs of malignancy such as cachexia or fatigue may be seen.

8.6.6 Ichthyoses

An erythroderma due to one of the inherited ichthyoses is usually present from birth or infancy. In neonates, one needs to consider non-bullous congenital ichthyosiform erythroderma, bullous congenital ichthyosiform erythroderma and Netherton syndrome [27].

8.6.7 Pityriasis Rubra Pilaris

The erythrodermic forms can begin in childhood or adult life. The presence of follicular keratotic plugs on the knees, elbows, and dorsae of the hands and toes is distinctive. Islands of uninvolved skin within erythrodermic regions (Fig. 8.5) are also highly suggestive of the diagnosis. The lesions usually have a salmon to orange-red colour, and the palms and soles show orange keratotic thickening [28].

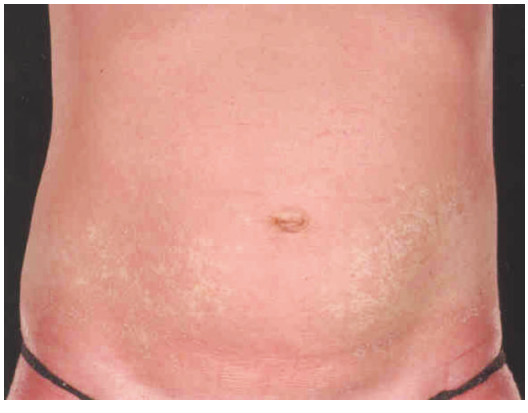

Fig. 8.5 Erythroderma in pityriasis rubra pilaris. Residual areas of normal skin persist amid the erythema

8.6.8 Bullous Dermatoses

Among the bullous dermatoses, the most common cause of erythroderma is pemphigus foliaceus. The erythroderma is usually preceded by impetigo-like lesions on the face and truck. Collarettes of scale and scale-like crusts are conspicuous, moist, and adherent.

8.6.9 Lichen Planus

Erythrodermic lichen planus is very rare, but lichenoid reactions to gold, quinine, and other drugs are not uncommon. In idiopathic lichen planus, typical violaceous papules may be revealed as the initial erythema subsides, and mucous membranes may show typical lacy white streaks.

8.6.10 Dermatophytosis

Dermatophytosis rarely presents as erythroderma [29]. If suspected, potassium hydroxide (KOH) preparation and fungal culture should confirm the clinical suspicion.

8.6.11 Crusted (Norwegian) Scabies

The heavily crusted hands and feet with thickened nails so characteristic of Norwegian scabies may occasionally be accompanied by generalized erythema and scaling. The condition can be mistaken for erythrodermic psoriasis. Careful attention to skin and nail examination for parasites is advised, especially in immuno-compromised patients.

8.6.12 Idiopathic Erythroderma

Thorough investigations and duration of observation diminish the percentage of cases of idiopathic erythroderma, but in any series it is rarely below 10% [18, 30–32]. The group consists primarily of elderly men with a chronic course of relapsing pruritic erythroderma in association with dermatopathic lymphadenopathy, marked palmoplantar keratoderma and a

raised serum IgE. These have been labelled 'red-man syndrome' [13, 33]. The three most common causes of idiopathic protracted erythroderma are probably atopic dermatitis, drug-induced, and pre-lymphomatous eruptions [28].

8.7 Complications

Erythroderma is associated with profound physiological and metabolic changes [34]. The blood flow through the skin is markedly increased and there is fluid loss by transpiration, with consequent tachycardia and a risk of high-output cardiac failure, especially in elderly patients [35, 36]. Furthermore, increased skin perfusion leads to thermoregulatory disturbances [33, 37]. Shivering and hypothermia may occur even though the skin feels deceptively warm. The chronic and excessive loss of heat leads to compensatory hyper-metabolism and subsequent cachexia.

Hypoalbuminaemia is common and probably has several causes including increased plasma volume [38], decrease in synthesis, increase in metabolism [39–41] and protein loss via scaling and exudation [42]. Oedema is almost invariable, and results partly from increased capillary permeability. This may be severe enough to justify plasma infusions and parenteral steroids.

Colonization of the skin with Staphylococcus aureus is common, and this can lead to secondary cutaneous infections. Respiratory infections are also common, and the majority who die, do so from pneumonia [43].

8.8 Prognosis

The prognosis of erythroderma depends on many variables including the underlying cause, age, speed of onset, concomitant medical conditions, early effective treatment and the development of complications. It is particularly dangerous in the very young [44] and in elderly people, where the prognosis must be guarded. However, with careful management, the vast majority of patients who are otherwise healthy will survive an episode of erythroderma. Drug-induced erythroderma in young adults has the best prognosis [1, 18]. Other forms of erythroderma eczematous, psoriatic or idiopathic may continue for months or years, with relapses without apparent cause [42]. Men with erythroderma from causes other than Sezary syndrome and CTCL have a lower survival than men in the general population [31].

8.9 Diagnosis and Investigations

The recognition of erythroderma is easy, but the diagnosis of the underlying cause may be difficult. The most vital steps to determine the cause are a careful history and review of the case notes. This may identify hereditary disorders, previous inflammatory conditions or drug reactions. Special attention needs to be paid to an accurate drug history, and this should include all self-medication and herbal medicines. Useful investigations include a full blood count, liver functions tests, electrolytes, serum protein levels, blood cultures, nasal and skin swabs for bacterial culture and sensitivity. Further investigations may be necessary depending on initial findings.

For erythrodermic CTCL, a methodical evaluation of skin, blood and lymph node samples using histology, immuno-histochemistry, and molecular analysis is recommended [45–47]. A skin biopsy may show only non-specific changes, and may need to be repeated before the subtle changes of early cutaneous CTCL become apparent. Peripheral blood sample for Sezary cells is an important investigation, but caution should be exercised when interpreting the results, as these are often observed in benign reactive erythrodermas. Only when they constitute more than 20% of peripheral mononuclear cells do they become diagnostic of Sezary syndrome. The definitive diagnostic criteria for patients with Sezary syndrome should include demonstration of a clonal T cell receptor gene rearrangement using polymerase chain reaction on peripheral blood [46]. Lymph node biopsy may be diagnostic of lymphoma but often shows only features of dermatopathic lymphadenopathy [48].

8.10 Management

Patients with acute onset of erythroderma and unstable patients are best managed in hospital, as frequent monitoring and skilled nursing care are mandatory. Regardless of the underlying disease, the initial management includes attention to nutrition, fluid and

electrolyte equilibrium, prevention of hypothermia, maintenance of normal haemodynamics, and treatment of infections [49].

The patient should be nursed comfortably at a steady temperature (preferably 30–32°C). Cooling and overheating must both be avoided by the use of extra blankets or fans respectively.

Management of fluid and electrolyte balance is critical to prevent hypernatraemic dehydration. Adequate fluid intake must be maintained, but if there is oedema, diuretics and/or plasma infusion should be considered. Cardiac failure is difficult to diagnose, as oedema in erythrodermic patients is not a reliable sign of heart failure. However, cardiac failure must be treated if it develops.

In the first instance, emollients and mild topical steroids are the mainstay of treatment. Frequent and large quantities of bland emollients soothe the skin and partially restore barrier function. Mild and moderate topical steroids control the cutaneous inflammation. High potency topical steroids should be used with caution, due to increased transcutaneous absorption. The majority of patients improve within a fortnight on this regimen, during which time the diagnosis of the underlying condition may become clear. Sedating antihistamines can also be very useful [27].

The use of more active topical treatment, such as coal tar, salicylic acid, vitamin D analogues and calcineurin inhibitors is potentially hazardous, as these are far more irritant and the systemic absorption is greater than in normal skin. Care should therefore be exercised with the use and quantities of such topical medication.

Antibiotics are required to control secondary infection. Topical antibiotics are often adequate, although systemic antibiotics are used depending on the extent and severity of the secondary infection. Beware of over-interpreting blood culture results, as specimens are easily contaminated with skin microflora. However, septicaemia, often caused by *Staphylococci*, is a complication requiring urgent hospital admission, intravenous antibiotics and intense supportive treatment which may include inotropic agents.

Definitive treatment depends on the diagnosis, but requires careful consideration. Some patients with erythroderma have multiple drug allergies, and immunosuppressive drugs may be contraindicated if malignancy is suspected (particularly CTCL). In psoriatic erythroderma, use of methotrexate [50], acitretin, azathioprine [51] or ciclosporin [52] is preferred to systemic steroids, given the risk of a pustular flare when the steroids are tapered [42]. There is also increasing use of biological agents [53, 54]. In eczematous erythroderma, phototherapy and ciclosporin may be helpful. For drug reactions, all non-essential drugs and all suspected drugs must be discontinued, and the erythroderma usually improves in 2–6 weeks. However, in severe and persistent cases, systemic prednisolone or even intravenous immunoglobulins may be useful. After careful exclusion of any underlying cause, idiopathic erythroderma may be treated with mild topical steroids and in refractory cases, ciclosporin and systemic steroids have been used successfully. The use of systemic steroids in drug-induced and idiopathic erythroderma remains controversial. Many dermatologists prefer to avoid systemic steroids, due to the dangers of fluid retention, secondary infection and diabetes. However, rapid and often persistent clearing of erythroderma has been achieved with an initial dose of 1–3 mg kg^{-1} day^{-1} prednisolone and a maintenance dose of 0.5 mg kg^{-1} day^{-1} [55].

The optimum treatment of erythrodermic CTCL is still debated. Options include systemic steroids, PUVA, total body electron beam irradiation, topical nitrogen mustard and systemic chemotherapy [56, 57]. Extracorporeal photopheresis appears to be effective for selected patients, although remission rates vary [58].

As previously discussed, many aspects of the management of a patient with erythroderma are similar, regardless of the aetiology. It is often necessary to treat a case without knowing the cause, and in such cases treatment should be directed at the most likely cause based on supportive findings. However, for optimal management in the longer term, it is vital to establish a more precise diagnosis when possible.

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Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

9

Maja Mockenhaupt

Core Messages

- Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, drug-induced skin reactions with a high morbidity and mortality.
- A consensus definition has allowed several epidemiological studies to estimate the risk of associated medications.
- Drugs with a high risk to induce SJS and TEN are allopurinol, antibacterial sulfonamides including sulfasalazine, carbamazapine, lamotrigine, nevirapine, oxicam-NSAIDs, phenobarbital, and phenytoin.
- Identification and withdrawal of the inducing drug(s) is crucial for the progression of the disease and the prognosis of the patient.
- Supportive management is important to improve the patient's state, probably more than immunomodulating treatments such as intravenous immunoglobulin, corticosteroids etc. that have been tried so far.

9.1 Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening conditions mainly induced by drugs. The terminology of these severe cutaneous adverse reactions has been inconsistent for decades. After several attempts to clarify the situation, a consensus definition published in 1993 suggests the differentiation between erythema exsudativum multiforme majus (EEMM) and SJS as well as an overlap between SJS and TEN. This consensus classification has been successfully used in several large epidemiological studies within the past 15 years. These studies provided reliable information on the incidence of SJS and TEN as well as on demographic data. Numerous drugs have been reported to be associated with SJS and TEN in case reports and case series. Epidemiologic studies for the first time allowed estimates of the risk for certain drugs and drug groups to induce severe cutaneous adverse reactions (SCAR). In addition, the investigation of biological specimen of patients with severe cutaneous adverse reactions provided a basis for pathogenetic considerations and new therapeutic approaches of SJS and TEN.

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9.2 Clinical and Diagnostic Aspects

Both SJS and TEN are characterized by erythema with a variable extent of blisters and erosions of the skin, fever and malaise. In addition, hemorrhagic erosions of mucous membranes, such as stomatitis, balanitis, colpitis, severe conjunctivitis and blepharitis occur.

9.2.1 Consensus Definition

The classification published by Bastuji-Garin et al. in 1993 is based on the type of single lesions and on the extent of blisters and erosions related to the body surface area (BSA).

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The lesions found in severe skin reactions are typical targets, with a regular round shape and a well-defined border with at least three different concentric zones: a purpuric central disk with or without a blister, a raised edematous intermediate ring, and an erythematous outer ring. In contrast, raised atypical targets present with only two zones and a poorly defined border, while flat atypical targets are characterized by vesiculous or bullous lesions in the center, which may be confluent.

Erythema multiforme with mucosal involvement, also called erythema exsudativum multiforme majus (EEMM) or bullous erythema multiforme, appears with typical or raised atypical targets, mainly on the limbs (Fig. 9.1). In contrast, SJS presents with widespread purpuric macules or flat atypical targets, mainly on the trunk (Fig. 9.2), as described in the original publication. Severe mucosal involvement is found in both conditions, and does not allow a differentiation. Skin detachment in EEMM is usually very limited, since only small blisters appear on the target lesions, and less than 10% of the BSA in SJS. By definition TEN requires skin detachment of more than 30% of the BSA, usually involving the complete trunk. In most cases, widespread spots and atypical targets, as seen in SJS, precede the epidermal sloughing (TEN with maculae; Fig. 9.3). [1–4].

Due to the fact that SJS and TEN can sometimes hardly be separated from one another, an overlap group of SJS/TEN has been defined, with blisters and erosions between 10% and 30% of the BSA called SJS/TEN-overlap. Hemorrhagic erosions of at least one site of mucous membranes are present in more than 90% of cases. (Figs. 9.4 and 9.5; Table 9.1).

Whereas SJS, SJS/TEN-overlap, and TEN with maculae are considered as a single disease evolving from one category to another, erythema exsudativum multiforme majus is different not only in terms of the clinical pattern, but also in terms of etiology [5, 6].

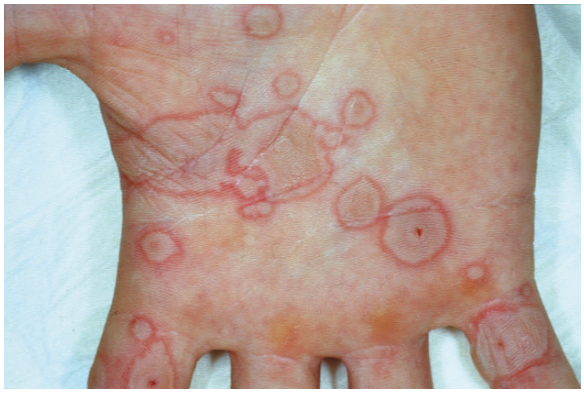

Fig. 9.1 Typical targets with three concentric zones on palms as seen in EEMM

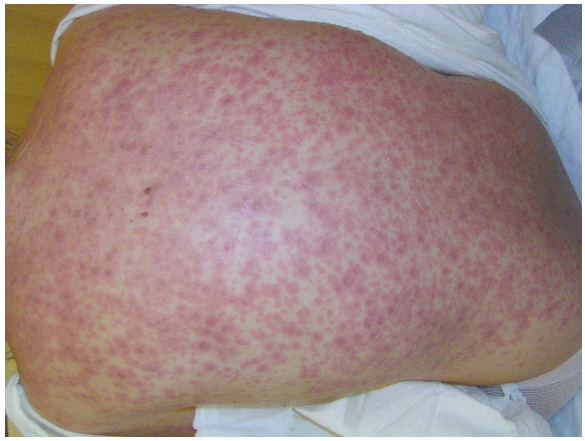

Fig. 9.2 Confluent purpuric macules and flat atypical targets in SJS

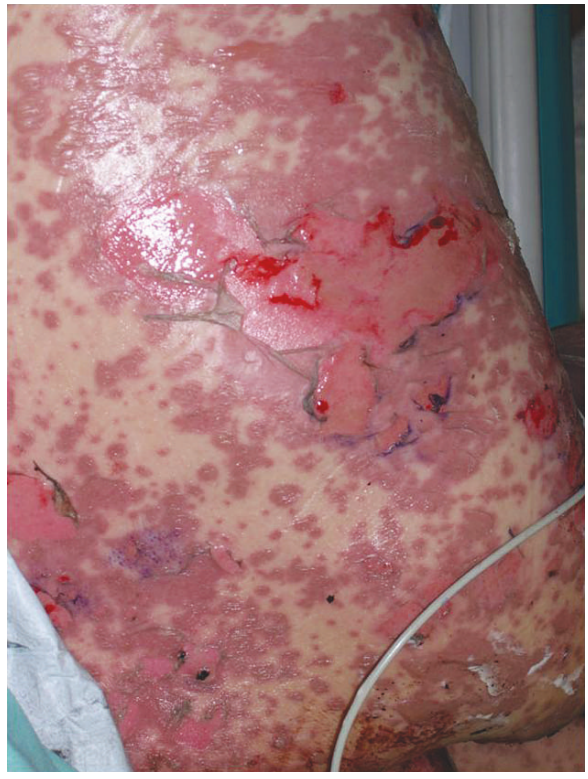

Fig. 9.3 Detachment of large epidermal sheets in TEN with maculae; atypical target lesions are still present

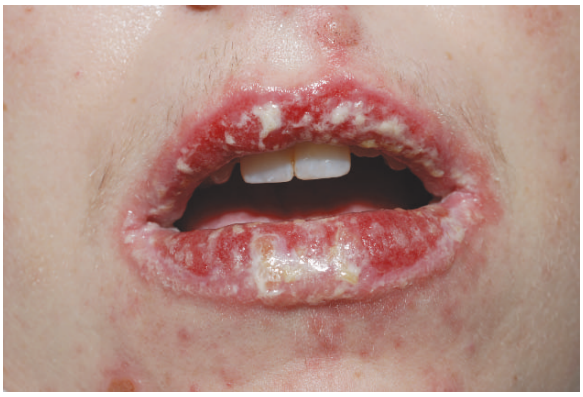

Fig. 9.4 Hemorrhagic erosions of the lips in EEMM, SJS, or TEN

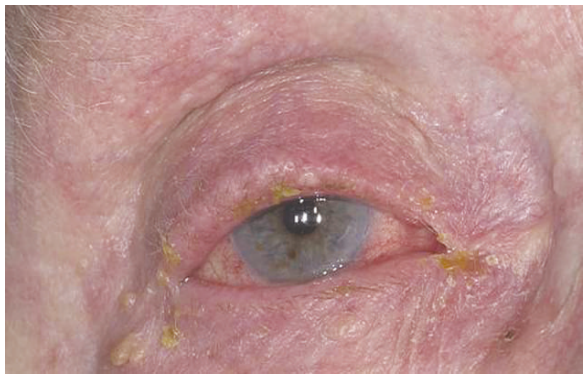

Fig. 9.5 Severe eye-involvement in EEMM, SJS, or TEN

Table 9.1 Classification of the consensus definition (according to Bastuji-Garin et al. [1])

Criteria	EM majus	SJS	SJS/TEN-overlap	TEN with maculae	TEN on large erythema (without spots)
Skin detachment (%)	<10%	<10%	10–30%	>30%	>10%
Typical target lesions	+	–	–	–	–
Atypical target lesions	Raised	Flat	Flat	Flat	–
Maculae	–	+	+	+	–
Distribution	Mainly limbs	Widespread	Widespread	Widespread	Widespread

EM erythema multiforme; *SJS* Stevens–Johnson syndrome; *TEN* toxic epidermal necrolysis

9.2.2 Histopathology

The characteristic pattern in the histopathology of severe skin reactions is the presence of necrotic keratinocytes in either wide dissemination or full-thickness necrosis of the epidermis. The basal membrane zone shows vacuolization leading to subepidermal blistering. In the upper dermis a superficial, often perivascular lymphohistiocytic infiltrate can be observed. Whereas eosinophils have been seen in about 50% of the biopsies ($n = 149$) of patients with EEMM, SJS, or TEN (but less frequently in severe forms of TEN) [7], other authors have reported less epidermal necrosis, more dermal inflammation, and more exocytosis in erythema multiforme majus compared to SJS [8]. Nevertheless, the histopathological findings can differentiate SJS and TEN from other diseases described below, but do not allow the clear differentiation between SJS/TEN and EEMM.

9.2.3 Differential Diagnoses

Maculo-papular drug rashes and erythroderma, both of which may lead to desquamation of the skin, have to be considered as differential diagnoses of SJS and TEN. The desquamation of large sheets of scales in exfoliative dermatitis in particular is sometimes clinically confused with epidermal detachment in TEN. In addition, autoimmune blistering diseases such as pemphigus vulgaris and bullous pemphigoid, as well as bullous phototoxic reactions, have to be taken into account as possible differential diagnoses. After confluence of dozens of non-follicular pustules in acute generalized exanthematous pustulosis (AGEP), a Nikolsky-like phenomenon may imitate detachment in TEN, however much more superficial [9, 10].

Whereas typical target lesions in erythema multiforme are somehow characteristic for the disease, SJS, especially in children, may appear like viral exanthematic infections, often also involving mucous membranes. In elderly patients, a multiforme-like or target-like skin eruption caused by drugs has to be considered as a differential diagnosis [11].

In terms of TEN, it is most important for the patient to rapidly exclude the possible diagnosis of staphylococcal scalded skin syndrome (SSSS) by performing a Tzanck test or cryostat histology for rapid information on the layer of epidermal separation. A biopsy for a conventional histopathological examination is also needed [12]. In contrast to the skin lesions described for SJS and TEN, generalized bullous fixed drug eruption

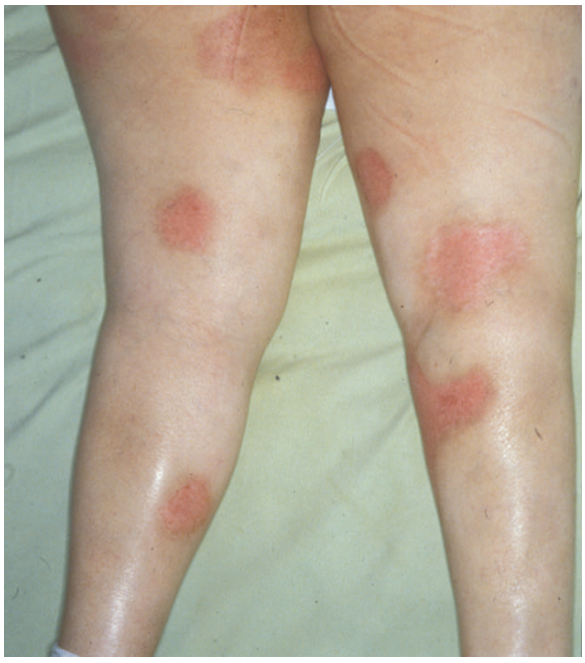

Fig. 9.6 Erosions in generalized bullous fixed drug eruption (GBFDE)

(GBFDE) presents with well-defined round or oval plaques of a dusky violaceous or brownish color. Blisters may occur on the plaques, but usually do not exceed more than 10% of the body surface area (Fig. 9.6). Fever, malaise, and mucosal involvement are less prominent in GBFDE than in SJS and TEN, and the prognosis is far better. Previous fixed drug eruptions are common in the history of patients with GBFDE [13].

9.3 Epidemiology and Etiology

9.3.1 Incidence and Demography

Over the years, mainly case-reports of severe skin reactions have been published in the literature. Population-based retrospective studies in the 1980s found incidence rates of 1.2 per 1 million inhabitants per year in France and 0.93 per 1 million per year in Germany for TEN [14, 15].

A population-based registry covering an average population of 65.76 million inhabitants in former West Germany and Berlin up to the end of 1995 calculated an incidence of 1.53 per million inhabitants per year for SJS, SJS/TEN-overlap, and TEN together in 1991, whereas the overall incidence between 1992 and 1995 was 1.89 for SJS, TEN, and their overlap, assuming that these reactions represent a single entity of different severity [16]. Since the beginning of 1996, the new federal states of former East Germany are also included in the registration, covering a population of about 82 million inhabitants.

More men develop EEMM (almost 70%), whereas for SJS and TEN a slight female preponderance can be observed.

Virtually no patient with EEMM has died. In contrast, the mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TEN-overlap and almost 50% for patients with TEN. For SJS, SJS/TEN-overlap, and TEN together, the mortality rate is almost 25% (unpublished updates of the German registry). About 5% of the patients with SJS and TEN are HIV-infected. Not surprisingly, the distribution of age and gender differs from that of non-HIV-infected patients with SCAR, whereas mortality rate and outcome are comparable [17].

9.3.2 Etiology and Risk Estimation

Cases of SJS and TEN without any drug intake seem to occur very rarely. Viral infections and mycoplasma pneumonia infection have been reported as etiologic factors. However, many patients with acute infections before their severe skin reaction also took anti-infective medication. Very often it is hard to determine whether the symptoms, e.g., oronasal soreness and conjunctival injection, are signs of the acute infection or the beginning of the severe skin reaction itself. A possible interaction of infection and medication, as well as the interaction of different drugs, has not yet been clarified. To date, there is no reliable in vitro or in vivo test to determine the link between a specific drug and the severe cutaneous adverse reaction in a single case. Even by undertaking a provocation test with the suspected drug, it was not possible to induce the reaction again in more than one out of ten patients with previous TEN, in contrast to GBFDE, where all patients responded to the suspected drug [13]. Thus, the detection of the culprit drug mainly relies on the time interval between introduction of the drug and onset of the skin reaction.

In order to have an idea how often a certain drug may be responsible for severe skin reactions, it is not sufficient to just look for the absolute number of cases exposed to that specific drug prior to the onset of the adverse reaction. In addition, it is necessary to compare the absolute number of cases to all people who have taken that drug in a certain time period, often expressed by sales or prescription data. Since SJS and TEN usually occur during the first course of drug intake (without prior sensitization), assumptions for risk estimation cannot only rely on prescription data in defined daily doses (DDD), and need further hypotheses on the percentage of new users. Concerning antiepileptic drugs causing SCAR, more than 90% of SJS and TEN cases occurred in the first 2 months of drug use, and the risk estimates vary between 1 and 10 per 10,000 new users for all anti-epileptic drugs other than valproic acid, for which estimates have been consistently lower [18].

Another possibility for risk evaluation of drugs is the case-control design. The international case-control study on SCAR (SCAR study) was performed in several European countries between 1989 and 1995. Concerning drugs usually taken for a short time, the risk was increased for co-trimoxazole and other anti-infective sulfonamides, aminopenicillins, quinolones, cephalosporines, and chlormezanone. In terms of drugs with a longer period of intake, the crude relative risk was increased for carbamazepine, phenobarbital, phenytoin, oxicam-NSAIDS (non-steroidal anti-inflammatory drugs), and allopurinol. For these drugs, the risk seems to be higher during the first 2 months of treatment [19]. The EuroSCAR study (European ongoing case-control surveillance of SCAR) with case and control recruitment between 1997 and 2001 comprises more recent data on drug risks for SJS and TEN. Three hundred and seventy nine 'community' cases of SJS and TEN (i.e., patients who developed the adverse reaction outside the hospital and who were admitted because of symptoms of SCAR) and 1,505 controls were compared. Among medications with prior alerts, two were highly associated with SJS or TEN: nevirapine and lamotrigine. Both shared the overall pattern of 'highly suspected' drugs (recent onset of use and infrequent co-medication with another highly suspected drug) [20]. For both, the manufacturers had proposed avoiding adverse reactions by slow titration of the doses, but obviously this did not work for SJS and TEN [17, 20].

A high risk was confirmed for all previously suspected drugs such as anti-infective sulfonamides (especially co-trimoxazole), allopurinol, carbamazepine, phenytoin, phenobarbital, and oxicam-NSAIDs, with increasing risk estimates for allopurinol, making it the leading cause of SJS and TEN in Europe [20, 21].

The median time latency between start of intake and index-day (i.e., onset of SCAR) was less than 4 weeks (15 days for carbamazepine, 24 days for phenytoin, 17 days for phenobarbital, 20 days for allopurinol). In general, no significant risk persisted after 8 weeks of use.

A large number of drugs of common use, such as beta-blockers, ACE-inhibitors, calcium channel blockers, sulfonamide-related diuretics and sulfonylurea antidiabetics, insulin, and propionic acid NSAIDs were not associated with a detectable risk to induce SJS or TEN [20].

9.4 Pathogenetic Considerations

As described above, drugs are the cause of the majority of all cases of SJS and TEN. However, it is not yet clear how the link between a certain drug and the (epidermal) necrosis is made. Several investigations have shown that T cells, especially CD8 + lymphocytes, play an important role in this process, which may be mediated by cytokines such as TNF-alpha, Fas, and Fas-ligand [22, 23].

On the other hand, drug metabolism has been studied, showing a low N-acetylating capacity in patients with SJS and TEN [24]. However, when CD8 + T cells taken from the blister fluid of patients with TEN caused by co-trimoxazole were tested for their cytotoxic function, they reacted without re-stimulation, towards the parent drug (co-trimoxazole, sulfamethoxazole), but not towards the metabolite [25]. This led to a re-evaluation of the potential role of cytokines in TEN, suggesting the production of Fas-ligand and TNF-Alpha, and Il-10 by keratinocytes could be a defense mechanism against cytotoxic T cells rather than a way of promoting apoptosis [26].

Almost 20 years ago, a genetic susceptibility was shown in patients with TEN, differing in certain HLA alleles depending whether the reaction was caused by a sulfonamide or an oxicam-NSAID [27]. In addition, a metabolic predisposition was suspected for patients with TEN induced by sulfonamides as well as anticonvulsants

[28]. A decade later, a publication from Taiwan was able to demonstrate that 100% of Han-Chinese patients with SJS or TEN due to the use of carbamazepine (n = 44) were positive for the allele HLA-B*1,502 [29]. This finding could not be confirmed in Europe, showing that ethnicity matters more than previously thought in this context [30, 31]

9.5 Therapeutic Concepts

9.5.1 Early Diagnosis

A mean of 4 days elapses between the first symptoms and hospitalization in adequate settings. This delay will not be acceptable as soon as effective therapies become available. At the very beginning, the skin eruption may resemble a benign maculopapular eruption, but unusual pain and anxiety, rapid progression of the lesions, high fever and mucous membrane symptoms should alert physicians to the risk of a severe drug reaction, especially in a patient who recently started a new treatment with one of the 'high risk drugs' listed in Table 9.2.

Table 9.2 Practical recommendations (according to Mockenhaupt et al. [20])

Practical recommendations for dealing with SJS/TEN
– A few medications are associated with high risks. Their use should be carefully weighed and they should be suspected promptly. ◦ Allopurinol ◦ Carbamazepine ◦ Co-trimoxazole (and other anti-infective sulfonamides and sulfasalazine) ◦ Lamotrigine ◦ Nevirapine ◦ NSAID (oxicam type) ◦ Phenobarbital ◦ Phenytoin
– An interval of 4–28 days between onset of drug use and adverse reaction is most suggestive of an association between agent and SJS/TEN
– When patients are exposed to several medications with high exceeded benefits, the timing of administration is the key factor in determining which must be stopped and which can be continued or re-introduced
– The risks of various antibiotics to induce SJS/TEN are comparable but considerably lower than that of anti-infectious sulfonamides

9.5.2 Management in the Emergency Room

As soon as a patient with suspected SCAR arrives at the emergency room, the following check list may help to deal with the problem adequately:

1. Check diagnosis accuracy (in case of doubt contact an expert with internet transmission of numeric pictures).
2. Organize transfer to a specialized ward.
3. Put the patient in a warm environment.
4. Begin intravenous fluid administration (peripheral veins).
5. Evaluate severity (extension of lesions on skin and mucous membranes, any clinical or biological evidence of lung involvement).

As long as the pathogenesis of SJS and TEN remains unclear, therapy is limited to non-specific and symptomatic management. The latter is of major importance for patients with a large amount of skin detachment who require intensive care in specialized units. In addition, sequelae-like strictures of mucous membranes and symblepharon that may lead to long lasting impairment should be avoided.

9.5.3 Topical Treatment and Supportive Care

The blisters are fragile, but should be left undisturbed or just punctured. The erosions can be treated with chlorhexidine, octenisept, or polyhexanide solutions and impregnated non-adherent mesh gauze. The latter is especially important when environmental factors (high room temperature, alternating pressure mattress) lead to rapid drying of the skin. Silver sulfadiazine should be avoided, at least until it is completely clear that the causative drug was *not* a sulfonamide. Some burn care experts prefer to debride the skin under general anesthesia, and apply allografts or forms of coverage; this drastic approach is not necessarily practical for many patients.

Specialized care of the mucosal surfaces is critical. The severity of the mucosal changes is often not in line with the amount of skin detachment. Overlooked mucosal lesions can lead to life-long problems.

Urethral involvement should be followed by urologists. Genital erosions in girls and women may lead to adhesions or strictures, which can generally be avoided by appropriately placed wet dressings or sitz baths. Oral erosions should be treated with desinfectant mouthwash and lip erosions with a bland ointment, such as dexpanthenol ointment.

Ophthalmological consultation is crucial in case of eye involvement. Daily specialized lid care is needed, and anti-inflammatory eye drops should be applied several times a day. In some patients, the massive blepharitis can lead to entropion with trichiasis (ingrowing lashes) which can cause corneal damage, especially if a sicca syndrome evolves because of lacrimal duct damage. A number of specialized approaches to ocular problems (stem-cell generation of replacement cells, scleral lens) do exist, but are not widely accepted yet [32] (experience of the German registry).

The patient should be kept in a warm room (30–32°C) on an alternating pressure mattress. Patients with skin loss of more than 30% are at risk for a variety of systemic complications. Where highly specialized skin centers are not available, the best solution is usually a burn unit or intensive care ward with daily dermatologic consultation. Patients require fluid replacement with macromolecular and/or electrolyte solution (1.5–2 ml kg^{-1} $\%^{-1}$ affected area), bearing in mind that TEN patients have around 70% of the requirements of a burn patient. In addition, many patients require feeding through a stomach tube (1,500 calories in 1,500 ml over the first 24 h, increasing by 500 calories daily to 3,500–4,000 calories daily). The patient should be monitored for infection and, if clinical suspicion arises, treated empirically with the local standard regimens until culture and sensitivity results are available. Depending on the disease severity, sedation and pain therapy should be employed [32].

9.5.4 Immuno-Modulating Treatment

In addition to supportive therapy, various immunomodulating treatments are discussed, such as glucocorticosteroids or intravenous immunoglobulins (IVIG). Most publications on steroid use are case reports or case series, the results of which can hardly be compared. Arguments against the systemic therapy with glucocorticosteroids are an increase of infections, a masking of septicemia, a delayed re-epithelization, a prolonged duration of hospitalization, and a higher mortality.

Case series reporting on the beneficial treatment of TEN with plasmapheresis, hyperbaric ogygen, cyclosporine, and cyclophosphamide have been published, but they are only of limited value, as the observations were not controlled.

Pathogenetic approaches have been used like the TNF-alpha inhibitor thalidomide, and a controlled clinical trial was performed in France. Based on the hypothesis that necrosis of keratinocytes in TEN is influenced by TNF-alpha, and the fact that thalidomide is an effective TNF-alpha-inhibitor in vitro successfully used in graft-versus-host disease, the authors wanted to investigate the efficacy and safety of thalidomide in the therapy of TEN. Due to a significantly increased mortality in the treatment group, the study was stopped earlier. Despite the logical theoretic approach, thalidomide led to the opposite result and, therefore, should be avoided in severe skin reactions [33].

At the same time, intravenous immunoglobulins (IVIG) were reported as an effective treatment of SJS and TEN. The clinical observation of ten patients was based on the hypothesis that keratinocytes usually express Fas-receptor CD95, and that antibodies in pooled human IVIG block the Fas-mediated necrosis of keratinocytes in vitro. The authors assumed that the up-regulation of keratinocyte Fas-ligand-expression is the critical trigger for keratinocyte destruction in TEN. As a result, a reduced mortality as well as a fast healing time was reported [23]. Further case compilations on SCAR patients treated successfully with IVIG have since been published [34, 35]. However, it has to be taken into account that numerous cases appear at least twice in these papers, making the compilation difficult to evaluate [36].

Meanwhile a controlled observational therapeutic study of IVIG in 34 patients with SJS or TEN has been undertaken in a highly specialized intensive care unit in a dermatology department in France. The evaluation on prognostic factors was based on SCORTEN, the specific severity of illness score for TEN [37]. The mortality was higher than predicted, and most patients who died experienced renal failure. Therefore, one has to be very careful using IVIG in patients with impaired renal function [38].

Two further studies from burn units suggest that IVIG does not improve the outcome of patients with

TEN [39, 40]. If a treatment is considered to be effective, it has to work in severely affected patients as well, i.e., mortality must be reduced in patients with a high risk of dying.

Recently, data on treatment modalities have been compared among patients included in the EuroSCAR study, primarily aimed at risk estimation of drugs inducing SJS and TEN. Mortality as an endpoint was related to the treatment with corticosteroids, IVIG, both in combination or supportive care only in 281 patients from France and Germany. The odds ratio calculated for treatment with corticosteroids suggests a benefit for affected patients, whereas treatment with IVIG did not. Despite the pitfalls of such a retrospective analysis, two major conclusions can be drawn: firstly, IVIG is *not* the solution for treating SJS and TEN, and secondly, a controlled trial using corticosteroids for treatment should be encouraged [41].

Despite all controversy, most experts agree on the fact that all medications which are potential triggers for the severe skin reaction must be withdrawn. Prompt attention to this point, which seems obvious but is often overlooked, clearly reduces the morbidity and mortality [42]. Medications with long half-lives or persistent reactive metabolites can continue to cause problems long after they have been stopped [43]. The most likely triggers are those medications which have been introduced in the 4 weeks preceding the onset of the skin reaction. The latency period varies; antiepileptic drugs and allopurinol are usually tolerated for weeks before causing problems, while antibiotics, especially sulfonamides, may lead to a more rapid onset [20].

The clinical challenge is to differentiate more or less severe reactions as early as possible in the evolution, and then to thoroughly but rapidly consider the treatment options for the individual patient. An interdisciplinary approach has turned out to be favorable, and is highly recommended.

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Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS/DIHS)

10

Koji Hashimoto, Mikiko Tohyama, and Tetsuo Shiohara

Core Messages

- Drug-induced hypersensitivity syndrome (DIHS/DRESS) is an adverse drug-induced reaction of severity similar to that of Stevens–Johnson syndrome.
- DIHS is distinguished from other drug reactions by certain characteristics: late onset, clinical similarity to mononucleosis-like syndrome, and prolonged course.
- Human herpesvirus 6 (HHV-6) can be reactivated 2–3 weeks after the onset of rash in the vast majority of DIHS patients.
- Patients with HHV-6 reactivation show more severe symptoms, including long-lasting fever, lymphadenopathy, leukocytosis, appearance of atypical lymphocytes, and hepatitis.
- DIHS may involve encephalitis, non-autoimmune (idiopathic) fulminant type 1 diabetes mellitus and myocarditis.
- The mortality rate for DIHS is 8%, which is higher than the mortality rate for Stevens–Johnson syndrome.

10.1 Introduction

Drug-induced hypersensitivity syndrome (DIHS/DRESS) is a severe adverse drug-induced reaction similar to Stevens–Johnson syndrome and toxic epidermal necrolysis. Over the past 50 years, this syndrome has been referred to as allopurinol hypersensitivity syndrome [1], dapsone hypersensitivity [2], and anticonvulsant hypersensitivity syndrome [3]. In 1994, Roujeau and Stern suggested the use of 'hypersensitivity syndrome', regardless of the culprit drug [4]. Later, Roujeau proposed the acronym DRESS (drug rash with eosinophilia and systemic symptoms) [5]. However, the lack of a specific and sensitive diagnostic test resulted in some confusion over the diagnosis of DRESS [6]. Interestingly, about 10 years ago, a French group and two Japanese groups demonstrated that human herpesvirus 6 (HHV-6) reactivation is involved in this syndrome [7–9]. Based on this observation, a Japanese consensus group proposed the term 'drug-induced hypersensitivity syndrome' or DIHS.

10.2 Clinical Characteristics of DIHS

DIHS is distinguished from other drug reactions by certain characteristics: a limited number of causative drugs, late onset, clinical similarity to mononucleosis-like syndrome, and prolonged course [4, 5]. Anticonvulsants are the most common cause of DIHS [3, 10]. Allopurinol, diaphenylsulfone (dapsone), salazosulfapyridine, minocycline, and mexiletine can also cause DIHS [10, 11]. The syndrome typically develops 2–6 weeks after the initiation of drug administration, and the initial symptoms are fever and maculopapular eruptions that may

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progress to exfoliative dermatitis (Fig. 10.1). A striking facial edema is a hallmark of the disease (Fig. 10.2). Lymphadenopathy, hepatitis, renal dysfunction, atypical lymphocytosis, and hematologic abnormalities, such as leukocytosis and eosinophilia, are observed to varying degrees. It is noteworthy that flare-ups involving clinical signs, such as fever, eruption, or hepatitis, often occurs several weeks after withdrawal of the causative drug [4]. Because the symptoms reappear upon re-administration of the drug, the syndrome is attributed to an immunological reaction against the drug or its metabolites [12, 13], However, the mechanism underlying clinical flare-ups in DIHS patients cannot be fully explained by this immune response.

10.3 Diagnostic Criteria for DIHS

In 1998, Shiohara's group and our own independently demonstrated that human herpesvirus 6 (HHV-6) can be reactivated 2–3 weeks after the onset of rash in the vast majority of DIHS patients, as evidenced by the rise in HHV-6 IgG titers and HHV-6 DNA levels. This occurred despite diverse clinical presentations at onset and regardless of treatment [8, 9]. As part of the Japanese consensus group reviewing this issue in 2002, we established a set of seven diagnostic criteria to identify the typical syndrome (Table 10.1) [13]. Subsequent patient case series using these criteria have shown that HHV-6 reactivation can be detected in patients with clinical manifestations consistent

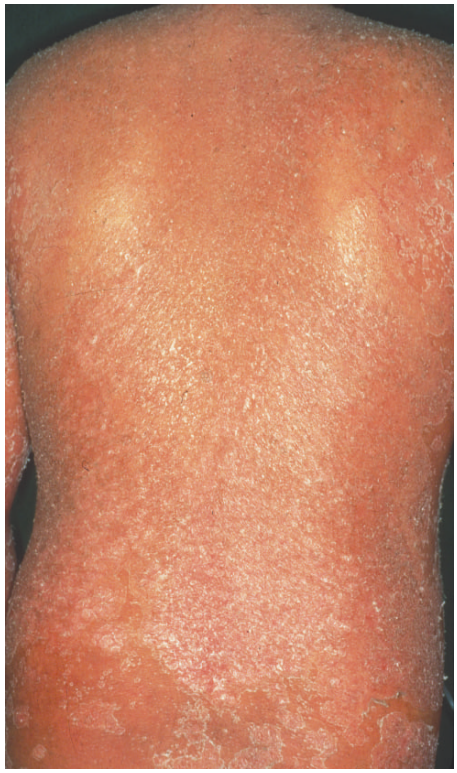

Fig. 10.1

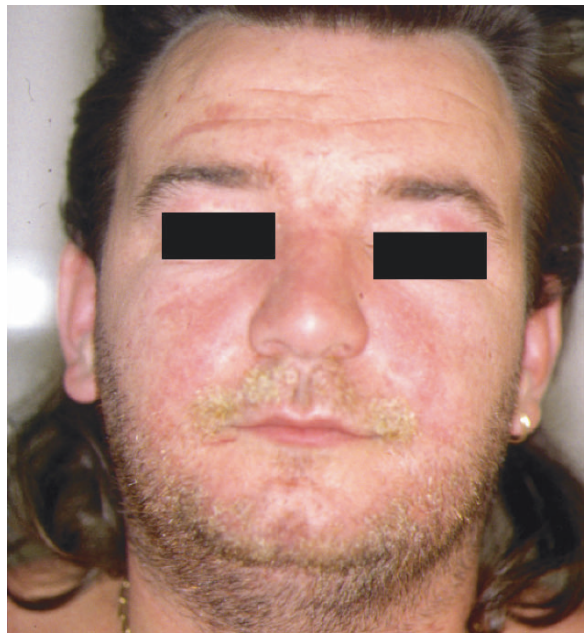

Fig. 10.2

Table 10.1 Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by a Japanese consensus group

1. Maculopapular rash developing more than 3 weeks after first administration of a limited number of drugs
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
3. Fever (> 38°C)
4. Liver abnormalities (alanine aminotransferase > 100 U L^{-1})[a]
5. Leukocyte abnormalities (at least one present)
   a Leukocytosis (> 11 × $10^9 L^{-1}$)
   b Atypical lymphocytosis (>5%)
   c Eosinophilia (> 1.5 × $10^9 L^{-1}$)
6. Lymphadenopathy
7. Human herpesvirus-6 reactivation

The presence of all seven criteria is indicative of typical DIHS, whereas the presence of five criteria (1–5) is indicative of atypical DIHS. [a]Abnormalities in other organs may also be considered, such as the kidney

with those reported by Roujeau et al. [6], but not in those with other types of drug reactions, such as maculopapular rash, Stevens–Johnson syndrome, or toxic epidermal necrolysis. Because the time of sampling is critical to detect the rise in HHV-6 IgG levels, which may be easily missed, concern has been raised regarding the appropriateness of these criteria as a clinical tool. Thus, the concept of an atypical syndrome can be used for patients who show typical clinical presentations, but do not exhibit HHV-6 reactivation, probably as a result of inappropriate sampling. It is important to bear in mind that the clinical criteria for this syndrome are not all present on any given day, and that the severity of clinical symptoms at onset provides only a rough guide for prognosis. In general, patients initially develop two or three features of these symptoms followed by a step-wise development of other symptoms. Thus, long-term follow-up is required to accurately identify DIHS patients.

10.4 Relationship Between DIHS and DRESS

The criteria for DIHS are stricter than those proposed in 1996 by Roujeau for DRESS, and the lack of a specific and sensitive diagnostic test was a major obstacle in the identification of all patients with DRESS [6], which may show milder forms in some patients. From this point of view, all DIHS patients are included in DRESS, but not vice versa. It should also be noted that eosinophilia is observed in 60–70% of the patients who satisfy the criteria for DRESS.

10.5 Characteristics of HHV-6

HHV-6 was first isolated in 1986 [14]. Two variants, HHV-6A and HHV-6B, have been identified, and HHV-6B was proven to be a causative agent of exanthem subitum [15]. CD46, a receptor for vaccine strains of measles virus, is the cellular receptor for HHV-6 [16]. HHV-6 and the measles virus employ distinct domains on the CD46 molecule for receptor function. Because some T-cell lines expressing CD46 are not permissive for HHV-6 infection, co-receptor(s) may exist. Although HHV-6 may infect various types of cells in vitro, including lymphocytes, monocytes, dendritic cells, fibroblasts, epithelial cells, endothelial cells, glial cells, and haematopoietic progenitor cells, activated $CD4^+$ T lymphocytes appear to be the preferential target for fully permissive replication. Seroepidemiological studies have shown that most children have antibodies against HHV-6 before 2 years of age. HHV-6 latently infects after primary infection, primarily in monocytes/macrophages and $CD4^+$ T lymphocytes, and persistently infects the salivary glands.

10.6 Relevance of HHV-6 Reactivation to Disease Severity in DIHS

We compared 62 patients with an increased anti-HHV-6 IgG titer against 38 patients whose anti-HHV-6 IgG titers did not change [17]. The characteristics of these two groups were very similar, except in average age ($p < 0.001$; Table 10.2). Sex ratios, causative drugs, and elapsed time between the drug administration and the appearance of clinical signs were not significantly different between two groups.

The severity of clinical course was, however, clearly different between these two groups. Patients whose anti-HHV-6 IgG titer increased showed more severe symptoms, including long-lasting fever,

Table 10.2 Clinical characteristics of 100 patients, sorted by increasing HHV-6 IgG titer

	Increase in HHV-6 IgG titer ($n = 62$)	No increase in HHV-6 IgG titer ($n = 38$)	p value
Number of cases	62	38	
Sex (M/F)	37/25	19/19	0.34
Age (years)	48.1 (5–88, 49)[a]	57.8 (21–90, 61)[a]	<0.001
Causative drug[b]			
Anticonvulsants	42	26	
Allopurinol	9	4	
Mexiletine	9	1	
Diaphenylsulphone	3	2	
Salazosulfapyridine	3	5	
Days after administration of the drug	41.7 (8–700, 29.5)[a]	66.6 (5–650, 29.5)[a]	0.29

[a]Average (range, median); [b]Multiple drugs caused drug rash in three patients with an increased HHV-6 titer

Table 10.3 Clinical course of 100 patients, sorted by increasing HHV-6 IgG titer

	Increase in HHV-6 IgG titer (n = 62)	No increase in HHV-6 IgG titer (n = 38)	p value
Symptoms and signs			
Fever	61 (98%)	29 (76%)	<0.001
Duration of fever (days)	12.4 ± 7.1	4.8 ± 2.9	<0.001
Lymphadenopathy	44 (71%)	10 (26%)	<0.001
Leukocytosis[a]	38 (61%)	8 (21%)	<0.001
Eosinophilia[b]	38 (61%)	19 (50%)	0.27
Appearance of atypical lymphocytes	55 (89%)	20 (53%)	<0.001
Renal Failure	10 (16%)	0 (0%)	0.01
Flaring	32 (52%)	7 (18%)	<0.001
Fever	22 (35%)	2 (5%)	<0.001
Hepatitis	32 (52%)	2 (5%)	<0.001
Skin rash	12 (19%)	5 (13%)	0.42
Use of systemic corticosteroid	50 (81%)	27 (71%)	0.17
Prognosis			
Duration of illness (weeks)	5.3 ± 2.6	2.8 ± 1.5	<0.001
Deaths	5 (8%)	0 (0%)	0.07

[a]Leukocytosis was evaluated based on WBC counts. Leukocytosis-positive patients were defined as those with > 1.1×10^{10} leukocytes L^{-1} if they had not received corticosteroids, or more than 5×10^{10} leukocytes L^{-1} after systemic corticosteroid treatment; [b]Eosinophilia was indicated by peripheral blood eosinophil counts > $1.5 \times 10^{9} L^{-1}$ or more than 10% of the WBC count; [c]Hepatitis was evaluated by measuring ALT levels. Severe hepatitis was indicated by ALT levels > 10-fold the normal value

lymphadenopathy, leukocytosis, appearance of atypical lymphocytes, and hepatitis (Table 10.3). This resulted in a prolonged disease course; the duration of illness was clearly longer in patients with increasing HHV-6 IgG titers (Table 10.3). It should be emphasized that all five patients with fatal outcomes and all ten patients with renal failure were in the HHV-6 reactivation group (Table 10.3).

10.7 Reactivation of Herpes Viruses Other than HHV-6 in DIHS

Recent papers have demonstrated the reactivation of herpes viruses other than HHV-6, including cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpesvirus-7 (HHV-7) [18]. In general, the cascade of virus reactivation initiated by HHV-6 extends to EBV or HHV-7, and eventually to CMV. The frequency of EBV and HHV-7 reactivation has not been studied in a large number of DIHS patients, and is thought to have no clinical relevancy. In contrast, CMV reactivation was observed in approximately 30% of 45 DIHS patients (unpublished data), some of whom showed recurring transient fever and skin rash. Interestingly, other groups have reported DIHS cases associated with CMV reactivation, and severe complications such as myocarditis, high fever, and continuous skin rash [11, 19].

10.8 Life-Threatening Complications of DIHS

Although rare, previous reports have indicated that DIHS may involve the brain, thyroid, heart, or lung [20]. It would be interesting to determine whether the involvement of these organ systems in DIHS is related to HHV-6 reactivation. Previously, three groups demonstrated HHV-6 reactivation in DIHS-related encephalitis [21–23]. The detection of HHV-6 DNA in cerebrospinal fluid strongly suggested a role for HHV-6 reactivation in encephalitis. Because HHV-6 shows neurotropism and induces central nervous system complications, these reports support the hypothesis that encephalitis associated with DIHS is caused by HHV-6 reactivation.

DIHS is also associated with diabetes mellitus. In a patient with allopurinol-induced DIHS, pancreatic exocrine abnormalities and new-onset type 1 diabetes mellitus were observed [24]. Sekine et al. [25] reported a case of fulminant type 1 diabetes mellitus associated with carbamazepine-induced DIHS. One week before the onset of diabetic ketoacidosis, HHV-6 DNA was detected in the serum via PCR amplification, but the viral DNA then disappeared again 1 month later. It is possible that DIHS induced a pan-pancreatopathy with irreversible β-cell injury via HHV-6 reactivation. Therefore, DIHS associated with HHV-6 reactivation may be one of the causes of non-autoimmune (idiopathic) fulminant type 1 diabetes mellitus.

Myocarditis associated with adverse drug reaction has been referred to as hypersensitivity myocarditis [26], which includes DIHS-associated myocarditis. However, no previous publication has demonstrated an

association between HHV-6 reactivation and myocarditis in DIHS. Recently, Sekiguchi et al. reported a marked reactivation of HHV-6 and CMV in one case of myocarditis associated with DIHS [11], suggesting a role for HHV-6 reactivation. It should be noted that myocardial infarction was associated with allopurinol-induced DIHS in two previous cases [27]. Other complications of DIHS potentially related to HHV-6 reactivation include myopathy [28] and transient hypothyroidism [29]. At present, no reports examining the involvement of HHV-6 reactivation in these complications are available. However, the accumulation of detailed case reports involving HHV-6 examination may soon provide answers.

Studies on the role of HHV-6 reactivation in DIHS complications such as encephalitis, diabetes mellitus, and myocarditis will provide essential insight into the pathogenesis of these life-threatening conditions.

In our recent study, the mortality rate for DIHS was 8% (5 out of 62 cases; Table 10.2) [17], which was higher than the mortality rate for Stevens–Johnson syndrome in Japan. Thus, DIHS should be recognized a significant, life-threatening dermatological disease.

10.9 Treatment of DIHS

Systemic corticosteroids (0.5–1.0 mg kg^{-1}) have been widely advocated for the treatment of DIHS [4]. However, the involvement of HHV-6 infection in DIHS pathogenesis has raised new questions regarding the validity of corticosteroid treatment. Some patients with DIHS recover without systemic corticosteroids. However, these patients tend to be those with less severe symptoms. In contrast, severe cases of DIHS are life-threatening, and require high doses of systemic corticosteroids (more than 1.0 mg kg^{-1}) or steroid-pulse therapy. In addition, unnecessarily prolonged use of systemic corticosteroids sometimes results in an unfavorable prognosis. In the case of severe DIHS, the use of combined systemic corticosteroids and high-dose intravenous immunoglobulin remains controversial and requires further investigation. Antiviral drugs for HHV-6 are not used in the treatment of DIHS. However, in severe cases of DIHS that are complicated by prolonged CMV infection, antiviral drugs such as gancyclovir or foscarnet sodium hydrate should be administered [19].

A few comments

Professor Koji Hashimoto and coworkers have largely contributed to major advances on DRESS/DIHS, especially by demonstrating in this condition the frequent reactivation of herpes viruses, principally HHV6. Using serology they found indirect evidence of reactivation in 62% of cases and using PCR on plasma or serum they found direct evidence of viremia in 40%. They also observed a strong statistical correlation between the severity and duration of the disease and virus activation. Correlation does not equal causality anyhow, and further studies are certainly needed to elucidate the complex relationship between an immune reaction to drugs, activation of the immune system, reactivation of herpes viruses that occurs 1 or 2 weeks AFTER the onset of the reaction and development of auto-immunity many weeks later. ALL these features seem rather specific of DRESS/DIHS within severe drug reactions, but better evaluation is still required. Waiting for such advances in understanding, I consider premature to consider a proof of virus activation as a *sine qua non* criteria for a diagnosis of DRESS/DIHS. In the best studied Japanese series, the sensitivity of HHV6 detection was no more than 62%, and even less with the 'gold standard' of PCR on serum. In a complex and not yet fully understood disease like DRESS/DHIS, it is probably more prudent to define cases on the basis of a constellation of clinical and biological criteria, without excluding the diagnosis or labelling it as 'atypical' when only one is missing. Considering positive anti-DNA antibodies as mandatory for a diagnosis of systemic lupus erythematosus would have resulted in a restrictive conception of SLE.

I totally agree with the list of diagnosis criteria, proposed by the authors:

1. Drug-induced immunologic phenomenon
2. Later onset than for other drug reactions
3. Longer duration than common 'drug rashes'
4. Multi-organ involvement (liver, kidney, lung….)
5. Lymphocyte activation (node enlargement, lymphocytosis, atypical lymphocytes)
6. Eosinophilia
7. Frequent virus reactivation

We should now explore together how many of these criteria are needed for a definite, probable, possible diagnosis and better define what is called 'late onset', 'long duration', or 'organ involvement'. Such a scoring

system is at present evaluated on cases collected by the RegiSCAR group in several European countries.
J.C.Roujeau

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Acute Generalized Exanthematous Pustulosis

11

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Core Messages

- AGEP, mostly caused by drugs, is characterized by the acute occurrence of numerous sterile pinhead-sized pustules on an oedematous erythema accompanied by fever and leucocytosis.
- The drugs with the highest risk to cause AGEP are antibacterial agents like ampicillin/amoxicillin, and quinolones, pristinamycin, anti-infective sulfonamides, the antimycotic drug terbinafine, (hydroxy)chloroquine, and diltiazem, but a large number of other drugs as well as infections have been reported as triggers.
- AGEP is an acute and sometimes severe reaction, but resolves quickly and without special treatment when the culprit drug is withdrawn.

11.1 Introduction

The justification for addressing acute generalized exanthematous pustulosis (AGEP) in the context of life-threatening skin diseases is not so much due to a high mortality rate, but rather explained by three circumstances. Firstly, AGEP often has a quite drastic clinical appearance which, by its acute evolution, suggests a very severe disease. Secondly, because of misinterpretations or misclassifications as well as real overlap-cases, AGEP is often positioned in the vicinity of much more severe diseases like Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Only as a third point, AGEP can be the cause of death in patients with poor general condition due to old age or underlying disease.

Although the term AGEP is now more and more recognized and used for a characteristic pustular reaction pattern mostly due to drug intolerance, the nomenclature in the literature has been very heterogeneous and even misleading over the years. Already in Baker and Ryan's report of 104 cases of pustular psoriasis, five patients showed a very acute and quickly resolving pustular eruption; no previous history of psoriasis and drugs and/or infections had been suspected as trigger. The authors used the term *exanthematic pustular psoriasis* for this particular subgroup of patients. Other names found in the literature for similar cases were *pustular drug rash* [1] or *toxic pustuloderma* [2] and often patients sharing similar clinical features were interpreted as suffering from special variants of other pustular diseases. The term *pustuloses exanthématique aiguës généralisés (PEAG)* was introduced to the French literature by Beylot et al. [3]. Adopted under the acronym AGEP *(acute generalized exanthematous pustulosis)* in the English literature, the term is now widely used for this type of reaction, although other denominations can still be found. In this context — to prevent confusion — it is important to emphasize that the term *pustulosis acuta generalisata* [4–6] describes a poststreptococcal disease arising mainly in children, which is an entity totally different from AGEP.

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11.2 Clinical Features

The clinical key feature of AGEP [7] is the appearance of at least dozens, but often hundreds to thousands of small, pinhead-sized, sterile pustules (Fig. 11.1). These pustules arise quite rapidly on a diffuse, sometimes oedematous erythema (Fig. 11.2) which may be accompanied by an itching or burning sensation. In typical cases, these skin manifestations are accentuated in the main folds of the body (inguinal, axillar, and submammary areas), but cases with a more irregular distribution of pustule-covered patches can also be observed. Often patients also show an oedematous erythema of the face. Other cutaneous lesions like purpura (especially on the legs), Stevens–Johnson-syndrome-like 'atypical targets', blisters and vesicles may be present, but are not characteristic of AGEP. Mucous membrane involvement is the exception (approximately 20% of the cases) and, if present, is mild and remains limited to one location (mostly oral). Fever above 38°C and leucocytosis (neutrophil counts above $7 \times 10^9 l^{-1}$ and sometimes a mild eosinophilia) are often present in the acute phase of the disease [8]. Internal organ involvement is not a common feature in AGEP, although a lymphadenopathy [9], a slightly reduced creatinine clearance or a mild elevation of liver enzymes may be observed. After withdrawal of the causative agent, skin lesions resolve within a few days and pustules are usually followed by a characteristic post-pustular desquamation. Slight post-inflammatory pigment chances may be visible for a variable period of time, but usually AGEP heals without residual changes.

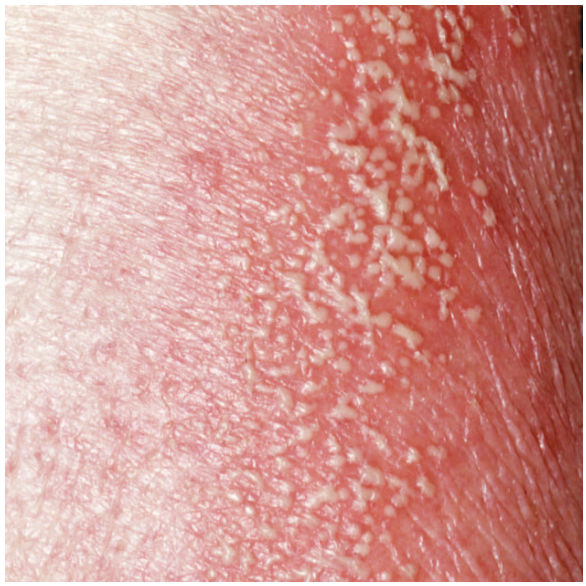

Fig. 11.1 Multiple pinhead-sized pustules with partial confluence

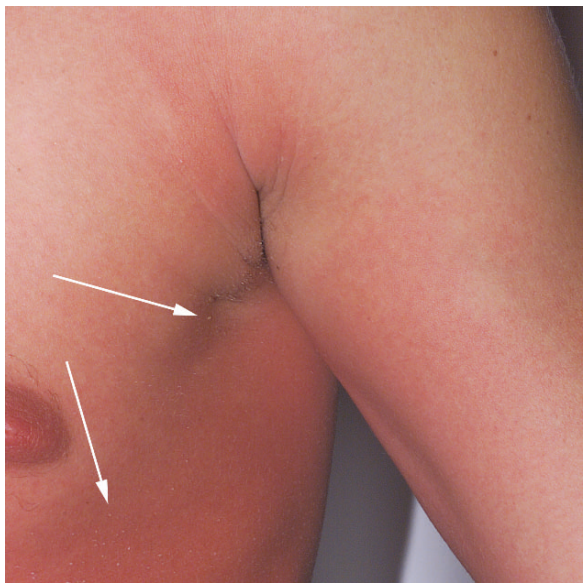

Fig. 11.2 Barely visible small pustules (*arrows*) on a diffuse erythema accentuated in the axilla

11.3 Histopathology

Due to the usually short duration of the disease, results of histological examination are often only available after the patient's condition has already improved. Yet it is advisable to perform biopsies for diagnosis, as they might prove helpful in cases where clinical features are not clear or where the course raises doubts on the diagnosis, and in clinical settings where the results of emergency biopsies can be obtained quickly.

Spongiform sub-corneal and/or intra-epidermal pustules are the histological key feature of AGEP. Some single-cell necrosis of keratinocytes may be present. The papillary dermis often shows a marked oedema. Other changes in the dermis show neutrophilic infiltrates, mostly peri-vascular, a variable number of eosinophils [10] and sometimes extravasation of erythrocytes.

11.4 Differential Diagnoses

11.4.1 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN)

Confluence of pustules may lead to larger blisters and erosions which may resemble lesions of SJS/TEN and mimic a positive Nikolski sign [11]. In addition, lesions similar to atypical targets can be present. Both may lead to misclassification of the reaction and suggest that it belongs to the SJS/TEN spectrum. This may even be complicated by the fact that cases with clear features of both reaction types, AGEP and SJS/TEN [12], have been exceptionally observed (clinically as well as histologically). In typical cases, though, detachment of the epidermis is more superficial in AGEP than in SJS/TEN and, as mentioned before, mucous membrane involvement is far less pronounced in AGEP and histopathology differs significantly, showing full-thickness necrosis and a rather sparse inflammatory infiltrate in TEN.

11.4.2 Generalized Pustular Psoriasis (Von Zumbusch Type)

An ongoing matter of debate is the differentiation of AGEP from acute generalized pustular psoriasis of the von Zumbusch type. In fact, clinical and histological features can be very similar and in some cases undistinguishable, especially when judgment is based only on a momentary impression of the clinical picture or on histology. Yet a number of differences exist that, in our opinion, seem to justify regarding the two diseases as distinct entities, the main points being the dynamic and course of the reaction and the association with drug intake. Drug history often reveals the administration of a drug as a probable trigger, and the duration of pustules and fever is usually shorter in AGEP, with a spontaneous resolution as soon as the culprit drug is withdrawn. Also (pustular) psoriasis may be triggered by drugs, but the spectrum (mainly beta-blockers or lithium) clearly differs from the one that usually causes AGEP. A personal or family history of psoriasis and arthritis has been demonstrated to be less common in AGEP, and would more speak in favor of psoriasis [13].

Histopathology of AGEP and acute generalized psoriasis may be indistinguishable. Oedema of the papillary dermis, erythrocyte extravasation, more eosinophils and necrotic keratinocytes may be more suggestive for AGEP, while a higher epidermal mitotic rate or psoriatic changes like acanthosis and papillomatosis [14] are more likely to be seen in generalized psoriasis. But until a systematic comparison of histological features from both patient groups has been performed, there is no reliable way of differentiating both diseases by means of histology alone.

11.4.3 Subcorneal Pustular Dermatosis (Sneddon–Wilkinson)

Sneddon–Wilkinson disease evolves much less acutely than AGEP, and characteristically shows larger flaccid blisters with hypopyon formation, which are often arranged in a circinate pattern.

11.4.4 Drug Hypersensitivity Syndrome

In drug hypersensitivity syndrome, also referred to as DRESS (an acronym for drug rash with eosinophilia and systemic symptoms) or DIHS (drug-induced hypersensitivity syndrome), papulo-vesicles and/or papulo-pustules may also be present, but pustules are rather the exception. In these systemic reactions, patients suffer from fever and lymphadenopathy, show eosinophilia and atypical lymphocytes and an often severe involvement of internal organs, especially hepatitis, nephritis, pneumonitis myocarditis and others. The severity of the disease and its often prolonged course (probably due to viral reactivation), even after withdrawal of the causative agent, usually make it easy to discriminate it from AGEP.

11.4.5 Pustular Vasculitis

Palpable purpura in leucocytoclastic vasculitis may also exhibit bullous or pustular lesions. Many small pustules that — in contrast to AGEP — are mainly located on the dorsum of the hands have been described

in a special form of leucocytoclastic vasculitis which might also be induced by drugs. In these cases, the diagnosis can be confirmed by histology which reveals pronounced changes of leucocytoclastic vasculitis [15, 16]. Semantic confusion might be caused by the term *pustulosis acuta generalisata* [4–6] for a poststreptococcal form of leucocytoclastic vasculitis. Another source of ambiguity might be related to the fact that some vasculitic changes may also be seen in the histological samples of AGEP patients.

11.4.6 Others

Many other cutaneous diseases may present pustules to a variable extent. Candida infection of the intertriginous areas can easily be confirmed by detection of hyphae. Differentiation from AGEP usually does not cause problems in all follicular eruptions like bacterial folliculitis, furunculosis, acne and acneiform pustules, but also localized pustular contact dermatitis, dermatophyte infections, impetigo, impetiginized eczema, varicella, pyoderma vegetans, Kaposi's varicelliform eruption, Sweet's syndrome, pemphigus foliaceus and other autoimmune bullous disorders (such as IgA pemphigus, which might have some resemblances histologically), infantile chronic acropustulosis, or pustules in migratory necrolytic eruption of glucagonoma, bowel bypass syndrome, or Behcet's disease. Also in cases with confluent pustules and erosions, differentiation from staphylococcal scalded skin syndrome (SSSS) does not represent a diagnostic challenge. In cases where pustules are few or have already ruptured, sometimes leaving large areas of desquamation, the differentiation from erythroderma or exfoliative dermatitis can be difficult.

11.5 Epidemiology

Because of the confusion in the nomenclature and the low level of spontaneous reporting of adverse drug reactions in many countries, only very vague estimates of the incidence of AGEP can be made. In addition, the transient nature of the eruptions often leads to the fact that some patients are not hospitalized and sometimes not even seen by a doctor. From the observations in a population that we have studied in recent years, we estimate the incidence rate of AGEP to range between one and five cases per million inhabitants per year, but as mentioned, these numbers are subject to reporting bias and are only very crude estimates. There seems to be no age predisposition, and some publications suggest that women are more often affected than men, especially in conjunction with paracetamol (acetaminophen) [17], and pregnancy may play a role [18, 19]. Bernhard et al. published a study in which HLA B51, DR11 and DQ3 were found to be more frequent than in the average population [20].

11.6 Etiology and Pathogenesis

The vast majority of AGEP cases is drug-induced, although for example viral infections can also trigger the disease. Literature provides a long list of single case reports and case series in which a large number of different drugs are documented as potential triggers. Giving all references would go beyond the scope of this textbook, but reports on the following anti-infective agents have been frequently reported: β-lactam antibiotics, macrolides, cephalosporins, quinolones, tertracyclins; other antibiotics (chloramphenicol, imipenem, gentamycin, isoniazid, metronidazol, trimethoprim–sulfamethoxazole, vancomycin); antimycotics (terbinafine, griseofulvin, itraconazol, nystatin, amphotericin B), other antiinfectives ((hydroxy-)chloroquine, diaphenylsulfone, nifuroxazide, pyrimethamine, protease inhibitors. Other drugs that have been described as causative agents are (in alphabetical order): azathioprine, acetylsalicylic acid, allopurinol, amoxapine, buphenine, bufexamac, calcium channel blockers, carbamazepine, carbimazole, carbutamide, high-dose chemotherapy, chromium picolinate, cimetidine, clemastine, clobazam, clozapine, contrast media (non-ionic), corticosteroids, deltaparin, dexamethasone, disulfiram, enalapril, eprazinon, fenoterol, furosemide, gefitinib, imantinib, kerorin, lansoprazole, morphine, nadoxolol, nifedipine, nimesulide, meladinine, mercury, olanzapine, paracetamol, piperazine ethionamate, pneumococcal vaccine, propafenone, prostaglandine E1, pseudoephedrine, quinidine sulbutiamine, sulfasalazine, thalidomide, as well as herbal medications (ginko biloba), topical agents, spider bites or PUVA. It has to be mentioned that this list is neither complete nor definite, as new reports are constantly being

published. A synopsis of these reports and the result of systematic studies make it possible to give a better estimate on which drugs have a higher risk of inducing AGEP [13, 21]: strongly associated drugs seem to be antibacterial agents like ampicillin/amoxicillin, and quinolones, pristinamycin (a macrolide not widely marketed), anti-infective sulfonamides, the antimycotic drug terbinafine, (hydroxy)chloroquine, and diltiazem.

These results show that the spectrum of drugs that often acts as trigger for AGEP differs from the compounds that are the usual suspects for other skin reactions like SJS/TEN. Classical triggers for the latter, like allopurinol, antiepileptic drugs, or nevirapine do not seem to play a prominent role in AGEP, while terbinafine, diltiazem and pristinamycin are not of major importance in SJS/TEN. Only antibiotic agents are often associated with both types of reaction.

A number of cases in which infections are the suspected trigger for AGEP can be found in the literature [8, 22–27]. Although in many cases the infectious trigger is well-documented and the sole probable reason for the reaction, AGEP caused by infectious agents seems to be an exception. In this context one must be aware that confounding by indication (drug given for an underlying infection or already for the first symptoms of the reaction) makes causality assessment for drugs particularly difficult. Yet present data suggests that infections — although possible — are not very common in triggering AGEP.

It is obvious that neutrophils play an important role in AGEP and the role of drug specific (CD4+) T-cells that produce neutrophil-attracting factors like interleukin-8 (IL-8) and cytotoxic (CD8+) T-cells has been extensively investigated [28–32]. Yet a number of questions in the pathomechanism of AGEP remain to be answered. One of them arises from the observation that there seem to be two timing patterns for the reaction. One is similar to that of other drug rashes, i.e. the reaction occurs in a time frame between 1 and 2 weeks. But for a large number of cases (especially those triggered by antibiotics), the interval between first intake and cutaneous reaction can be as short as a few hours. This could be explained by prior sensitization and rechallenge to the specific drug, but in the majority of cases evidence for such a prior exposure cannot be found [13]. Another field of interest for future research is the genetic predisposition that might lead patients to react in a ‘neutrophilic direction’.

11.7 Treatment

In those cases where AGEP is a drug reaction, the main therapeutic measure is to detect and withdraw the causative agent. The detection of the culprit drug, though, may be complicated by two facts. First, patients might have taken a large number of drugs. Second, drugs that have been started after the onset of the reaction could only be ruled out if the exact time point of the onset of the reaction was clear. As this often isn’t the case, sometimes drugs that have been given for unspecific first symptoms of the reaction cannot simply be deleted from the list of suspected drugs. Only a very thorough drug history, including timing and duration of drug intake and knowledge of how high the risk of causing an AGEP is for different drugs, may make it possible to confine the list of drugs taken to one or a few probable triggers.

In most cases, withdrawal of the causative agent leads to a very rapid resolution of the lesions. Within a few days, active inflammatory signs (redness and oedema) resolve, and at the site of pustules a characteristic post-pustular desquamation may persist for a few more days. Nevertheless, topical and systemic steroids are often administered. There is no data that prove that this has any beneficial effect, but as long as systemic steroids are only given for a short period of time and potential side effects are kept in mind, this therapeutic approach seems acceptable. The lack of evidence, though, does not allow for a general recommendation other than withdrawing all potentially culprit drugs and monitoring and symptomatically stabilizing the patient’s general condition (e.g. with antipyretics if they are not the suspected trigger).

The causality assessment mentioned above is not only necessary in the acute phase to withdraw the culprit agent. Reexposure to the drug should be avoided to prevent patients from experiencing another episode of AGEP [33]. In contrast to other drug reactions like SJS/TEN, patch testing with the culprit drug often leads to positive results [34, 35]. Morphologically, the local reaction resembles AGEP by displaying multiple small sterile pustules on the test site. One has to be aware, though, that strong, even systemic reactions can occur [36]. Although a negative patch test does not mean that a substance was not the cause for the reaction, positive patch testing is especially helpful for identifying the culprit agent where two or more drugs are under suspicion of having caused the reaction.

Drug-specific in vitro tests have been reported, but are not being used as standardized diagnostic tools so far. Macrophage migration inhibition factor (MIF) test, mast-cell degranulation (MCD) test [37, 38], interferon gamma release tests [39] and lymphocyte proliferation responses [40] have been investigated. For the latter, it has been demonstrated that it correlated with patch tests in two patients [41]. Yet thorough drug history and patch testing remain — up to now — the main pillars of determining the culprit drug.

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Autoimmune Bullous Diseases

12

Pascal Joly

Core Messages

- Life-threatening autoimmune blistering disorders include bullous pemphigoid and the different subtypes of pemphigus: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus.
- Major extent of skin and mucosal lesions results in the failure of main skin functions.
- Severe infections, including septicaemia and pneumonia and cardiovascular disorders, are the major cause of death in these patients.
- The aim of treatment is to stop the production of autoantibodies. Corticosteroids and immunosuppressants are widely used in the treatment of autoimmune blistering disorders.
- New biologic agents such as rituximab are currently proposed for the treatment of the most severe, life-threatening types of these disorders.

12.1 Introduction

Autoimmune bullous diseases (AIBD) are a group of autoimmune disorders of the skin characterized by the production of auto-antibodies directed against adhesion proteins of the desmosomes (pemphigus), or the hemi-desmosomes (AIBD of the dermal–epidermal junction (DEJ) [1, 2]. Most of these auto-antibodies are pathogenic, as demonstrated in various animal models [3]. Binding of auto-antibodies to their target antigens leads to the disruption of intra-epidermal or dermal–epidermal junctions [4]. The common consequence is the formation of cutaneous and/or mucosal blisters evolving to erosions. Extent of erosive areas can lead to failure of main skin functions, in particular defence against infections. Treatment of AIBD aims at stopping the production of pathogenic antibodies by B-lymphocytes and plasmocytes, using corticosteroids, immuno-suppressants and more recently, biologics such as anti-CD20 monoclonal antibodies: rituximab or intravenous immune globulins [5, 6].

Pemphigus and bullous pemphigoid (BP) are potentially life-threatening AIBD, whereas in cicatricial pemphigoid and epidermolysis bullosa acquisita, severe functional impairment may occur in some cases.

12.2 Bullous Pemphigoid

12.2.1 Incidence and Pathogenesis

Bullous pemphigoid is the most frequent type of AIBD. The incidence rate of BP ranges between seven and 22 cases per million inhabitants per year [7–9]. It is six to 20 times more frequent than pemphigus in Western Europe. The disease mainly affects the elderly, with mean age being between 80 and 83 years, which is an important characteristic in the management of BP [9–11].

BP patients develop circulating and tissue-bound antibodies that are directed against two proteins of the hemidesmosomes, a key structural component of the DEJ. The target of these antibodies are proteins of 230 and 180 kD in length, and are termed bullous pemphigoid antigen 1 (BPAG1), an intracellular protein of the

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hemidesmosome, and bullous pemphigoid antigen 2 (BPAG2), a transmembrane protein, respectively [1, 12]. Anti-BPAG2 antibodies react with the first extra cellular domain of the molecule, and appear to be more pathogenic than anti-BPAG1 antibodies. Following antibody binding to these proteins, the Fc portion of the antibody activates both the classical and alternative pathway of complement. Poly-morphonuclear cells recruited to the area release inflammatory mediators, ultimely leading to the occurrence of clinical features of BP [13].

12.2.2 Clinical Features and Diagnosis

Typical clinical features of BP include pruritus, large, tense cutaneous blisters, urticarial plaques, vesicles, and erosive areas located on the trunk, abdomen, thighs and upper limbs (Fig. 12.1). Numerous atypical types have been described, including mucosal involvement, which is present in about 20% of patients. If cutaneous erosions become widespread, loss of the protective functions of the epidermis can occur, and patients may develop infections and fluid imbalance.

The diagnosis of BP is easily made by combining clinical criteria and routine histological examination and direct immuno-fluorescence testing of a skin biopsy [14]. Histological features include a subepidermal blister with an infiltration of polymorphonuclear eosinophils in the superficial dermis and/or, more suggestively, along the DEJ [15] (Fig. 12.2). Direct immuno-fluorescence shows linear deposits of IgG and C3 along the DEJ. Antibodies directed against the DEJ are detected in 70% of patients' serum by indirect immuno-fluorescence. In some atypical cases, indirect immuno-fluorescence testing on 1 mol l^{-1} NaCl-split normal skin may be a useful test for discriminating between BP, cicatricial pemphigoid and epidermolysis bullosa acquisita. BP antibodies bind to the epidermal side of salt-split skin, whereas epidermolysis bullosa acquisita antibodies bind to the dermal side [16, 17]. Cicatricial sera bind either to the epidermal or dermal side of salt-split skin, depending on the antibodies present. Anti-BPAG1 and anti-BPAG2 antibodies can also be detected in the serum of patients using immunoblot analysis on human epidermal extracts, or more recently, ELISA assays [14].

12.2.3 Prognosis

The prognosis of BP is severe, since the 1-year mortality rate reported in the different European series,

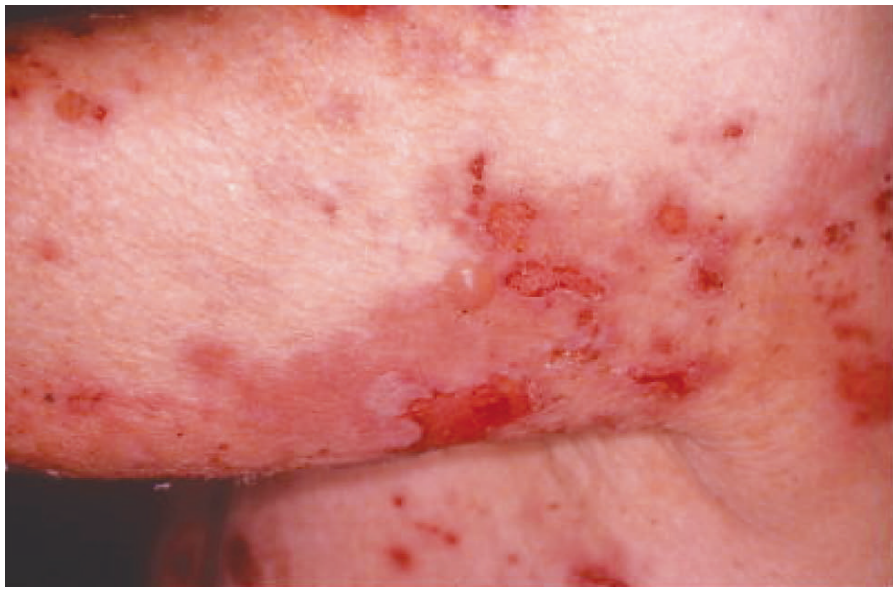

Fig. 12.1 Clinical features of a patient with bullous pemphigoid. Tenseblisters and erosions associated with urticarial lesions

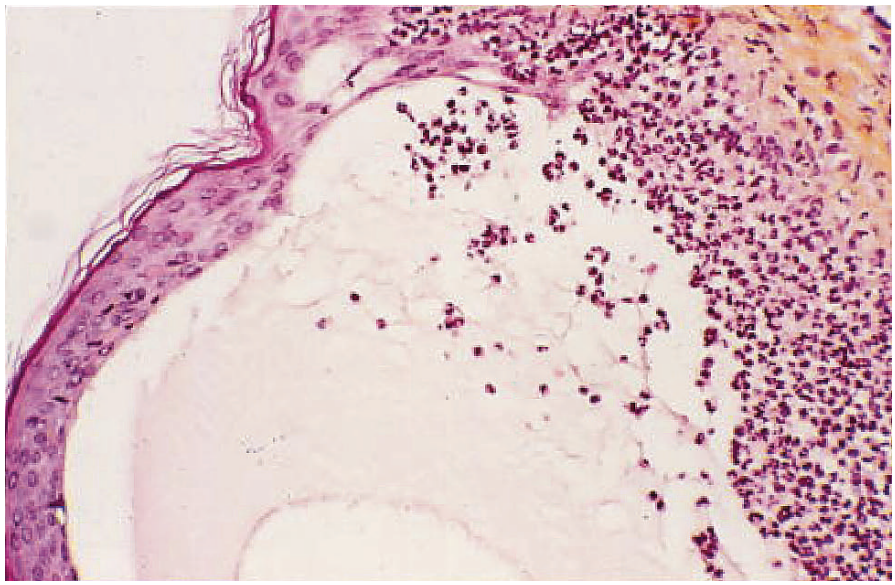

Fig. 12.2 Histological picture of bullous pemphigoid showing a subepidermal blister containing poly-morphonuclear eosinophils

and in a recent US study, ranges between 25% and 40% [10, 18, 19].

Main causes of death are severe infections including septicaemia and pneumonia, cardiovascular causes, especially congestive cardiac failure and myocardial infarction, and neurological diseases including stroke and the evolution of Alzheimer disease [11, 20]. A randomized control multi-centre study performed in France, clearly demonstrated that high doses of systemic corticosteroids, i.e., prednisone, 1 mg kg^{-1} per day, were responsible for a higher level of mortality, since the 1-year mortality rate of patients treated with high dose of corticosteroids was 40%, as compared with 25% in patients who were treated with topical super potent corticosteroids or low doses of oral corticosteroids, prednisone, 0.5 mg kg^{-1} per day [10]. Indeed, most of the deaths were either a direct consequence of corticosteroid side effects, or at least were favoured by the high doses of corticosteroids used. It should be noted that this prospective randomized study confirmed two retrospective French and German studies, which previously suggested that high doses of oral corticosteroids were a major deleterious prognostic factor in BP patients [19, 21]. A recent analysis of the prognostic factors of BP patients showed that the main deleterious predictors were demographic factors (i.e., older age, age and female sex), associated medical conditions (i.e., cardiac insufficiency, history of stroke, and dementia), and low Karnofsky score, which is a measure of the patient's general condition [11]. Interestingly, no factor directly related to BP, in particular extent of cutaneous lesions, was shown to be related to patients' prognosis. Based on multivariate analysis, only older age and low Karnofsky score appeared independently predictive of death. Indeed, from the Cox model including these two predictors, the predicted 1-year survival rates were 90% for patients younger than 83 years in rather good general condition, whereas it was only 38% for patients older than 83 years in poor general condition. These predictors are easy to use, and can facilitate the management of BP patients. In particular, these findings should prompt clinicians to be cautious in the treatment of BP patients, especially the older patients.

12.2.4 Treatment

Systemic corticosteroids have been considered the main treatment of BP for more than 40 years because of the vast body of clinical experience with these agents [22]. The usually recommended dosage of oral corticosteroid for the treatment of BP was 0.75–1 mg per kg-body weight per day of prednisone or equivalent. When pooled, the results of the few controlled

trials comparing oral corticosteroids alone to oral corticosteroids plus immunosuppressant suggested that the rate of disease control was 0% with 0.3 mg kg^{-1} per day, 60–80% with 1 mg kg^{-1} and 90% with 1.5 mg kg^{-1} per day of prednisone or equivalent [23, 24]. Based on the above-mentioned results, the most commonly used dosage was 0.75–1 mg kg^{-1} per day. Unfortunately, there is no randomized or even open series which studied the effect of 0.5 mg kg^{-1} per day of prednisone on patients with extensive BP. The only study available in the literature, which used this dosage for the treatment of patients with moderate BP (less than ten new blisters per day) demonstrated a good efficacy, since control of BP by day 21 was achieved in 95% of patients [10]. Our experience is that, unfortunately, medium doses of oral corticosteroids are only occasionally effective in controlling patients with extensive BP.

Topical corticosteroids were first proposed by Westerhof in 1989 [25]. Subsequently, uncontrolled trials confirmed the efficacy of this treatment on limited forms of BP. Two large randomized controlled trials performed in France on more than 700 patients have clearly demonstrated the extremely high efficacy of medium/high doses of super potent topical corticosteroids, since a control of disseminated BP by day 21 was achieved in 97–100% of patients, depending on the initial dose of clobetasol propionate used, 30 g or 40 g per day. In addition to providing a better control of BP than medium/high doses of oral corticosteroids, topical corticosteroid treatment was responsible for a lower number of severe adverse effects (29% vs 54%, $p = 0.006$), and allowed a longer 1-year survival of patients, when compared with high doses of oral corticosteroids (76% vs 58%, $p = 0.009$) [10]. Whereas topical corticosteroids have become the first line of treatment of BP, widely performed in Europe, the practicality of this approach is considered difficult in the US, mainly because of differences in the Health Care organization. The recent demonstration of the efficacy of shorter-duration topical treatment for BP will perhaps improve the acceptance of this treatment.

Many efforts have been devoted to finding corticosteroid-sparing agents for the treatment of BP. Uncontrolled studies have suggested the usefulness of immunosuppressive drugs, including azathioprine, cyclosporine, mycophenolate mofetil, and more recently, methotrexate [23, 26]. Unfortunately, the only controlled study published to date failed to demonstrate any benefit from the addition of azathioprine to corticosteroid therapy [23].

Moreover, there was a higher incidence of treatment side-effects in patients receiving the combined treatment, as compared to those treated with corticosteroid alone, mainly infections sometimes leading to death. There is preliminary evidence that methotrexate could be useful in patients with BP [27]. First, relatively low doses of methotrexate (up to 12.5 mg per week) may be expective to control lesions in most BP patients. The use of these low doses could limit treatment side-effects, especially bone-marrow suppression. Second, methotrexate seems to have anti-inflammatory properties that are greater than the immunosuppressive properties, making infections perhaps less likely to occur when compared to 'traditional' immunosuppressants. Third, the long-term side effect of liver fibrosis does not seem to be a problem in these elderly patients. Furthermore, methotrexate is inexpensive. However, methotrexate has to be compared with other treatments of BP in a randomized study, in order to robustly evaluate its interest in the treatment of BP.

12.3 Pemphigus

12.3.1 Incidence and Pathogenesis

Pemphigus is a rare, chronic, potentially life-threatening, autoimmune vesiculobullous disorder. Three subtypes have been described; (1) pemphigus vulgaris (PV), which is characterized by the occurrence of mucosal and occasional skin lesions, (2) pemphigus foliaceus (PF), where patients only have cutaneous blisters, and (3) a more recently described type, called paraneoplastic pemphigus (PNP) because of its association with various neoplasms [28].

The incidence of PV is variable. Estimates range from 0.076 per 100,000 in Finland to 1.61 per 100,000 in Jerusalem. The incidence is approximately one case per million inhabitants per year in Europe and in the US. However, endemic types of pemphigus exist in some areas in the world, namely in Brazil and some other South American countries (Fogo selvagem), as well as in North Africa (Tunisian endemic pemphigus) [29]. In these endemic areas, the incidence of pemphigus reaches 20–40 cases per million per year. Interestingly, these endemic types of pemphigus are PF, which occur both in South America and North Africa. The disease mainly

affects adult patients (mean age of patients is about 50 years old), although children and even neonates can be affected.

Pemphigus is characterized by the production of autoantibodies directed against adhesion proteins of the desmosomes which are located on keratinocyte plasma membrane. Binding of autoantibodies to desmosome structures results in the loss of adhesion between keratinocytes and the formation of an intra-epidermal blister. Two major proteins belonging to the cadherin family are targeted by auto-antibodies in pemphigus: desmoglein 1 (Dsg1), which is located in the upper epidermis of the skin, and desmoglein 3 (Dsg3), which is mainly located in mucosa and in the basal portion of the epidermis [30]. Anti-Dsg3antibodies are therefore responsible for mucosal lesions of patients with PV, whereas anti-Dsg1 antibodies induce skin lesions in patients with PF, and in PV patients when they are associated to anti-Dsg3 antibodies. Both types of antibodies are pathogenic, as demonstrated in animal models [31]. In addition, serum from patients with PNP contains antibodies directed against a complex of proteins of the desmosomal plaques, which belong to the plakin family. Plakin proteins recognized by PNP sera are desmoplakins 1–2 (250–210 Kd), envoplakin (210 Kd), periplakin (190 Kd), and the BPAG1 protein (230 Kd) [28].

12.3.2 Clinical Features and Diagnosis

Patients with PV usually complain of dysphagia, which is due to painful oral erosion. In the most severe forms, patients can lose weight, and their general condition may be altered. Other mucosa can occasionally be involved, including genital, anal and pharyngolaryngeal mucosa. Additionally, some patients have cutaneous lesions, which consist of superficial blisters without pruritus located on the scalp, folds, and trunk. These lesions rapidly evolve into limited or large erosive areas, which can be responsible for fluid imbalance and septicaemia (Fig. 12.3). PF patients have crusted or exfoliative lesions, mainly located on the head, back and the anterior part of the trunk. Also, PF patients with the most severe form can present with an exfoliative erythroderma. Patients with PNP can have clinical features of both PV, BP, erythema multiforme, drug-induced-like lesions and sometimes lichenoid lesions, with oral and genital erosions, urticarial bullous lesions, target-like lesions or areas of epidermal necrosis [28, 32]. Additionally, some patients have conjunctival involvement. This particular type of pemphigus is characterized by its association with various neoplasms, in particular lymphoproliferative disorders, including chronic lymphoid leukaemia, dysglobulinemia and Hodgkin and non-Hodgkin

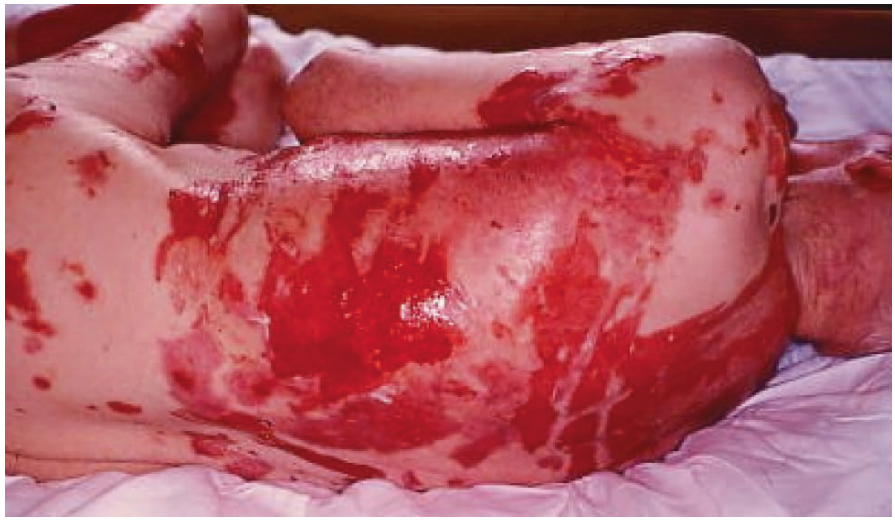

Fig. 12.3 Large erosive areas in a patient with pemphigoid vulgaris

lymphoma. Thymoma, carcinoma, sarcoma and Castelman's disease are less frequently associated.

The diagnosis of the different types of pemphigus is made by a combination of clinical, histological and immunological criteria [33]. Histological analysis shows the epidermal detachment called acantholysis, responsible for the formation of an intra-epidermal blister. The level of the acantholysis depends on the subtype of pemphigus: suprabasal in PV and in the upper epidermis in PF. Other histological features can be observed on biopsy from PNP patients, in addition to acantholysis, including keratinocyte necrosis, subepidermal blister, lichenoid infiltrate of the superficial dermis and interface dermatosis. Depending on the predominant histological features, biopsy from PNP patients can be initially suggestive of PV, BP, erythema-multiforme, drug-induced reaction or lichen planus. Direct immunofluorescence shows IgG and C3 deposits on the epithelial cell surface (ECS), which predominate on the basal cell layers in PV biopsies, whereas the whole epidermis is labelled in PF (Fig. 12.4). Additionally, biopsies from PNP patients can exhibit granular deposits of C3 and sometimes IgG on the DEJ, showing a dual ECS + DEJ labelling. Anti-ECS antibodies can be detected in patient's serum using indirect immunofluorescence on various substrates, including normal human skin and monkey oesophagus. Titres of circulating anti-ECS antibodies depend on disease severity, and are a useful tool for the management of patients under treatment. In addition, PNP sera exhibit a dual (ECS + DEJ) labelling of rat bladder, which is not observed with PV and PF sera. Circulating anti-Dsg1 and anti-Dsg3 antibodies can also be detected in patients' serum using commercially available ELISA assays, and immunoblot analysis on human epidermal extracts [34]. In addition, this latter technique allows the detection of anti-plakin antibodies, especially anti-envoplakin and anti-periplakin antibodies. According to the compensation theory, PF patients only produce anti-Dsg1 antibodies, PV patients with only mucosal lesions produce anti-Dsg3 antibodies, whereas PV patients with cutaneous and mucosal lesions have both anti-Dsg1 and anti-Dsg3 antibodies [35].

12.3.3 Prognosis

The use of systemic corticosteroids and a better management of patients have improved the prognosis of PV and PF patients, since the mortality rate has dramatically decreased, from 75% before corticosteroids to 5–10%. Currently, most deaths are related to severe infections which occurred either during the acute phase of the treatment in patients with recalcitrant types of pemphigus who require very high doses of corticosteroids, that are often associated with immuno-suppressants to obtain epithelialisation, or in patients with relapsing types of pemphigus. Indeed, these latter patients who experienced numerous relapses should have their doses of corticosteroids increased, leading to high cumu-

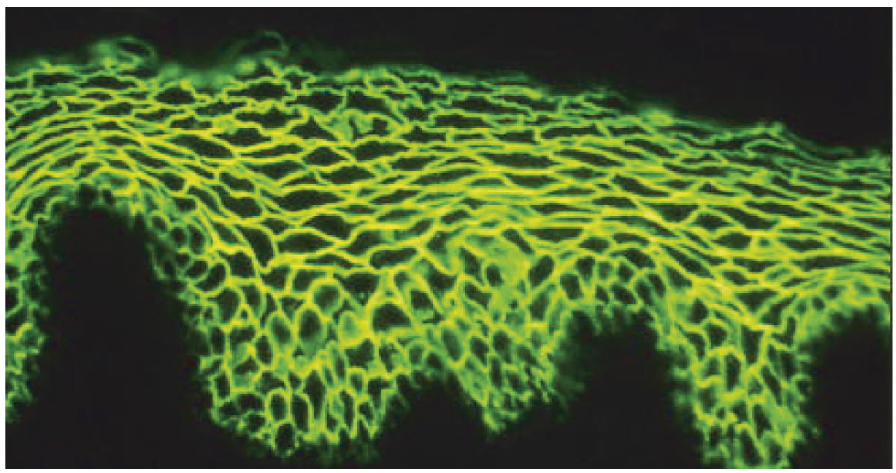

Fig. 12.4 Direct immunofluorescence in a patient with pemphigus vulgaris, showing IgG deposits on keratinocyte membrane

lative corticosteroid doses. The prognosis of PNP patients remains extremely severe, with a mortality rate between 50% and 70% [28]. In addition to the common causes of death in patients with classical types of pemphigus, PNP patients can die from bronchiolitis obliterans leading to respiratory failure, and from the evolution of the associated neoplasm. We recently studied the prognosis of PNP in a series of 30 patients, and identified the following deleterious prognostic factors: older age, association with a non-Hodgkin lymphoma (as opposed to chronic lymphoid leukaemia), extent of cutaneous lesions, conjunctival involvement, histological features of keratinocyte necrosis, and failure of disease control after initial treatment.

12.3.4 Treatment

High doses of systemic corticosteroids are the mainstay of treatment for severe types of pemphigus. However, a significant proportion of patients who have their pemphigus diagnosed at an early stage, with few cutaneous and/or mucosal lesions and low titres of circulating anti-ECS antibodies (mild pemphigus), can be successfully treated with the Lever regimen [36]. This treatment is a combination of low doses of corticosteroids — i.e., prednisone 40 mg every other day, and an immunosuppressant, initially azathioprine 2 mg kg^{-1} per day (which can be replaced by mycophenolate mofetil 2 g per day). The combined treatment is prescribed at the initial dose during the first year of treatment. Thereafter, corticosteroid doses are slowly tapered and stopped at the end of the second year of treatment. The doses of immunosuppressants are then tapered, and finally stopped at the end of the third year of treatment.

Prednisone doses of 1–1.5 mg kg^{-1} per day are usually required to control pemphigus patients with extensive cutaneous or mucosal lesions, irrespective of the subtype (PV, PF or PNP) of their pemphigus [37]. The aim of the initial phase of treatment is to obtain 'control of disease activity', which has been defined by the recent 'consensus statement on definitions of disease endpoints and therapeutic response for pemphigus' as 'the time interval from baseline to the time at which new lesions cease to form and established lesions begin to heal'. This is also considered the beginning of the consolidation phase of treatment, during which corticosteroid doses will be gradually tapered. Failure of treatment, which is considered as 'the continued development of new lesions, continued extension of old lesions, or failure of established lesions to begin to heal despite 3 weeks of therapy on 1.5 mg kg^{-1} per day prednisone equivalent' requires the use of the following agents: cyclophosphamide 2 mg kg^{-1} per day for 12 weeks, azathioprine 2.5 mg kg^{-1} per day for 12 weeks (if TPMT level is normal), methotrexate 20 mg per week for 12 weeks, or mycophenolate mofetil 3 gm per day for 12 weeks. The risk of severe treatment side-effects, especially infections, is a major factor in these patients, who need to be managed very carefully.

Patients with life-threatening recalcitrant pemphigus who have persistent extensive erosive lesions despite the association of high doses of corticosteroids and an immunosuppressant can be treated with rituximab, a new biologic agent, and/or with IV immune globulins [5, 6]. Rituximab is a monoclonal antibody directed against the CD20 antigens of B-lymphocytes. It has been initially reported to be effective in occasional cases of life-threatening cases of pemphigus, including PNP [38]. Recently, the combination of multiple cycles of rituximab and IV immune globulins has been reported by Ahmed et al.to be effective in a mono-centre series of 11 patients with severe PV [5]. We have recently reported a multi-centre series of 21 patients treated with a simple regimen of one cycle of rituximab without associated immune globulins [6]. Eighteen out of 21 patients (89%) achieved complete remission 3 months after rituximab treatment. At the end of the study, after almost 3 years of follow-up, 18 patients (89%) were free of disease, including eight patients who had not received corticosteroids. Rituximab treatment was rather well-tolerated with no severe side-effect in the series by Ahmed et al., and with a pyelonephritis in one patient and a septicaemia leading to death in another patient from our series. This latter patient had rheumatoid arthritis, and was concomitantly treated with the anti-tumour necrosis factor, etanercept. Intravenous immune globulins have been reported to be effective in case reports and small open series of patients with pemphigus who did not respond satisfactorily to conventional agents. Although its efficacy is rather difficult to evaluate from these reports, some authors have suggested that this treatment was effective and well-tolerated, providing good disease control and allowing a substantial decrease of corticosteroid doses. Due to its high cost

and the potentially severe side-effect of rituximab, these treatments should be limited to the most severe types of pemphigus.

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Part III
Cutaneous Manifestation in Life Threatening Diseases

13 Skin Manifestations of Systemic Bacterial Infections

Pascal del Giudice and Olivier Chosidow

Core Messages

- The clinical manifestations of a systemic bacterial infection may be caused directly by the bacteria and/or by its toxins.
- Secondary locations of bacteremias occur mainly during the course of endocarditis or septic vasculitis during acute or chronic meningococcaemia and gonococcaemia.
- Ecthyma gangrenosum is a particular form of secondary septic location occurring mainly in neutropenic subjects and mainly caused by *Pseudomonas aeruginosa*.
- Toxinic manifestations are mainly caused by *Staphylococcus aureus*, responsible for toxic shock syndrome and staphylococcal scalded skin syndrome, and *Streptococcus pyogenes*, responsible for streptococcal toxic shock syndrome and scarlet fever.
- Purpura fulminans is a particular severe form of bacterial sepsis associated with vasculopathy and necrosis of the extremity.

The clinical manifestations of a systemic bacterial infection may be caused directly by the bacteria and/or by its toxins. Similar clinical manifestations may be caused by different bacteria, and the same bacteria may be responsible for different clinical manifestations. Therefore, the skin manifestations of systemic bacterial infections can be classified according to the clinical syndrome or to the bacteria (Table 1). For example, bacteria such as Staphylococcus. aureus may cause toxic shock syndrome, purpura fulminans and septic emboli. Indeed, a clinical syndrome such as purpura fulminans may be caused by different bacteria such as *Neisseria meningitidis, Streptococcus pneumoniae or Staphylococcus. aureus.*

13.1 Skin Manifestation Caused by Secondary Locations During the Course of a Bacteriemia

13.1.1 Skin Manifestations of Endocarditis

Two main forms of endocarditis are described in patients with native cardiac valves, i.e., acute endocarditis mainly caused by *S. aureus* and sub-acute endocarditis caused by non-typable *Streptococci* or *Enterococci*. In rare cases, endocarditis is caused by non-cultivable bacteria such as *Coxiella burnetti* and others. In addition, an increasing number of cases of endocarditis occur on prosthetic valves. The physiopathology may thus differ from one type of endocarditis to another, and also according to the bacteria involved.

Description of endocarditis-related skin manifestations is confusing; Janeway lesions and Osler's nodes were described at the beginning of the twentieth century, a period where bacterial endocarditis was different from at the present [1].

Classically reported Janeway lesions are macular, purpuric lesions that occur on hands and feet (Fig. 13.1). Histologically, they show neutrophilic microab-

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Table 13.1 Cutaneous features of bacterial infections

Staphylococcus aureus	Janeway lesions, septic vasculitis
	Purpura fulminans abscess
	Toxic shock syndrome
	Staphylococcal scarlet fever
	Staphylococcal scald skin syndrome
Beta-haemolytic *Streptococcus* group A	Streptococcal Toxic shock syndrome
	Scarlet fever
	Purpura fulminans
Streptococcus pneumoniae	Purpura fulminans
Non-typable *Streptococci* and *Enterococci*	Osler nodes
Neisseria meningitidis	Purpura (septic vasculitis) abscess
	Purpura fulminans
Neisseria gonorrhea	Purpura (septic vasculitis) abscess
Pseudomonas aeruginosa	Ecthyma gangrenosum
Nocardia sp	Sub-acute abscess
Atypical *Mycobacteria*	Sub-acute abscess
Mycobacterium tuberculosis	Acute miliary tuberculosis of the skin
	Cold abscess

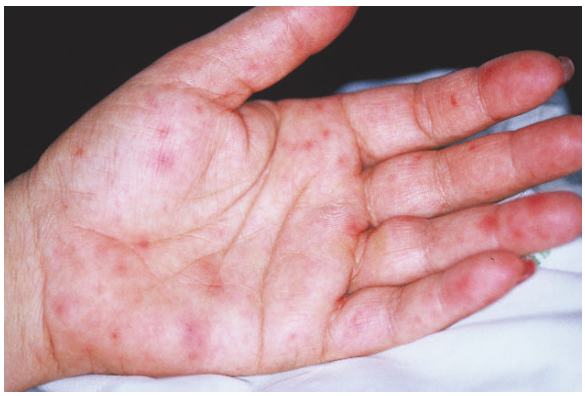

Fig. 13.1 Staphylococcus aureus acute endocarditis

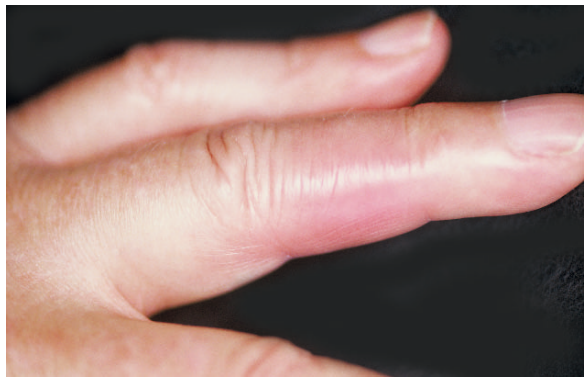

Fig. 13.2 Non-typable *Streptococcus* sub-acute endocarditis

scesses in the dermis and vessel thrombosis [1]. These lesions are thought to be caused by septic microemboli; the results of culture of specimens being frequently positive [2–5]. Osler's nodes are described as small, painful, nodular lesions of the fingers or toes (Fig. 13.2). Only a few biopsied Osler's nodes yield positive results on culture, and histological examinations have revealed diverse findings [2–5].

The distinction between acute endocarditis and sub-acute endocarditis is probably the most important question, in order to consider such lesions as embolic or resulting from the immunologic process. Further histological and clinical studies should focus on this question in order to clarify these historical clinical entities.

13.1.2 Septic Vasculitis

Janeway lesions of acute endocarditis due to *S. aureus* are caused by septic microemboli. The main clinical manifestation is purpura. Petechial lesions resulting from septic thombosis of the dermal vessels can be caused by other bacteria, mainly *N. meningitidis* and *Neisseiria gonorrhea*.

13.1.2.1 Acute Meningococcaemia

Meningococcaemia is characterized by an abrupt onset of fever and petechial eruption that can progress to purpura fulminans [6]. Petechies can occur anywhere

on the skin or mucous membrane, but predominate on the extremities (Figs. 13.3, 13.4). Non-specific urticarial and erythematous eruptions have been detected sometimes [7]. The petechies may be pustular. Skin biopsies or needle aspirations can be Gram-stained and cultured. Information for parents about a purpuric rash in an ill child and the need for urgent treatment is crucial [8]. Cellulitis has exceptionally been described in meningococcaemia [9].

13.1.2.2 Chronic Meningococcaemia

Chronic meningococcaemia is defined as meningococcal sepsis of at least 1 week in duration without meningeal symptoms [10–12]. It is characterized by a prolonged clinical course with intermittent fever, rash and migratory arthralgia. A rash consisting of erythematous macules evolves into tender nodules which become purpuric [10–12]. With appropriate antibiotics, the outcome is favourable. Fever and arthralgias resolve within 24–48 h, and the rash within 5 days. Undiagnosed, it may have a fatal outcome [10–12].

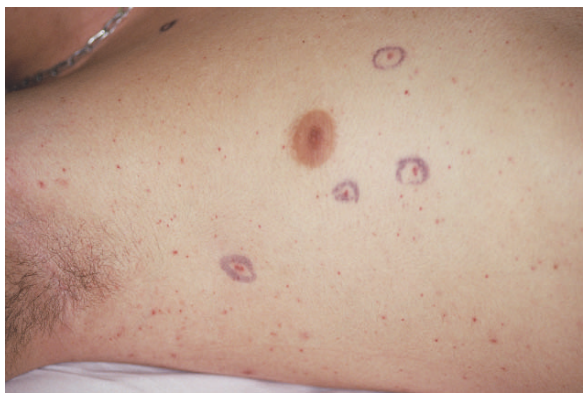

Fig. 13.3 Acute meningococcaemia

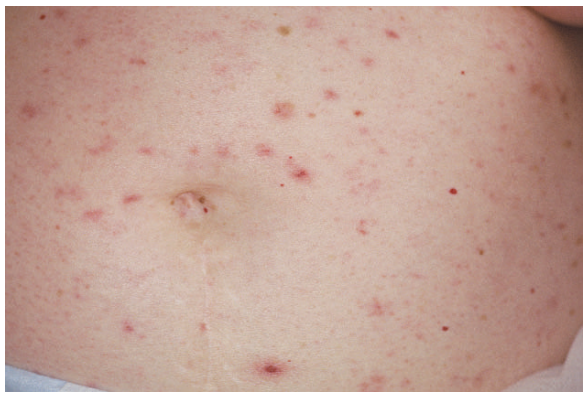

Fig. 13.4 Acute meningococcaemia

13.1.2.3 Disseminated Gonococcal Infection

Despite the large number of gonococcal infections, disseminated infection from haematogenous spread occurs in only 0.5–3% of patients. [13–16]. Systemic manifestations of disseminated gonococcal infection are usually characterized by both skin and joint lesions. Joint involvement ranges from tenosynovitis to suppurative arthritis. Skin manifestations are clinically and histologically consistent with vasculitis, similarly to what is described with chronic meningococcaemia. A few purpuric papulo-pustules on the extremities in patients with fever and polyarthritis could suggest systemic gonococcal infection. In rare cases an extensive, vesiculobullous, haemorrhagic, and necrotic cutaneous vasculitis is the sole manifestation of the disease [13]. Rare skin abscesses resulting from disseminated infection have been reported [16].

13.1.3 Skin Abscesses

Dermal abscesses are rarely associated with disseminated bacterial infection as a secondary focus. They can be unique or multiple. Depending on the bacteria, it is possible to distinguish three different types of skin abscesses: acute, sub-acute and cold abscesses.

Acute abscesses form an inflammatory dermal mass occurring during bacteriemia. These abscesses are rare; they can be caused by any pyogenic bacteria, but are mainly caused by *S. aureus*.

Sub-acute abscesses occur several days to weeks after a bacteriemia, and are caused by pathogens such as *Nocardia* (Fig. 13.5) or non-tuberculosis *Mycobacteria,* or in the particular cases of immunorestoration syndromes with tuberculosis and non-tuberculosis *Mycobacteria*.

Finally, cold abscesses occur several months after the systemic dissemination and are mainly caused by *Mycobacterium tuberculosis*.

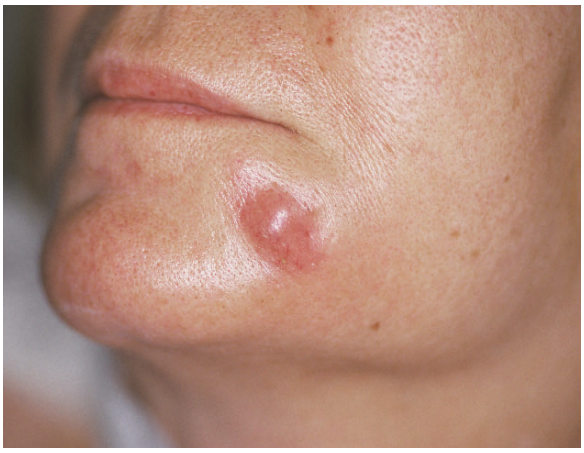

Fig. 13.5 Abscess of the face during the course of systemic *Nocardia asteroides* infection

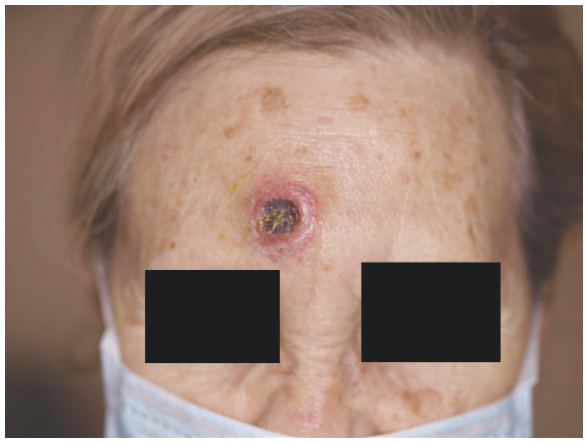

Fig. 13.6 Ecthyma gangrenosum during the course of a neutropenia

13.1.4 Ecthyma Gangrenosum

Ecthyma gangrenosum is a localized cellulitis with necrotizing and ulcerative evolution occurring in immunocompromised or neutropenic patients, mainly caused by *Pseudomonas aeruginosa*. Two pathogenic mechanisms in ecthyma gangrenosum are recognized; one occurring as the result of the presence of *P. aeruginosa during* bacteriemia, the second as a primary lesion followed (but not necessarily) by bacteriemia [17–24]. The prognosis of echtyma gangrenosum is mainly in relation to the underlying immunosuppression and its potential recovery.

P. aeruginosa has a low-to-moderate virulence potential in healthy patients, but in immunocompromized subjects it acts as an opportunistic pathogen. Neutropenia is one of the conditions in which *P. aeruginosa* may be associated with severe and life-threatening complications such as ecthyma gangrenosum. Profound and prolonged neutropenia is the most important factor predisposing to *P. aeruginosa* severe invasive infections, but even a deep transitory neutropenia can also result in echyma gangrenosum (Fig. 13.6) [23, 24]. Other Gram-negative bacilli and mycosis have occasionally been reported associated with ecthyma gangrenosum.

Ecthyma gangrenosum manifests usually as an inflammatory nodule or plaque that becomes a necrotic ulceration in a patient with high fever and deterioration of the general health status. It can occur anywhere, but the axillae and anogenital areas are the most commonly affected sites [17, 24].

The treatment is based on systemic antibiotics active against *P. Aeruginosa*, namely betalactams such as imipenem, ceftazidim, aztreonam, piperacilline–tazobactam associated with ciprofloxacin or aminosides. Granulocyte colony-stimulating factor (G-CSF) therapy can be used in cases of severe neutropenia [23, 24]

13.1.5 Acute Miliary Tuberculosis of the Skin

Miliary tuberculosis is a particular clinical form of systemic tuberculosis characterized by the acute haematogenous dissemination of the bacilli. In miliary tuberculosis, lungs are affected, showing the typical bilateral diffuse reticulo-nodular infiltrate, but many organs can be involved, such as meninges, liver and spleen [25]. Cutaneous manifestations are extremely rare, and occur mainly in immunocompromised patients [26]. The typical cutaneous lesions consist of discrete erythematous papulo-pustules. Other cutaneous manifestations include macules, large pustular lesions, ulcerations, purpuric lesions and sub-cutaneous nodules. Any part of the body can be affected, the lesions are widely distributed and usually do not exceed 20–30 in number [25–34]. In HIV-infected patients, these lesions are difficult to differentiate from other more common cutaneous diseases, namely prurigo and eosinophilic folliculitis.

Acute miliary tuberculosis of the skin must be differentiated from paradoxical tuberculosis. Paradoxical expansion tuberculosis is an extremely rare manifestation characterized by the expansion of a pre-existing lesion or the appearance of new ones developing from a few days to several months after appropriate treatment of tuberculosis. The outcome has been favourable in all cases, suggesting that paradoxical tuberculosis could result from a restored immunologic response. By contrast, acute miliary tuberculosis of the skin results from a failure to control bacilli dissemination.

13.2 Toxinic Manifestations

13.2.1 Toxic Shock Syndrome

Toxic shock syndrome (TSS) was first described by Todd (1978) in seven children who had a generalized erythema, fever, hypotension, diarrhea and multi-organ failure [35, 36]. In 1980, a hundred cases were reported in young women who used certain tampons [37, 38]. The incidence of menstrual TSS in the US peaked in 1980, and decreased significantly during the past 20 years, after the removing of these particular super-absorbent tampons and the provision of public information [39].

TSS has been associated with the production of a toxin by *S. aureus,* mainly the toxic-shock syndrome toxin 1(TSST-1).responsible for most menstrual TSS and the majority of non-menstrual TSS. The rest of the cases are mediated through staphylococcal enterotoxins, particularly enterotoxin B, and less commonly other enterotoxins [36].

In the 1997 CDC definition [40], the following clinical criteria one included: fever (greater than or equal to 38.9°C), a diffuse macular erythroderma, desquamation (1–2 weeks after onset of illness, particularly on the palms and soles), hypotension and *multisystem* organ involvement.

TSS develops from a *S. aureus* focus. In the study of 130 TSS by Reingold [38], the following focuses were found: skin infection in 30% of cases, genital focus 27% (after delivery or abortion), 18% post-surgery, 13% non-identified.

The pathogeny of TSS is linked to the property of superantigens (BSAgs) by staphylococcal toxins. These superantigens bind to both human major histocompatibility antigen class II molecules on the surface of antigen-presenting cells and the specific T-cell receptor variable chain on T lymphocytes, and activate greater numbers of T lymphocytes resulting in production of high levels of cytokines [36–40].

Skin manifestations of TSS include a generalized erythema (with involvement of palms and soles). Palmar, sole and finger desquamation may occur after recovery. Transient alopecia, the falling-off of nails and an increased sweating of hands and feet have been described [41].

Treatment is based on the treatment of the multi-organ failure and the *S. aureus* focus. Some antibiotics acting as protein-synthesis inhibitors with antitoxic properties can provide a beneficial outcome [42].

Takahashi et al. [43] reported, from Japan, neonates who developed systemic exanthema and thrombocytopenia in the first week of life associated with MRSA producing TSST-1. They propose neonatal toxic-shock-syndrome-like exanthematous disease (NTED) as the name for this disease. A similar case has been reported in Europe [44].

13.2.2 Streptococcal Toxic Shock-Like Syndrome

In 1987, Cone reported two patients who had a severe infection caused by beta haemolytic group A *Streptococcus* (GAS) and a clinical presentation similar to TSS [45]. Stevens described 20 patients, with GAS infection, shock, and multi-organ failure and mortality reaching 30% [46].

In contrast to staphylococcal TSS, the causal association with streptococcal toxins to streptococcal toxic shock syndrome (STSS) is much less clear. Staphylococcal TSS and STSS share many features: high-grade fever, hypotension, myalgias, multi-organ involvement such as diarrhea, vomiting, renal failure and hematological abnormalities [45–49]. Similarly to TSS, skin manifestations are characterized by a generalized erythema and a delayed palmo-plantar desquamation. Streptococcal toxic shock syndrome is mainly associated with severe soft-tissue infections such as cellulitis, necrotizing cellulitis and necrotizing fasciitis [45–49].

In TSS, the treatment is based on the treatment of the multi-organ failure and the GAS focus. Antibiotic treatment is based on the use of antibiotics active against GAS, such as betalactams, associated with antibiotics acting as protein-synthesis inhibitors with

anti-toxinic properties, such as clindamycin [50]. The additional use of intravenous immunoglobulin G has been suggested to be beneficial [50, 51].

Other bacteria have been reported to cause TSS-like syndromes such as Group C beta-haemolytic streptococci [52], *Streptococcus mitis* [53], *Streptococcus* [54], *Staphylococcus lugdunensis* [55], group B Beta haemolytic *Streptococcus* [56].

13.2.3 Scarlet Fever

Scarlet fever is characterized by acute pharyngitis, a generalized macular erythema sparing the soles and hands, and high-grade fever. Characteristic clinical features of scarlet fever include: an initial white covering of the tongue, followed by enlargement of the papillae, giving a distinctive 'strawberry tongue' appearance. Patients with severe infections often have nausea and vomiting. The incubation period is short, usually 1–3 days. The disease is caused by GAS infection which produces erythrogenic toxin [48]. Rarely, typical rash of scarlet fever is reported with GAS infection from another focus than pharyngitis, such as skin infection [57].

Staphylococcal scarlet fever, also called scarlatiniform erythroderma/rash, was first described in the 1920s. Lina et al. [58] found that 16 and 17 *S. aureus* isolated from patients with staphylococcal scarlet fever produced TSST-1, enterotoxins, or both. Therefore, it is likely that most cases of staphylococcal scarlet fever are a clinical manifestation of mild TSS. Enterotoxin B was the predominant toxin involved in staphylococcal scarlet fever in a study from Taiwan [59].

13.2.4 Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a generalized blistering disease induced by the exfoliative (epidermolytic) toxins (ETs) of *S. aureus* [60]. Neonates and young children are mainly affected, and exceptionally adults with underlying diseases. Exfoliative toxin is produced by staphylococcal species, causing blisters in human and animal skin. Bullous impetigo is caused by the local production of ET; blisters occur at the site of infection with *S. aureus*. In SSSS, the toxin is produced at distant foci of infection and causes generalized blistering due to its systemic circulation [60].

Two major serological forms of ET, ETA and ETB, have been linked to SSSS. Both toxins cause intraepidermal cleavage through the granular layer, without epidermal necrolysis or an inflammatory response of the skin. Amagai et al. recently identified desmoglein 1(Dsg1) as the specific substrate for ETA and ETB [61–63].

Its clinical manifestations begin abruptly with fever and generalized erythema, followed by large fragile blisters involving the entire skin surface within the next few hours to days, which rapidly rupture on the slightest pressure (with a positive Nikolsky sign) (Fig. 13.7). Widespread involvement of the entire skin surface can occur, but the mucous membranes are usually spared.

The disease usually follows a localized infection of the upper respiratory tract, inner ear, conjunctiva, or umbilical stump, although rare cases of SSSS caused by staphylococci isolated from patients with pneumonia, septic arthritis, pyomyositis, and maternal breast abscesses have been reported. Many nosocomial outbreaks have been reported, usually due to several asymptomatic carriers of ET-producing *S. aureus* strains [60].

Poor renal clearance of the toxins by neonates and by adults with impaired renal function is a major risk factor for developing SSSS. The prognosis of SSSS in children who are appropriately treated is good, with mortality of less than 5%. But up to 60% of affected adults die, usually due to underlying diseases [60].

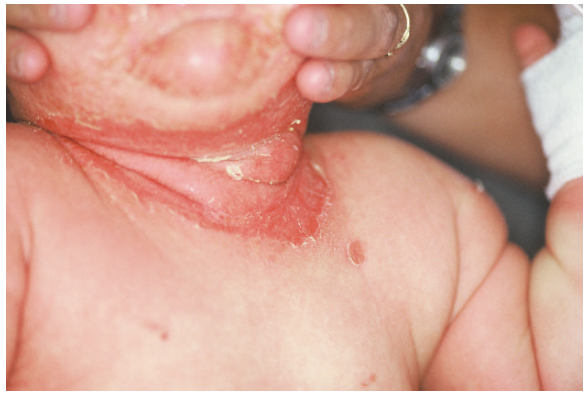

Fig. 13.7 Staphylococcal scald skin syndrome

Most cases of SSSS are diagnosed on a clinical basis. Exotoxins are produced by staphylococci at a distant site; the blister fluid in generalized SSSS is usually sterile. Staphylococci producing ET can usually be cultured from the nares, conjunctiva, or nasopharynx.

There is no specific treatment. A staphylococcal focus should be treated. Hygiene measures must be applied to prevent to prevent cross-transmission.

13.3 Purpura Fulminans

Purpura fulminans, also described as the Waterhouse–Friderichsen syndrome, first reported in 1911 by Waterhouse [64], is a rare clinical condition characterized by the sudden development of extensive bilateral and symmetrical skin necrotizing purpuric and haemorrhagic lesions. It occurs predominantly on the extremities, and is associated with disseminated intravenous coagulation (DIC) cardiovascular collapse, and bilateral adrenal haemorrhage [65–68]. The skin histologic features show dermal vascular thrombosis, with subsequent necrosis and haemorrhagic necrosis of affected tissues [65–68]. This disease is complicated by a high mortality rate or amputation of the extremities (Fig. 13.8) [65–68].

Purpura fulminans may occur in three situations; acute severe sepsis, preexisting inherited coagulation disorders, or referred to as 'idiopathic' when there is no evidence of known abnormalities of coagulation or acute infections [65–68].

Septic conditions include mainly meningococcaemia and pneumococcal sepsis in asplenic patients. However, isolated cases of purpura fulminans have been reported in severe sepsis due to other infectious agents such as group B *Streptococcus*, Gram-negative bacilli, *S. aureus* including community-acquired methicillin *S. aureus* and beta-haemolytic group A *Streptococci* [65–70].

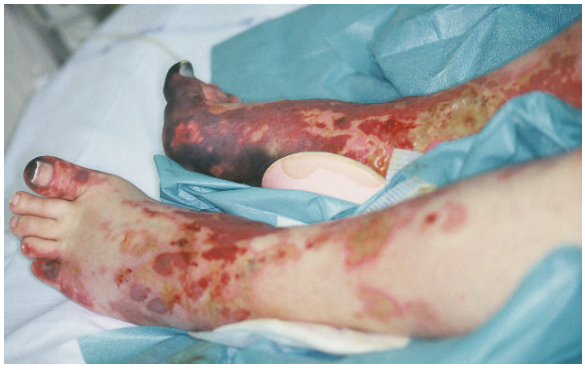

Fig. 13.8 Purpura fulminans

13.4 Specific Manifestations

Some well known systemic bacterial diseases such as syphilis, rickettsiosis, bartonellosis, rat bat fever etc. with specific clinical manifestations are not included in this review.

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14 Severe Mycoses in Immunodepressed Patients

Delphine Kerob, Martine Feuillhade-de-Chauvin, and Celeste Lebbe

Core Messages

- Severe cutaneous and systemic fungal infections are frequent in profoundly immunodepressed patients, i.e., haematological malignancies and organ transplant recipients.
- Candidiasis and aspergillosis are the most frequent, but emerging 'new' fungi are more and more responsible for life-threatening infections.
- Identification of the responsible agent relies on the study of multiple biologic samples: skin, blood, etc.
- Histological examination including special stains, culture of tissue, andantibody detection may be necessary to establish a precise diagnostic. The results may be delayed for weeks.
- The therapeutic armentarium has been enriched with new systemic antifungal, but identification of the responsible organism is necessary to select the appropriate drug.

The incidence of invasive opportunistic and nosocomial fungal infections has increased substantially over the past 30 years, largely because of the increasing size of the population at risk, such as haematological malignancies, or patients undergoing stem cell or solid organ transplantation [1–4]. It is estimated that invasive opportunistic fungal infections develop in 10–25% of patients with acute leukemia and those receiving stem-cell transplantation. The incidence of invasive fungal infection occurring in the post-transplant setting is between 5% and 10%, with the incidence varying according to the pathogen and organ transplanted [5–8]. Whereas *Aspergillus spp* and *Candida spp*. collectively account for the majority of deeply invasive and life-threatening fungal infections, epidemiological trends during the past decade indicate a shift towards infections by *Aspergillus spp* and *Candida spp*, as well as previously uncommon opportunistic fungi [9–11]. These emerging fungi are *Trichosporon spp*, *Fusarium spp*, dematiaceous moulds, *Scedosporium spp*, Zygomycetes, as well as endemic dimorphic fungi such as *Penicillium marnefeii* and *Histoplasma capsulatum* [12].

The increasing importance of these isolates as causes of life-threatening invasive fungal infections in immunodepressed patients requires familiarity with dermatological aspects of these infections and the microbiology [13] (Scheme 14.1).

Every cutaneous lesion in immunosuppressed patients should be considered for biopsy. Histological examination including special stains, such as periodic acid Schiff (PAS) and argentic staining (Gomori–Grocott stain) are critical for diagnosis, but the diagnosis depends on the identification of the organism by mycological culture. Culture of tissue is essential in deep mycoses, but may not always show yield viable organisms (zygomycosis) or may take several weeks to grow organisms (phaeohyphomycosis), but is essential for diagnosis of species and testing antifungal susceptibility. Blood cultures can be helpful in disseminated *Candida* infections, and are most commonly positive in disseminated *Fusarium, Cryptococcus*, and *P. marneffei* infections. Antibody detection assays may not be initially positive in immunocompromised patients. ELISA (enzyme-linked immunosorbent assay) for antigen detection is a test preferable to polymerase chain reaction (PCR). Serum antigen testing is very useful for cryptococosis and acute pulmonary aspergillosis.

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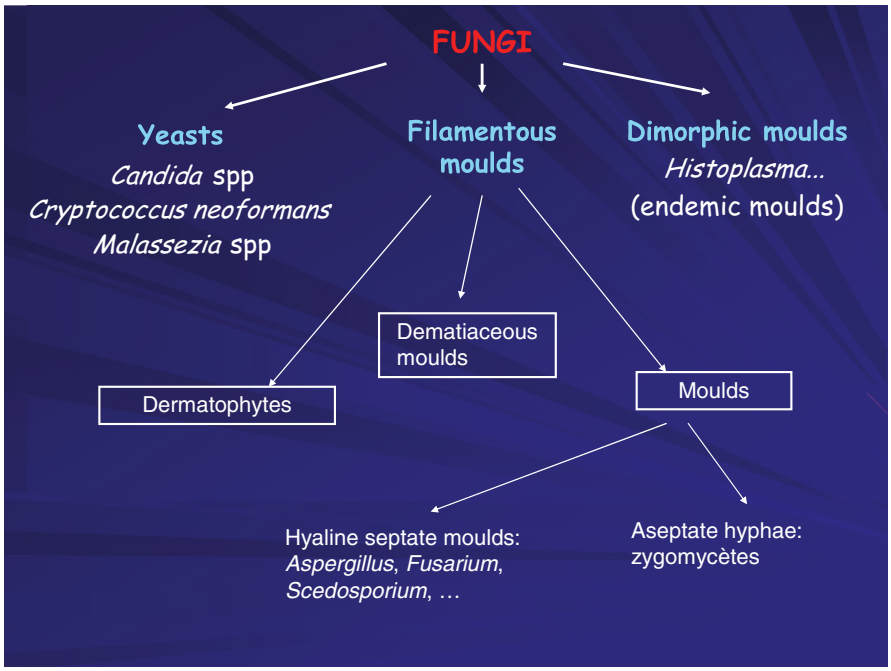


Scheme 14.1

If drug-resistant fungi are appearing in patients, exciting developments in antifungal therapy have emerged to address this concern. Lipid-based formulations of amphotericine B, extended spectrum triazoles that inhibit ergosterol synthesis, such as voriconazole and posaconazole overcome problems associated with the ineffectivity of fluconazole against *Aspergillus spp*. or the variable bioavailability of itraconazole. But, like itraconazole, voriconazole and posaconazole have a high incidence of drug interactions in the HIV-infected population and solid organ transplant population, because of its inhibition of the CYP3A4. Itraconazole is also limited by its unpredictable oral absorption, although voriconazole and posaconazole have a best oral bioavailability. Echinocandins represent a new family of antifungal agents with few side-effects and few drug interactions. Other new antifungal drugs such as nikkomycins and sordarin derivatives are in development [14, 15]. Combination antifungal therapy has been described with increasing frequency in the literature, but there is a lack of evidence-based studies for its use. However, the best treatment of deep mycosis is immune restitution, when it is possible. Clinicians should be aware of the possibility of immune reconstitution syndrome (IRIS) associated with opportunistic mycoses [16].

14.1 Cutaneous Fungal Infections with High Risk of Systemic Disease

14.1.1 Candidiasis (Candida species)

Candida spp have become common pathogens and cause serious opportunistic infection in humans, particularly in immunocompromised patients, and are now recognized as major agents of hospital-acquired (nosocomial) infections. Blood stream infection (BSI) with *Candida species* (candidemia), especially *Candida albicans,* is the most clinical presentation of systemic candidiasis, and is responsible for high morbidity and mortality rate in hospitalized patients [17]. Risk increases when patients have multiple indwelling catheters and are receiving IV antibiotics. The incidence of invasive candidiasis has declined in subsets of organ transplant recipients (e.g., liver transplant patients) as a result of fluconazole use [18]. Skin lesions of disseminated candidiasis are present in 10–13% of affected individuals, and are helpful for diagnosis, since only 25–50% of disseminated candidiasis cases experienced positive blood cultures. These lesions are typically represented by clusters of asymptomatic pustules on erythematous papular localized to extremi-

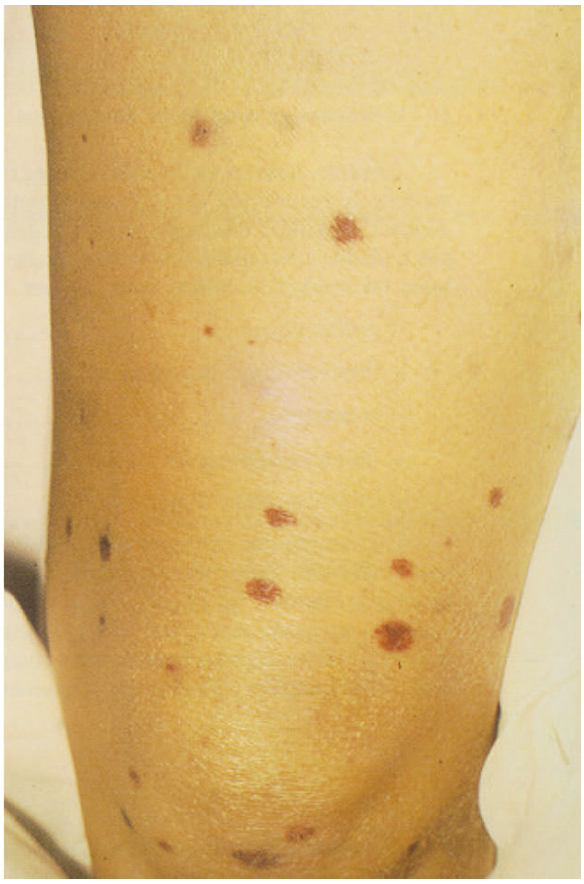


Fig. 14.1 Disseminated candidiasis (*C. tropicalis*) with skin erythematous lesions centered with pustules in a leukemic patient

ties and abdomen (Fig. 14.1), although larger nodules with central necrosis are also possible. The estimated mortality attributed to candidemia is 19–24% depending on the patient's age [19], but levels as high as 70% for solid-organ transplant recipients have been reported despite antifungal therapy [20]. In addition to the amphotericin B formulations and fluconazole, all new antifungal agents exhibit potent activity against *Candida spp*. [20, 21]. Removal of indwelling lines and catheters is an important additional step to hasten resolution in the majority of cases.

14.1.2 Aspergillosis (Aspergillus species)

Aspergillus spp. are the most commonly isolated invasive moulds. *Aspergillus* species are ubiquitous soil inhabitants. Risk factors for invasive aspergillosis include prolonged and severe neutropenia, allogeneic or autologous hematopoietic stem-cell transplantation and solid organ transplantation, prolonged high doses of corticosteroid or cytotoxic drugs, and chronic granulomatous disease [22, 23]. Cutaneous aspergillosis can be classified into (1) primary, which is rare in immunodepressed patients, or more usually (2) secondary, from hematogenous spread. Clinically, cutaneous aspergillosis is characterized by the presence of violaceous papules, hemorrhagic bullae, ulcerations with central necrosis, pustules or subcutaneous abscesses (Fig. 14.2). Laboratory diagnosis includes direct microscopy examination, culture and histopathology. The treatment approach to primary cutaneous aspergillosis (PCA) is surgical excision of the primary lesion and antifungal therapy. Secondary cutaneous aspergillosis should be treated as invasive and life-threatening aspergillosis. The drug of choice for invasive infection is voriconazole, which appears to be superior to both itraconazole and amphotericine B [24]. Caspofungin, lipid formulation of amphotericin B, and posaconazole may be a helpful salvage therapy [25, 26].

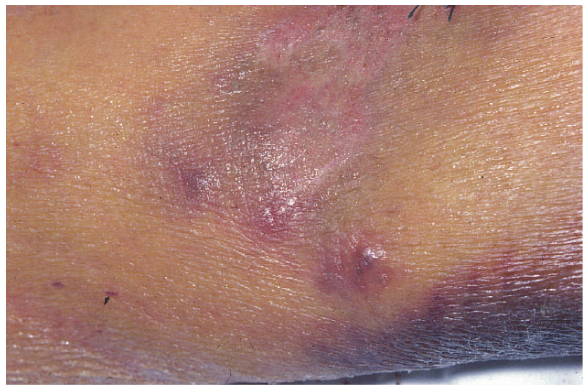
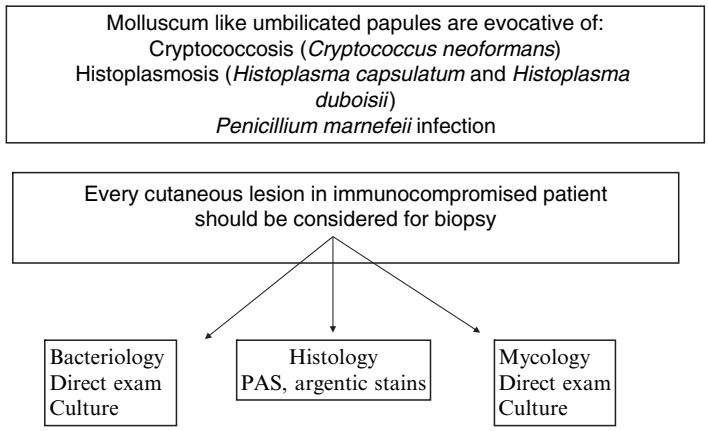


Fig. 14.2 Disseminated aspergillosis with violaceous maculopapules in a patient under immunossupressive therapy (steroids)

14.1.3 Cryptococcosis (Cryptococcus neoformans)

Cryptococcus neoformans is an encapsulated yeast responsible for meningitis in immunocompromised hosts. *C. neoformans* is responsible for most common invasive fungal infection in HIV-infected patients, and is also common in transplant recipients, usually



Scheme 14.2

after 6 months post-transplantation and lymphoma, and may be the result of new acquisition of infection or, more commonly, reactivation of latent infection [27]. Nearly 3% of organ transplant recipients are concerned about cryptococcosis and the overall death rate can reach 42% [28, 29]. Skin manifestations of disseminated cryptococcosis occur in 10–20% of patients. Cutaneous presentations include abscesses, verrucous nodules, molluscum-like lesions (Scheme 14.2) (especially in HIV-infected patients), erythematous, indurated plaques, cellulitis, pustules, and ulcers. Histologically, lesions reveal numerous encapsulated cryptococcal organisms in a gelatinous pattern, highlighted with PAS, mucicarmine, and methenamine silver stains [30].

Primary cutaneous cryptococcosis is a distinct epidemiological and clinical entity, with a favourable prognosis even for immunocompromised hosts. The diagnosis relies on the absence of dissemination and, predominantly, a solitary skin lesion on unclothed areas presenting as a whitlow or phlegmon, a history of skin injury, participation in outdoor activities, or exposure to bird droppings, and isolation of *C. neoformans* serotype D most of the time [31]. The laboratory diagnosis of cryptococcosis is established by the isolation of organism in culture, histopathology, and/or detection of its polysaccharide capsular antigen in cerebrospinal fluid (CSF). For patients without CNS disease, fluconazole 200–400 mg per day is the treatment of choice. Itraconazole may be a suitable alternative for patients unable to take fluconazole.

14.1.4 Histoplasmosis (Histoplasma capsulatum)

Disseminated histoplasmosis is more frequent in HIV/AIDS patients than in transplant recipients, and represents an AIDS-defining illness, as is the case with *Cryptococcus*, and coccidioidomycosis. *Histoplasma capsulatum* is a dimorphic fungus found as a soil saprophyte in areas contaminated with bird and bat droppings. The largest endemic focus is in the south-eastern and midwestern United States. In HIV patients, the risk of disseminated infection is increased with lack of antiretroviral therapy and lack of triazole prophylactic therapy [32]. Histoplasmosis may occur after primary infection, reactivation of latent infection, or more rarely by transmission through an infected allograft from a donor with unrecognized infection in solid-organ transplantation [6]. Fever and weight loss are common complaints of disseminated disease. Skin lesions occur in 10–20% of patients with disseminated histoplasmosis, and presentation is highly variable, including nodules, molluscum-like umbilicated papules, plaques, ulcers, vesicles, pustules, abscesses, general dermatitis, erythroderma, cellulitis, petechiae, purpura, ecchymoses, or necrotizing vasculitis. But cutaneous or mucocutaneous histoplasmosis can be primitive, as has been reported most of the time in immunocompromised patients. The diagnosis is made by identifying the characteristic small yeasts in biopsies, peripheral blood, or sputum, and is confirmed by culture. Detection

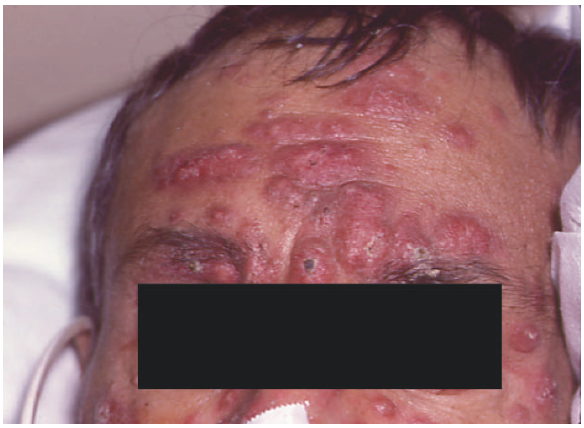


Fig. 14.3 Disseminated histoplasmosis with multiple nodules in a patient with AIDS

of *H. capsulatum* antigen in serum or urine may be more appropriate for patients with AIDS (Fig. 14.3).

Intravenous amphotericin B should be the first-line treatment in the management of disseminated disease, whereas localized can be treated with itraconazole [33]. However, AIDS patients with successful response to HAART do not require lifelong antifungal maintenance therapy to prevent recurrence [34].

14.1.5 Penicillium Marneffei Infection

Penicillium marneffei is also a dimorphic fungus that is endemic to Southeast Asia and southern China, where it represents the second most common invasive mycosis in HIV-infected individuals [35, 36]. Transplant recipients may also develop disseminated disease with lung, liver, and cutaneous involvement [37]. Presentation is characterized by weight loss, fever, malaise, and lymphadenopahy. Seventy percent of disseminated cases present with skin lesions, which are characterized by small papules with central umbilication (with or without necrosis). Lesions are usually localized on the face, scalp, upper trunk, and upper extremities, and (rarely) in the genital area. The diagnosis of penicilliosis is traditionally confirmed by isolation of the fungus from clinical specimens. Serological tests can be performed [38]. Treatment relies on either amphotericine B or itraconazole. Secondary prophylaxis with itraconazole can be recommended in the HIV-infected population [39].

14.1.6 Zygomycosis (Zygomycetes)

Zygomycosis is a rare opportunistic fungal infection caused by *Zygomycetes*, environmental fungi found in soil and decaying vegetation. *Zygomycete* organisms refer to fungi in the order of Mucorales. In a review of 929 cases of zygomycosis, skin was found to be the third most common site infected, representing 19% of zygomycosis infections, whereas 39% were located in the sinus, and 24% in the lungs [40]. While zygomycosis is commonly associated with diabetes mellitus when located in the sinus and with neutropenia when located in the lungs, cutaneous zygomycosis is the least likely location to be associated with an underlying disease. HIV-infected patients and solid-organ transplant recipients are both at risk of invasive zygomycosis, but it is relatively rare in these populations. Cutaneous disease may begin with plaque-like or pustular lesions or cellulitis that evolve into gangrenous ulcers with necrotic edges. Deep abscesses and intradermal nodules have also been described. As is the case with *Aspergillus species*, *Zygomycete* hyphaes invade blood vessels, causing necrosis, infarction, and dissemination. Dissemination resulted in an increase in overall mortality approaching 90%, compared with an overall mortality of approximately 30% in localized cutaneous zygomycosis [40, 41]. Mycological examination has the advantage of providing quick results, and a culture is indispensable to identify the species of *Zygomycetes* involved and to test its susceptibility to antifungal drugs. Thus, aggressive surgical excision paired with promptly initiated antifungal therapy is associated with a favourable prognosis [42–44]. The mainstay of antifungal therapy relies on high-dose amphotericin B. Critical to successful outcome of zygomycoses is the reversal of the immunological or metabolic defects that precipitated its development.

14.1.7 Fusariosis (Fusarium species)

Fusarium spp. are cosmopolitan soil saprophytes and facultative plant pathogens. Among immunocompromised patients, *Fusarium* spp. are the second most common pathogenic mould. Risk factors for disseminated fusariosis include severe immunosuppression (neutropenia, lymphopenia, graft-versus-host disease, corticosteroids), colonisation, tissue damage, and receipt of a graft from an HLA-mismatched or unrelated donor.

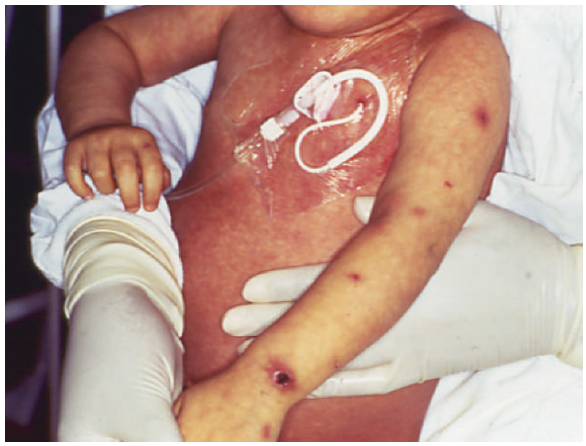


Fig. 14.4 Disseminated fusariosis with multiple erytematous papules and nodules in a leukemic child

Fusarium infections in solid-organ transplant recipients tend to occur late after transplantation, at a median of 9 months, with an overall mortality of 33% [45]. Clinical presentation of disseminated infection includes refractory fever (> 90%) and myalgia, which are unresponsive to broad-spectrum antibiotherapy during periods of neutropenia. Skin lesions occur in two-thirds of cases, usually presented as multiple erythematous subcutaneous nodules, painful erythematous macules and papules with central progressive infarction (Fig. 14.4). Lesions are most commonly seen on the extremities [46]. Isolation of the fungus from blood and biopsy from the skin lesions are the two most effective ways for the diagnosis. Histopathology, with specific stains reveals hyaline acute-branching vesiculous septate hyphae a bit similar to those found in aspergillosis.

Amphotericin B stays the antifungal treatment of choice, but resistance is frequent. Combination anti-fungal therapy using both liposomal amphotericin B and voriconazole may be considered for such patients [47]. However, in all reported cases, survival is almost always associated with the recovery from neutropenia.

14.1.8 Trichosporonosis (Trichosporon species) and Blastoschizomycosis

Trichosporon beigelii can cause disseminated infection in immunodepressed subjects, particularly those who are neutropenic. The portals of entry are the gastrointestinal tract and vascular catheters. This infection may disseminate to multiple organs, and is difficult to diagnose and treat [12]. *Trichosporon cutaneum* has been increasingly recognized as a cause of life-threatening systemic illness in immunodepressed patients, including those with leukaemia. Cutaneous involvement occurs in about 30% of patients with *T. cutaneum* septicaemia. Skin lesions are frequent, usually occurring as disseminated papulae or purpural nodules very similar to lesions of disseminated candidiasis. Pathology examination and skin biopsy culture can provide rapid diagnosis, allowing appropriate treatment. Tests for *C.neoformans* antigen may be positive and could be useful in diagnosis. Monotherapy of amphotericin B and new antifungal agents are thought to be unsuccessful for these infections, but some clinical reports and animal models suggest that triazoles and combination therapies can be more effective. [48]. In certain cases, additional surgical treatment may be necessary (soft-tissue infections).

Blastoschizomyces capitatus, formerly *Trichosporon capitatum*, produces a pattern of infection similar to that of *Trichosporon*, but with more frequent CNS involvement, especially in neutropenic patients. The mortality rate in immunocompromised patients can be as high as 90% [32]. High doses of fluconazole or voriconazole seem to be the drugs of choice for these infections.

14.1.9 Trichoderma Species Infection

Trichoderma is a hyaline mould of the class Hyphomycetes, rapidly growing, most commonly recovered from soil. *T longibrachiatum* is the most frequent of them. *Trichoderma spp*. have emerged as new fungal pathogens in immunocompromised patients, while relative paucity of virulence have been suggested in immunocompetent hosts. In disseminated infection, cutaneous lesions are very rare. However, overall mortality is high between 50% and 100%. Most isolates of *Trichoderma* show resistance to fluconazole and 5-flucytosine, and are found to be intermediate to amphotericin B, itraconazole, ketoconazole and miconazole. More recently, voriconazole and caspofungin have been shown to be effective in vitro against filamentous fungi, including *Trichoderma sp* [49, 50]. Surgical debridement of localized infection is recommended when possible, in association with antifungal therapy.

14.1.10 Coccidioidomycosis (Coccidioides immitis)

Coccidioidomycosis occurs in arid and semi-arid regions of the New World. *Coccidioides immitis* live in the soil, and produce pulmonary infection via airborne arthroconidia. The organisms are considered to be potential agents of bioterrorism [51, 52]. Cutaneous reactions seen with acute disease include erythema nodosum, erythema multiforme, urticarial lesions, morbilliform eruption, interstitial granulomatous dermatitis, Sweet's syndrome and vesicular lesions, where *C immitis* organisms are not present on histology. On the contrary, cutaneous lesions associated with disseminated disease range from papules and pustules to nodules, ulcers, subcutaneous abscesses, pyogranulomas, verrucous lesions, and plaques, and *C immitis* is present on histology [52]. Primary treatment involves oral therapy with fluconazole or itraconazole. CNS infection requires lifelong suppressive therapy. Amphotericin B regimens are used in severely ill patients or those that relapse.

14.1.11 Blastomycosis (Blastomyces dermatitidis)

Blastomycosis is an increasingly recognized infection in an immunocompromised host, with a much more severe course with dissemination to multiple organs and high mortality rate. Skin and subcutaneous tissue are the most common sites of extrapulmonary disease (20%), and may present with verrucous or ulcerative papules or pustules, or subcutaneous nodules. *Blastomyces dermatitidis* is endemic to parts of the midwestern and south-central United States and Canada, but has also been reported in Africa. Diagnostic tests include direct examination of tissue, sputum or exsudate. A positive fungal culture is the gold standard, but it may take up to 30 days to grow the fungus. Intravenous amphotericine B is the drug of choice for life-threatening blastomyosis, but oral itraconazole is a good alternative for mild-to-moderate disease [53].

14.1.12 Scedosporium Spp Infection (S. apiospermum (Pseudallescheria boydii), S. prolificans)

Scedosporium infection is a rare opportunistic mycosis that has been increasingly recognized as cause of death in profoundly immunosuppressed patients, especially in patients with neutropenia. The rate of disseminated *Scedosporium* infection is 69% in haematopoietic stem-cell transplantation and 46% in organ transplant recipients [54]. *Scedosporium apiospermum* is a saprophytic mould found in soil, polluted water, sewage, decaying vegetation and manure. Apart from mycetoma, cutaneous and subcutaneous infection is rarely encountered in clinical practice in immunosuppressed patients [55]. Treatment of *Scedosporium sp* is difficult, especially for *S. prolificans*. Amphotericin B exhibits variable invitro activity against isolates of *S apiospermum*. Triazoles are more effective for *S apiospermum*, and association with terbinafine should be considered for *S. prolificans*

14.1.13 Paecilomyces species Infection

Infections due to *Paecilomyces* are uncommon but devastating in immunocompromised patients, especially in haematopoietic stem-cell transplant patients. *Paecilomyces lilacinus* is able to infect both immunocompromised and immunocompetent hosts. The portal of entry of the fungus usually involves breakdown of the skin barrier, indwelling catheters or inhalation. Cutaneous and sub-cutaneous infections usually appear insidiously, and can manifest as solitary or disseminated skin eruptions with erythematous macules, papules, vesicles or nodules with a necrotic centre. Mortality of patients with cutaneous infection caused by *P. lilacinus* is about 14% [56]. The diagnosis is based on the culture of the fungus and histology of the lesions. Correct diagnosis of *P lilacinus* is important because of its intrinsic resistance to conventional antifungal drugs. Recovery of neutropenia, decrease of immunosuppression level if possible, and removal of central venous catheters are essential. Voriconazole seems to be the most effective agent for the treatment of this fungal

infection. Posaconazole and ravuconazole may be good alternatives on the basis of their excellent activity in vitro [57]. On the contrary, *P. variotii* is universally susceptible both in vitro and in vivo to Amphotericine B, which is considered the agent of choice.

14.1.14 Scopulariopsis species Infection

Scopulariopsis species are hyaline moulds. Even if rare, *S. brevicaulis* have been reported to cause deeply invasive infection, including sinusitis, pulmonary, and multiple subcutaneous lesions in immunocompromised patients, even in solid-organ transplant patients [58]. Diagnosis depends upon culture of the organism from tissue and in histology. For treatment of deep infection, amphotericin B, a lipid formulation of amphotericin B, itraconazole or voriconazole may be useful therapy.

14.1.15 Paracoccidioidomycosis (Paracoccidioides Brasiliensis)

Paracoccidioidomycosis (PCM), the most prevalent systemic fungal disease in Latin America, is endemic in Brazil, especially in the area of Sao Paulo [59]. Only in a minority of individuals does the infection progress to overt disease, evolving into one of the two major clinical forms: (1) acute/subacute — juvenile type, or (2) unifocal or multifocal chronic — adult type. Opportunistic forms of PCM have been reported in immunocompromised patients, including AIDS patients [60]. Diagnosis relies on the direct visualization of the multiple-budding cells in the biological fluids or tissue sections, or the isolation of the fungus from human specimens, but serologic tests can provide earlier results. PCM is a serious systemic disease with slow evolution and high mortality, requiring treatment maintenance for a minimum of 24 months. Preferred drugs are sulfamethoxazol-trimethoprim, itraconazole, and amphotericin B.

14.1.16 Acremonium species Infection

Acremonium spp. (formerly *Cephalosporium* spp.) are saprophytic hyaline moulds. Among this specie, *A. stricutum* has been reported as one of the more common causes of infection by this genus [61].

Mycetoma, which is the most common non-ocular infection caused by *Acremonium spp* in immunocompetent patients, usually develops a complication of a penetrating trauma. *Acremonium* infections in the immunocompromised host exist, including mycetoma-like abscess, subcutaneous abscesses, nodules, ulcers, but also true mycetoma following solid-organ transplantation [62]. The response to antifungals has generally been disappointing. Treatment consists of combined medical and surgical therapy. Some authors advocate high-dose amphotericin B as the treatment of choice for *Acremonium* mycetomas, while others report resistance and have found it to be of little use. Recent reports have cited resistance to ketoconazole, but successful treatment with fluconazole, itraconazole, or posaconazole [61, 63]. Consequently, *Acremonium* susceptibility testing is recommended to assist in choosing adequate treatment of infections caused by this filamentous fungus [64].

Invasive disease, however, is almost exclusively seen in patients with neutropenia, transplantation, or other immunodeficiency [61].

14.2 Cutaneous Fungal Infections with Lower Risk of Systemic Dissemination

14.2.1 Dematiaceous Septated Mould Infections

Dematiaceous moulds are often found in soil and generally distributed worldwide. While dematiaceous moulds typically cause diseases in normal hosts, such as localized lesions of skin and subcutaneous tissues following a penetrating injury, these pathogens have been increasingly recognized to cause sinusitis, pneumonia, infection of the central nervous system, and disseminated infection in immunocompromised patients. Alternariosis has been increasingly reported in solid-organ transplant recipients; it is possible that corticosteroid therapy and transplant-associated diabetes increase the risk for phaeohyphomycosis [62, 63]. The incidence of phaeohyphomycosis in solid-organ transplant recipients is similar to that of non Aspergillus hyalohyphomycosis, and was found to be approximately 9% in one recent review [65]. Phaeohyphomycosis usually occurs in the early or

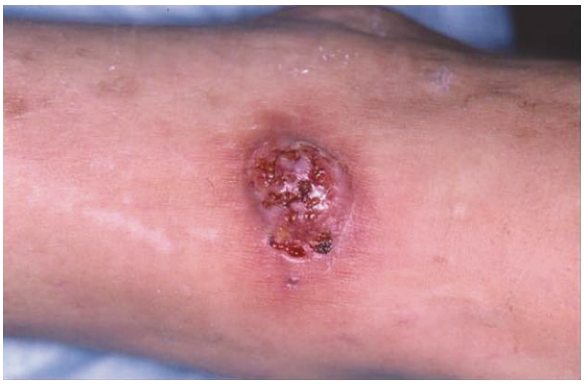


Fig. 14.5 Cutaneous alternariosis in a kidney transplant patient

intermediate post-transplant periods, and is characterized by pigmented, firm nodules or papules that evolve into ulcerated plaques. The prognosis is good when the infection remains localized, but mortality approaches 80% in disseminated phaeohyphomycosis. Fortunately, disseminated disease is a relatively rare event in immunocompromised patients. Diagnosis relies on careful microscopical and pathological examination, as there are no simple laboratory tests to reliably identify these fungi. Culture may be very long. Local infection may be cured with excision plus an antifungal agent such oral itraconazole or voriconazole, while systemic disease is often refractory to therapy [66]. In many cases, reducing the level of immunosuppresion is also helpful. Posaconazole and caspofungin appear to have potential for use in treatment of this rare infection [67] (Fig. 14.5).

14.2.2 Sporotrichosis (Sporothrix Schenckii)

Sporotrichosis, caused by the dimorphic fungus *Sporothrix schenckii*, is a result of either traumatic inoculation or inhalation of fungal spores. It occurs more frequently in tropical and subtropical areas. Skin lesions which develop after direct inoculation are characterized by papules or nodules with lymphocutaneous spread (sporotrichoid pattern). Lesions are erythematous with a smooth or a verrucous surface, or violaceous and ulcerated. Sporotrichosis without lymphatic involvement (fixed) and disseminated sporotrichosis are rare, with possible articular, pulmonary or CNS involvement. For cutaneous and lymphocutaneous sporotrichosis, itraconazole 200 mg is recommended. Amphotericine B is required for disseminated and meningeal forms [68].

14.2.3 Dermatophytosis

Trichophyton rubrum, a predominantly anthropophilic fungus, is the most frequent dermatophyte. But true dissemination of *T rubrum*, even if reported in a few cases, is exceptional, even in severely immunosuppressed patients [69]. Treatment relies on oral terbinafine.

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Skin Manifestations Associated with Malignant Haemopathies

15

Sélim Aractingi and Boutros Soutou

Core Messages

- Specific skin lesions may reveal a previously unknown malignant haemopathy.
- Specific skin lesions are an early indicator of acute transformation in myelodysplastic syndromes.
- Features of severe cutaneous infection in bone marrow aplasia are pseudo-benign.
- There are multiple types of paraneoplastic dermatoses that may herald haematologic malignancies.
- Skin reactions to chemotherapy are diverse, sometimes dose-dependent, and frequently difficult to manage.

Skin manifestations of malignant haemopathies often request urgent diagnostic or therapeutic procedures. Such cutaneous lesions mainly include (a) skin localizations of leukaemia and lymphoma, (b) severe cutaneous infections, (c) paraneoplastic syndromes, and (d) adverse cutaneous reactions to drugs and/or to procedures such as bone marrow transplantation. Some of these manifestations are shared by dermatologists and haematologists, and are paradoxically poorly known by both disciplines. The aim of this review is to give an overview of skin signs in malignant haemopathies that may require urgent decision, and to stress the importance of this domain.

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15.1 Skin Localizations of Leukaemias and Lymphomas

Skin-specific localizations of leukaemias and lymphomas are defined by the presence of malignant haematopoietic cells in the skin tissue. Such blood-cell-derived malignancies are divided into myeloid and lymphoid proliferations. Myeloid malignancies usually arise from bone marrow, and invade skin through the blood stream. Lymphoid malignancies may arise from any lymphoid cell niche; therefore, they may originate from the skin or, in contrast, invade the skin secondarily. Primary cutaneous lymphomas will not be discussed here, because the great majority of these consists of progressive diseases thoroughly detailed in dermatology textbooks.

15.1.1 Myeloid Malignancies

Skin localizations of myeloid malignancies are usually easy to recognize. They are featured as brown or violaceous nodules of variable size that develop in a few days or weeks (Figs. 15.1 and 15.2). There are no "epidermal" signs, namely scales, vesicles or erosions because the infiltrate spares the upper part of the dermis (called "Grenz zone") as well as the epidermis. A haemorrhagic red or blue halo is frequently present. The number of lesions is variable ranging from one to dozens of tumours. When facing such a "typical" situation, the diagnosis of metastatic skin invasion is easily evoked. If the malignancy is not yet known, the first step will be a blood cell count and smear that bring a quick diagnosis. Since prognosis and consequently treatment modalities of some leukaemias are altered

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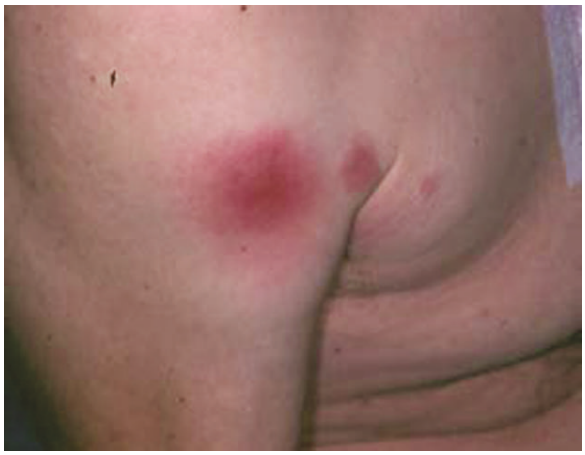

Fig. 15.1 Skin localization of an acute myeloid leukaemia

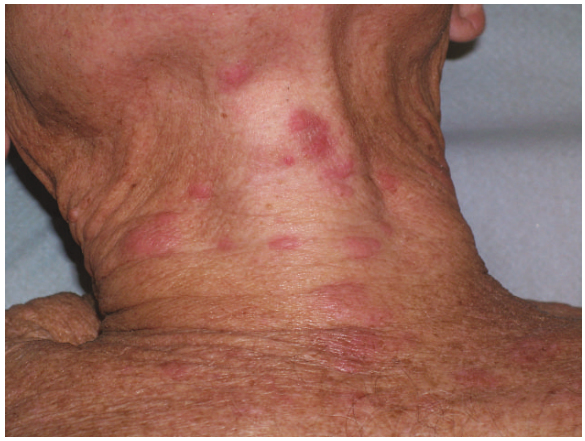

Fig. 15.2 Skin localization of an acute myeloid leukaemia

following specific skin involvement [1], a skin biopsy should also be performed later on. Acute myeloid leukaemias of type 4 (myelomonocytic AML 4) and type 5 (monoblastic AML 5) are those that most frequently give skin localizations.

More important is the fact that clinicians may be faced with "non-typical" cutaneous localisations. Atypical eruptions are frequent in eosinophilic proliferations, and they constitute the majority of skin localizations that herald acute transformation of myelodysplastic syndromes (MDS). Diverse presentations are possible like blisters, necrotic lesions, pruritic papules, cutis verticis gyrata, or mucosal erosions [2–4]. When facing such lesions, the dermatologist's role is to assess the presence of myeloid proliferation in the skin. This needs to take into account history, skin-lesion presentation and histological features, bearing in mind that molecular tools cannot characterize minimal monoclonal myeloid proliferations in skin infiltrate. The presence of membrane markers such as CD4(+), CD11c(+), CD33(+), CD43(+), CD68(+), the absence of others (KP1(−), CD8(−), CD45RO(−), CD45RA(−), CD20(−)), and the positivity of cytoplasmic myeloperoxydase, chloracetate esterase (in classical myeloid malignancies), or major basic protein (in hypereosinophilic syndromes) may be useful, since cytology of myeloid cells on fixed embedded tissues is frequently difficult to appreciate [5]. Demonstration that skin-invading cells are indeed myeloid is of real importance in myelodysplastic syndromes, because such lesions usually precede other features of acute transformation [6]. Since skin-specific lesions of MDS are atypical and different from skin tumours, and sometimes first to reveal acutisation, the role of the dermatologist in depicting such diagnosis is capital.

Aleukaemic leukaemia cutis is a rare entity characterized by skin nodules or tumours containing myeloid infiltrate without any demonstrable myeloid proliferation in blood or marrow. Phenotyping of the infiltrate should be done using all varieties of available antibodies detailed above. Secondary myeloid leukaemia occurs after a variable delay of weeks to months. The pathogenesis of this condition remains unknown. It has been speculated that it could correspond to a discrete marrow myeloid proliferation, not detectable by means of classical histology that displays elective homing in the dermis. Therefore, cells accumulate in the dermis and are "seen" only in the skin [7]. Several authors believe that skin is a sanctuary for myeloblasts, just as testes and meninges are sanctuaries for lymphoblasts.

15.1.2 Lymphoid Malignancies

Lymphomas may reach the skin and lead to metastatic nodules that are, in some cases, the unique presentation of the disease. Skin findings may include nodules, plaques, tumours, and, rarely, necrotic lesions. Many different B or T cell lymphomas will not be reviewed here. Some may develop in an acute pattern. The diagnosis is made by performing an urgent skin biopsy with the help of the additive tools of immunostaining, using various B, T and NK markers and/

or molecular demonstration of T or B cell receptors clonality. Adult T cell leukaemia/lymphoma (ATL), and angio-immunoblastic lymphadenopathy type of peripheral T cell lymphoma (AILD) are those that are most frequently revealed through skin localisations [8, 9]. It is interesting to remind that skin involvement in AILD usually presents as an acute non-specific rash mimicking adverse drug reaction or viral eruption (Fig. 15.3). This skin eruption is initially isolated, general signs developing later. Pathology is also difficult to interpret initially. Here too, dermatologists need to take into account context, clinical signs, pathology, immunohistochemistry, and T cell receptor rearrangement. All these situations illustrate the importance of the dermatologist's role in the management of malignant haemopathies.

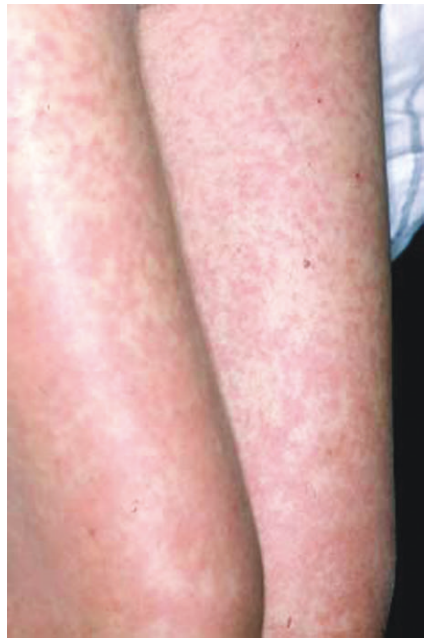

Fig. 15.3 A non-specific skin eruption revealing an angio immunoblastic lymphadenopathy with dysproteinemia (AILD)

15.2 Severe Cutaneous Infections

Patients affected with malignant haemopathies are prone to infections mainly because of the immune deficiency secondary to marrow lineage defects, chemotherapy or radiation regimen. Most cutaneous infections primarily develop in the skin, favoured by skin repair alterations under steroids, chemotherapy, and/or central venous catheterization. However, cutaneous infections may also develop after septicaemia — or less frequently from extension of an underlying locoregional infection. The following statements apply to patients with bone marrow aplasia: (a) there is a wide variety of organisms able to induce skin infections in these recipients, and (b) the "classical" symptoms reported in skin infections are not observed in these situations because leucopoenia limits the development of inflammatory features, including pus formation. Therefore, there is no correlation between clinical presentation, severity of infection, and causative organisms. In this way apparently benign lesions may be due to severe infections [10]. These peculiar observations have led to the rule that clinicians — when facing any suspicion of cutaneous infection in a patient with bone marrow aplasia — should biopsy such lesions systematically with three types of specimens: one for histology including special stainings for pathogens (Grocott, Gram, Periodic Acid Schiff, May Grunwald Giemsa, Ziehl), one for bacterial cultures and the third for fungal direct examination and cultures [10]. It should be noted that the features of such unpredictable infections do not concern viral skin infections, which usually remain close to the classical presentation.

The severity of skin infections may be due (a) to the type of skin infection itself, or (b) less frequently to the organism and its resistance to treatments, such as a localized infection induced by *Alternaria* or *Fusarium sp*. Severe skin infections include mainly septicaemia and dermo–hypodermal ("cellulitis") infections.

Clinicians should be alerted to possible septicaemia when facing monomorphous disseminated lesions of the trunk and extremities with frequent involvement of hands and feet. Similar faint erythematous macules or papules may feature *Candida* septicaemia as well as other micro-organisms infections. If usually drawn blood cultures are negative, multiple biopsies will be the most efficient diagnostic tool, especially if patients have already received anti-infectious treatments [11].

Dermo–hypodermal infections may develop, and appear like eythematous infiltrated plaques. However, the persistency of the infection in the hypodermis, usually taking the mask of a necrotizing cellulitis in immunocompetent individuals, may resemble a benign erythematous resistant plaque. Ecthyma gangrenosum is characterized by unique or multiple plaques with an

escharotic center and a red halo around. These infections are mainly due to *Pseudomonas aeruginosa* more than other Gram-negative bacteria, and may develop in the context of either a septicaemia or a local skin infection.

In conclusion, management of skin infection often requests multiple biopsies in order to help establish a precise diagnosis.

15.3 Paraneoplastic Syndromes

Paraneoplastic dermatoses may develop in the context of an already known malignant haemopathy, and eventually indicate a worsening of the prognosis and a need for treatment modification. Alternatively, such disorders may be diagnosed in patients with no previously known malignancy: they constitute a diagnostic emergency for early recognition of the haemopathy. It should be noted that the term "paraneoplastic" relates to a category of signs with relation to a malignancy and considered to evolve in parallel with this malignancy. However, many of these paraneoplastic syndromes, although clearly related to the haemopathy, will not show this parallelism. The dermatoses that are described below may be associated to a malignancy, but could also be idiopathic or associated to something else. Therefore, stating that a dermatoses is paraneoplastic requires the exclusion of other confounding factors. There is no accepted classification for these dermatoses, which are reported below.

15.3.1 Vascular Abnormalities

15.3.1.1 Acrosyndromes

Most of them develop in myeloid haemopathies, particularly those inducing an increase in blood viscosity, as in myeloproliferative syndromes. The main sign is a non-infiltrated distal *livedo reticularis* of the lower limbs [11]. Ulceration may secondarily occur. Histology can disclose intimal thickening of ascending arteries and arterioles [12]. Superficial *thrombophlebitis* may develop in the same myeloproliferations, mainly in polycythemia vera. *Erythermalgia* is a peculiar symptom characterized by crises of acute painful redness of the hands and/or the feet, triggered by external exposure to heat or less frequently by alcohol intake. In the presence of one of these acrosyndromes, blood cell count with a smear is a simple and sufficient test to address the question of an underlying haemopathy. It should be noted that *acral lividiosis* is a rare digital necrosis induced by the occlusion of dermal vessels with myeloblasts, as may happen in advanced stages of some acute myeloid leukaemias.

Raynaud's phenomenon and/or acrocyanosis are rarer, and rather triggered by lymphoid proliferations through cryoglobulinemia. The signs and symptoms are not different from classical Raynaud's and acrocyanosis. In view of the importance of this diagnosis, clinicians should make repeated efforts to depict an eventual underlying cryoglobulinemia. Lymphomas are usually associated with type I or type II cryoglobulinemias. There is no relationship between the intensity of type II cryoglobulinemias and the severity of the cutaneous involvement.

Vasculitis associated with malignant haemopathies affects the skin much more frequently than other organs such as kidneys, peripheral nerves, digestive tract or articulations. Therefore, skin manifestations should allow early diagnosis. The most frequent picture is characterized by the development of infiltrated purpuric papules of lower limbs that may sometimes evolve to bullous or necrotic lesions (Fig. 15.4). Histology is not different from non-paraneoplastic counterparts, showing small vessel vasculitis. The infiltrate is neutrophilic with leukocytoclasia, but giant cell granulomas are observed in about 30% of cases [13]. Dermo–hypodermal skin nodules are another

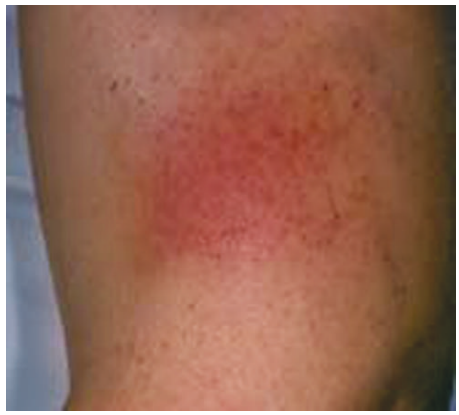

Fig. 15.4 Skin lesion of a sweet's syndrome

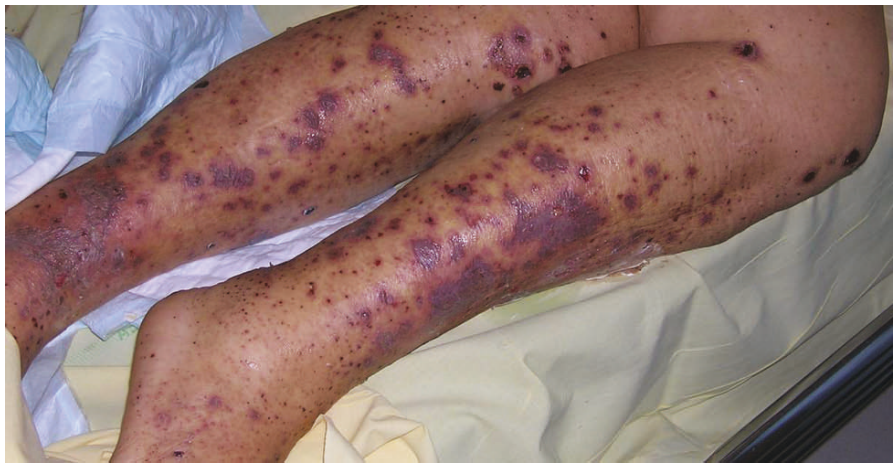

Fig. 15.5 Skin vasculitis associated with a myeloid hemopathy

manifestation of paraneoplastic vasculitis [14]. Vasculitis precedes or comes with the diagnosis of haemopathy in 26% and 39% of cases respectively [13]. All types of malignant haemopathies may be responsible for vasculitis. In literature, myeloid haemopathies are the most often found [14] but our own series showed in contrast a slight predominance of lymphoproliferations [13]. In this series, we found that when investigating vasculitis in patients with malignant haemopathy, causes such as infections or drug intake were responsible for 26% of cases. Therefore, before assessing paraneoplastic vasculitis, careful evaluation of other confounding factors is requested.

15.3.2 Neutrophilic Dermatoses

These are defined by diseases presenting skin infiltration with mature neutrophils that are not secondary to an infectious agent. Several studies have led to the concept that these dermatoses constituted a spectrum of disorders [15]. They have in common the feature of possibly being associated with myeloproliferations. But, the difficulty comes from the fact that most of neutrophilic dermatoses may be spontaneous or associated with auto-immune or auto-inflammatory diseases and/or other neoplasms. Therefore one should manage these as a primary or a secondary disease with several possible causes. Finally, since the clinical features and precise circumstances of development of most of these neutrophilic dermatoses remain different, they will be described below separately, as it is classically done.

Sweet's syndrome (acute febrile neutrophilic dermatosis; SS) presents as erythematous papules, plaques or nodules (Fig. 15.5). The number of lesions is variable. The diagnosis is confirmed by a biopsy that discloses dermal infiltration with mature neutrophils associated with oedema of superficial dermis. There is no vasculitis. The intensity of the oedema may lead to blistering. Blood cell count may find neutrophilia. Case control studies have shown that presence of blisters, involvement of upper limbs and anaemia were significantly associated with Sweet's syndrome accompany in malignancies [16]. In patients with haemopathies, pathological and/or molecular analyses have shown that the infiltrate may include a mixture of neutrophils and immature myeloid cells. Drugs given in the course of haemopathies are able to induce Sweet's syndrome. These are mainly granuclocyte colony stimulating factors (G-CSF) and all trans retinoic acid. G-CSF-induced Sweet's syndrome appears to display an important amount of histiocytes in the infiltrate [17]. These may have been mobilized by the G-CSF. Sweet's syndrome may precede the haemopathy by a period that may reach 11 years [16]. Accordingly, the so-called isolated Sweet's syndrome requires prolonged follow-up every 6 months in order to diagnose eventual occurrence of myeloid disease.

Neutrophilic eccrine hidradenitis (NEH). This condition is characterized by erythematous plaques or papules. Pustules are possible. Histology shows neutrophils around eccrine glands and coils. NEH could

therefore be viewed as a kind of "perisudoral Sweet's syndrome". However, there are two major differences from SS. The first is that NEH develops in patients with acute myeloid leukaemias and almost never in patients with other neoplasms or inflammatory conditions. The second peculiar point is that most cases of NEH develop during or after chemotherapy-induced bone marrow aplasia [18]; this timing has led authors to hypothesize that NEH could be a reaction to cytotoxic drugs. However, it is now clear that NEH is a paraneoplastic neutrophilic disorder, electively developing during bone marrow aplasia. The knowledge of this skin condition is mandatory for clinicians managing patients treated with chemotherapy. NEH is indeed a differential diagnosis of cutaneous infections and/or cutaneous adverse drug reactions. The paradox of having neutrophils accumulating in the dermis while these are nearly absent in peripheral blood remains unexplained. It has been hypothesized that such a phenomenon was the consequence of the differentiation followed by the migration of a myeloid clone known to display a peculiar skin tropism (such as AML4 or 5 leukaemias) [18, 19].

In contrast to the previous neutrophilic dermatoses, *Pyoderma gangrenosum* (PG) is usually easily evoked by clinicians. It is characterized by a deep unique ulcer whose periphery is spread with pustular orifices. Lesions of PG may affect any site. Nevertheless, they have been electively reported at sites of traumatism. When facing such features, the objectives are (a) to exclude any infectious cause, particularly if the patient has an established haemopathy, (knowing that superficial swabbing of a PG ulcer may grow microorganisms colonising, not causing the ulcer), and (b) to assess that PG is related to a haemopathy or other neoplasms. Histology is less specific, showing not only dermal neutrophilic infiltrate but also changes secondary to ulceration. In some patients, lesions of Sweet's syndrome and others of PG may occur concomitantly. There are also lesions that begin with Sweet's syndrome features and evolve later to a PG aspect [15].

Other neutrophilic dermatoses are much rarer. *Erythema elevatum* and *diutiunum* is characterized by red papules and plaques developing at the dorsum of fingers, elbows, and knees. *Subcutaneous sterile skin abscesses* appear as deep nodules filled with pus. Cases of *neutrophilic folliculitis* are even rarer, and may be an early step of PG.

15.3.3 Disorders Linked to Monoclonal Gammopathy

These are exclusively the consequence of lymphoproliferative disorders in which the clone secretes a monoclonal component.

AL amyloidosis (amyloid light chain) is an important life-threatening skin disorder. Clinical signs are various, but the most frequent are purpuric macules electively developing at traumatism sites such as skin folds, and more particularly eyebrows. Other features consist of brown papules sometimes coalescing to form plaques, macroglossia, blisters, hair loss, scleroderma or onychoatrophy. All these signs are the consequence of the deposition of light chains, mainly λ, that display a peculiar tridimensional β sheet configuration. The skin is a major target organ of amyloid deposition as it is found in 95% of affected patients in fat aspiration [20]. Skin (or more specifically hypodermal fat) specimens are therefore an important tool for the diagnosis of the disease, regardless of lesions development. Skin biopsy will show the presence of an amorphous substance displaying metachromasia after Red Congo, Thioflavin T or crystal violet staining. Recognizing this amyloid substance as secondary to Ig light chain deposition requires direct immunofluorescence that will display monotypic deposition of one type of light chain, and serum immunofixation or immunoelectrophoresis that will diagnose the monoclonal immunoglobulin. Amyloidosis may develop in many deep organs such as heart or intestine, and its early recognition is crucial.

Xanthomas are an important but rare feature of some monoclonal components (Mc Ig) which will not be detailed here.

Cryoglobulinemia is a disease induced by the physical properties of a monoclonal (Mc) component that precipitates in tissues at cold temperatures. There are three types of cryoglobulinemia. Type I consists of a pure cryoprecipitating Mc component; type II is a antigen–antibody complex with a Mc cryoprecipitating antibody reacting against the Fc portion of polyclonal Ig; type III is composed only of polyclonal cryoprecipitating immunoglobulins. Importantly, type II cryoglobulinemia corresponds to an antigen–antibody complex whose deposition in vessel walls triggers complement activation. Only types I and II are associ-

ated with lymphoid malignancies. Such haemopathies may be revealed — or complicated — by clinical signs induced by cryoglobulinemia, namely vasculitis (see above, in cases of type II cryoglobulinemia), cold urticaria or Raynaud's phenomenon (in all). Vasculitis may result in long-standing necrotic lesions. The diagnosis relies on the demonstration of cold precipitating globulins followed by electrophoretical identification of these globulins.

15.3.4 Blistering Auto-Immune Skin Diseases

These consist of rare disorders leading to auto-immunity against skin antigen(s) that are important for skin adhesiveness. This auto-immune activity may be secondary to a Mc component reacting against a cutaneous antigen, or more frequently to a polyclonal auto-immunity against a cutaneous antigen, similarly to what happens in thyroiditis or haemolytic anaemias associated with lymphomas. *Paneoplastic pemphigus (PNP), epidermolysis bullosis acquisita (EBA)* and *linear IgA dermatoses* are paraneoplastic disorders that may relate to lymphoid malignancies [22, 23] (Fig. 15.6). Details on these rare disorders are not in the scope of this chapter. However, one should bear in mind that the lesions may be discrete (especially for EBA), initially non-blistering (especially presenting as lichenoid lesions for PNP) and sometimes limited to mucous membranes. The diagnosis relies on immunofluorescent and/or immunoblotting techniques, using sometimes anti-light-chain antibodies to determine whether the reactivity is monotypic.

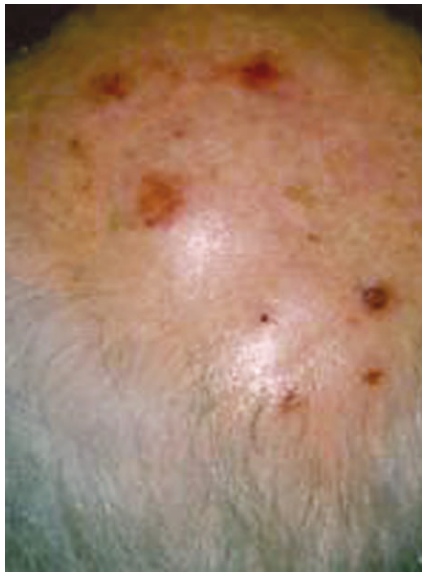

Fig. 15.6 Paraneoplastic epidermolysis bullosis acquisita (EBA)

15.3.5 Miscellaneous Paraneoplastic Dermatoses

They will not be detailed here. However, one should imperatively be aware of the fact that prurigo and ichtyosis may be the hallmarks of a lymphoma. The diagnosis relies on the morphological investigations undertaken in unexplained forms of these two entities.

15.4 Adverse Drug Reactions in Treatment of Malignant Haemopathies

This is an important domain that has been partly addressed in the chapter of severe adverse drug reactions. Some important points will be overviewed below.

15.4.1 Blistering Reactions to Cytotoxic Chemotherapy

Cutaneous reactions to chemotherapy regimens are poorly described. Trial investigators who reported large series have managed patients themselves without the help of dermatologists. Therefore, they gave scarce description of clinical cutaneous features, and did not adequately evaluate either drug imputability or confusion factors. Despite this major difficulty, clinicians should be informed that several cytotoxic regimens may be responsible for disseminated eruptions. The clinical presentation may resemble toxic epidermal necrolysis or Stevens–Johnson/erythema multiforme

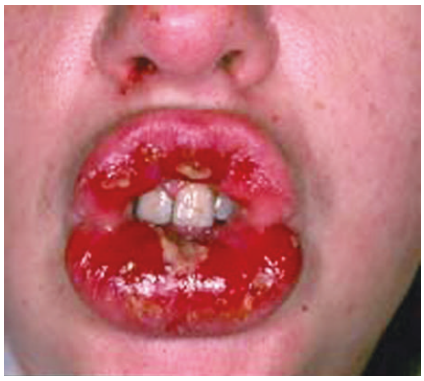

Fig. 15.7 Mucitis following chemotherapy

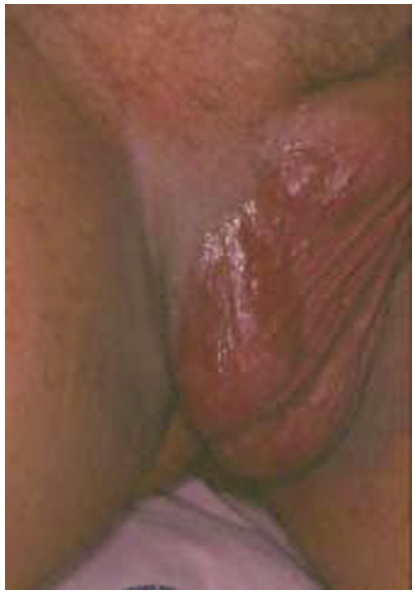

Fig. 15.8 Scrotal blistering due to methotrexate

(Fig. 15.7). The mechanisms of some of these appear to be possibly "toxic", dose-dependent rather than "allergic", or dose-independent [24]. Methotrexate and imatinib may definitely induce such blistering eruptions (Fig. 15.8). Other drugs have less well-identified cases. The classical chronological rules for drug imputability cannot be applied to suspected cases of chemotherapy. It is therefore always difficult to answer the questions raised by the corresponding haemato-oncologists, which may be summarized as follows: (a) 'is the cutaneous eruption drug-induced, and if yes which molecule is responsible?', and (b) 'is it allowed to continue the same protocols?' Skin biopsy has been shown to be non-specific, since histological features are "compatible" with those of drug adverse reaction, known to be similar to other disorders such as viral infections. Liver, kidney and mucous membranes may be involved. The following points, when present, may help in evoking a reaction induced by chemotherapy: (a) previous infusions have led to similar or more attenuated features, (b) palms and soles are predominantly and initially involved, and/or (c) epidermal abnormalities (vacuolisation, necrosis) are pressure, contrasting with the absence of skin mononuclear infiltrates, and evoking direct cytotoxicity of the conditioning regimen. The final answer to the above questions will rely on a common dermatologist/haematologist discussion in which the severity of the reaction, the assessment of imputability, and the importance of the drug in the disease management will be taken into consideration.

15.4.2 Anaphylactoid Reactions

Urticaria, angioedema and/or collapses may be linked to chemotherapy agents. It is mandatory to recognize them and to strictly avoid rechallenge. L-Asparaginase and platins are the main causes. In vivo testing with prick and/or intradermal injections should be done in specialized departments since these molecules may produce skin necrosis. These tests seem possible only for platins.

15.4.3 Acute Graft versus Host Reaction

Allogeneic bone marrow recipients may present in the first 3 months after grafting an acute graft versus host disease (GvHD). It corresponds to the reactivity of donor T lymphocytes — contaminating the marrow — against host antigens. There are four grades of severity, which go from a moderate rash to a blistering disseminated fatal disease. These are usually diffuse and scarlatiniform. They involve palms, soles, and ears. Mucous membranes are also frequently involved. Skin and mouth lesions can evolve to blistering, a severe life-threatening complication. Managing of rash after bone marrow transplantation is always difficult, because the question is about discriminating between the

toxicity of the conditioning regimen, the virus reactivation, and the acute GvHD. Distinguishing one entity from the other remains difficult, since histology and immunohistochemistry are non-specific. The presence of extra-cutaneous organ involvement, such as liver and digestive tract involvement, may bring help. As a consequence, most patients who have clinical and histological features "compatible" with acute GvHD will be managed as such, since this condition requires an urgent systemic treatment with steroids. However, and although there is no real alternative, this attitude leads to overdiagnosis of GvHD and overtreatment of such cases.

15.4.4 Others

Digital necrosis has been reported with bleomycin and interferon. It is a severe reaction that needs urgent withdrawal of the drug. Skin extravasations of cytotoxic agents may lead to necrosis of variable severity and depth. However, necrosis may persist for long periods due to the leucopoenia.

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16 Skin Manifestations Useful for the Management of Patients in an Intensive Care Unit or an Emergency Room

(Except Lesions Directly Related to the Acute/ Life-Threatening Disease)

Camille Francès

Core Messages

- For an emergency doctor, the most important challenge is to recognize the dermatologic manifestations, which may be helpful for the diagnosis or for the management of the patient, and to differentiate them from those which are without consequences.
- Among the significant dermatologic manifestations, three groups may be schematically distinguished:
- Skin lesions which are evidences of the background: generalised pigmentation, purpuric macules, pigmented spots, thin and translucent skin, etc.
- Skin change that may be helpful for the diagnosis in three clinical situations: acute abdominal syndrome, cerebrovascular events, haemorrhagic syndrome.
- Some nail abnormalities, resulting from internal disorders, may be important for the management of patients: half and half nail, multiple subungual splinter hemorrhages, clubbing.

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16.1 Skin Changes Which Have Evidences of the Background

(1) *Generalised pigmentation* including mucosal pigmentation is indicative of systemic disease, mainly metabolic or endocrine (Figs. 16.1, 16.2). Whatever the cause, it is more marked over sun-exposed and traumatized areas. When organomegaly is present, hemochromatosis or another metabolic disease is evoked. The presence of diarrhoea is suggestive of malabsorption with multiple vitamin or trace element deficiencies. Other skin changes due to malabsorption included acquired dry, loose skin and itch, hair and nail changes, and eczematous or psoriatic rashes. If the diffuse pigmentation is isolated, it is important to look for a chronic adrenal insufficiency due to primary adrenal failure [1]. Indeed, this chronic adrenal failure might become acute on the occasion of the present emergency with a lethal risk.

(2) *Purpuric macules* are common on the sun-exposed areas, especially on the dorsal forearms of old patients, surrounded by a severely sun-damaged skin with stellate scars (Fig. 16.3). Skin is thin, and tears after minimal trauma. When present in younger patients, these skin manifestations are usually observed after months of corticosteroids therapy or in Cushing disease. They are associated with lipodystrophy. Indeed, excessive deposits of fat over the clavicles and back of the neck (buffalo hump) contrast with loss of subcutaneous fat over the extremities. In addition, deposition of fat in the cheeks and telangiectasia give a moon appearance of the face. If the patient is unconscious, it is important

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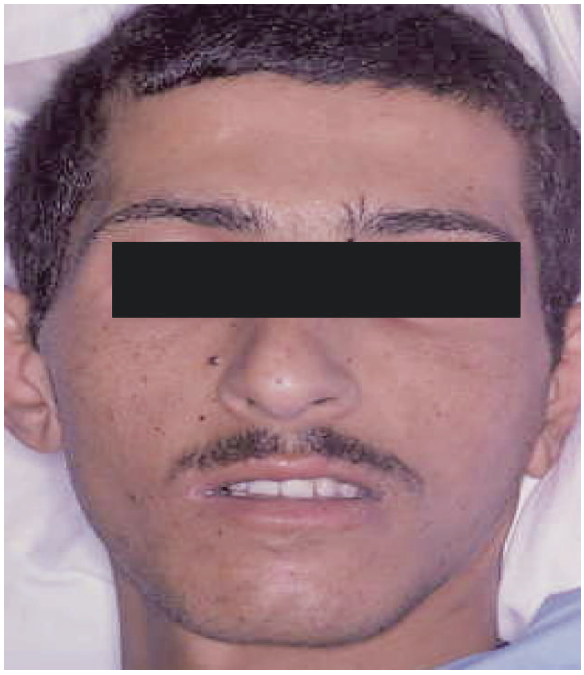

Fig. 16.1 Diffuse brown pigmentation of the face in Addison's disease

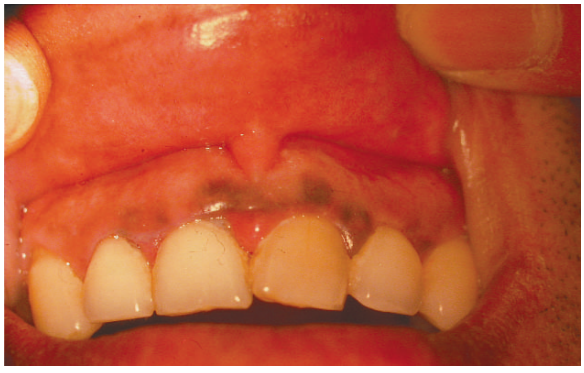

Fig. 16.2 Mucosal pigmentation in Addison's disease

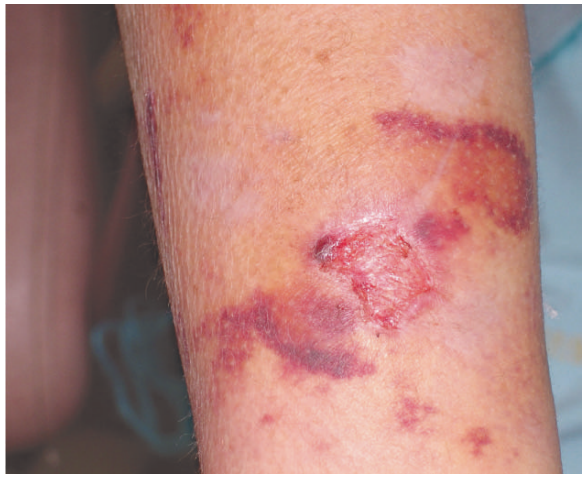

Fig. 16.3 Bateman purpura on the forearm with thin atrophic skin and stellate scars

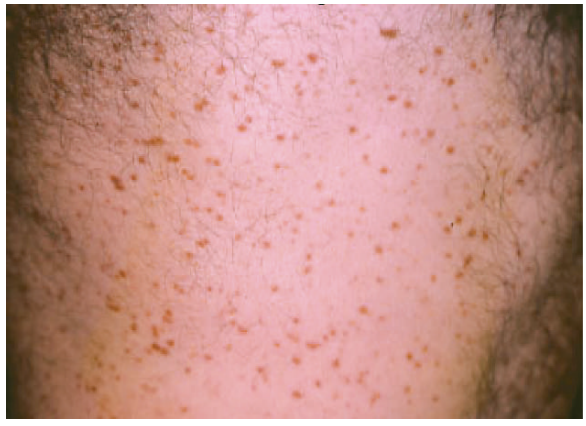

Fig. 16.4 Pigmented spots on the trunk suggestive of urticaria pigmentosa

to ask relatives about his current treatment, and not to suddenly stop corticosteroids to avoid acute adrenal insufficiency.

(3) *Pigmented spots* on the trunk may be induced by the presence of mast cells as in urticaria pigmentosa which is the most common skin manifestation of *mastocytosis* both in children and adults (Fig. 16.4). Skin lesions appear as small, yellow-tan to reddish-brown macules or slightly raised papules. Mild trauma, including scratching or rubbing of the lesions, frequently causes urtication and erythema (Darier sign). Mast-cell degranulation may occur on exposure to various stimuli and drugs. The release of histamine, heparin and vasoactive substances such as prostaglandin D2 may cause severe hypotension and other anaphylactoid manifestations. Anaesthetic management should include perioperative stabilization of mast cells and avoidance of the use of histamine-releasing drugs. Intradermal skin testing is useful in predicting sensitivity to drugs that may be used during anaesthesia [2].

(4) *A thin, translucent skin* with a clearly visible venous network on the trunk may be the sole manifestation of a rare genetic disease named *Ehlers–Danlos* type IV (Fig. 16.5). When the skin is softly stretched between fingers, a dotted yellow colour appears (Fig. 16.6). Usually, easy skin bruisability is present. However, Ehlers–Danlos type IV is clinically distinct from other

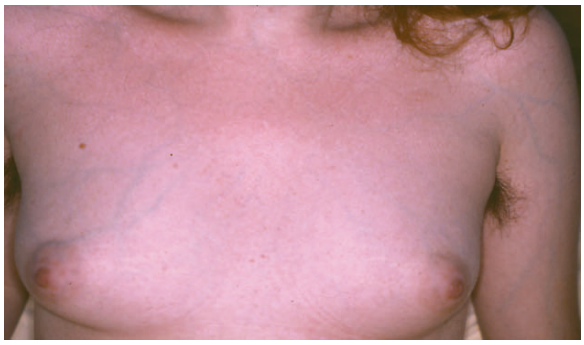

Fig. 16.5 Thin translucent skin with visible veins

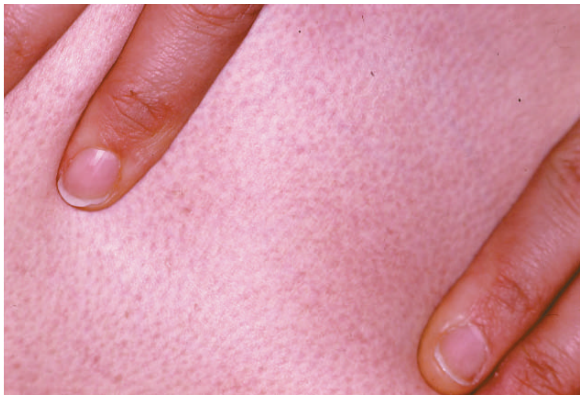

Fig. 16.6 When skin is stretched, the dotted yellow colour is suggestive of Ehlers–Danlos type IV

Fig. 16.7 Joint laxity

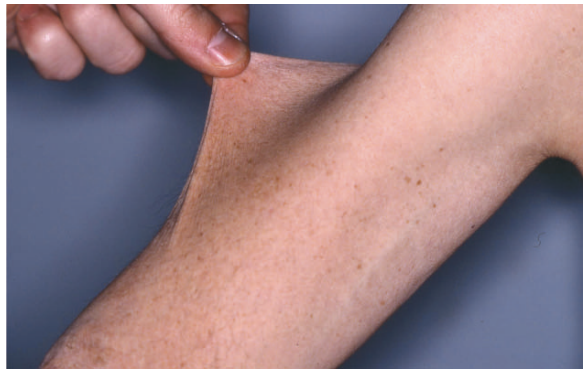

Fig. 16.8 Skin hyperextensibility

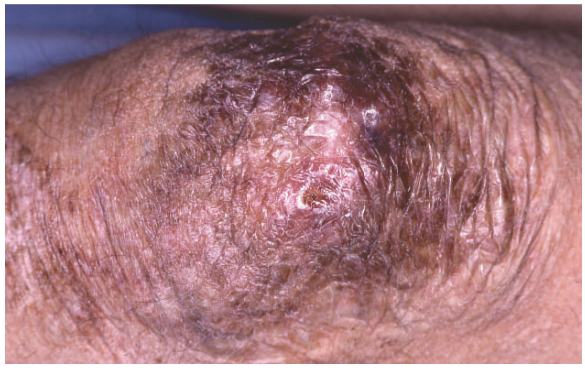

Fig. 16.9 Skin fragility with thin atrophic scars on the knee

Ehlers–Danlos subtypes because there is no skin hyperextensibility, abnormal scarring or joint laxity. Affected individuals are at high risk for life-threatening rupture of arteries or large intestine. Therefore, investigative investigations such as arteriography or colonoscopy should be avoided. Surgical operations should be limited to those required by a fatal risk.

These risks are less threatening for patients with other Ehlers–Danlos subtypes characterized by joint laxity, skin hyperextensibility and skin fragility. Arterial ruptures are also reported in type I [3]. Patients with this subtype are usually easily recognizable due to severe joint laxity (Fig. 16.7), skin hyperextensibility (Fig. 16.8) and skin fragility with thin atrophic scars (Fig. 16.9). Only essential invasive explorations will be performed. In contrast, patients with the more common type III Ehlers–Danlos have a benign disease which allows all invasive investigations.

(5) When *petechiae, purpura*, and *ecchymoses occur spontaneously* or after minor trauma on an apparently normal skin, without evidence of haemostasis abnormality, amyloid infiltration of the blood vessels walls is suspected. In *primary* and *myeloma-associated systemic amyloidosis*, purpuric lesions are especially found in flexural regions, such as the eyelids (Fig. 16.10). They may be also present on nasolabial folds, neck, axillae, and anogenital areas. Other frequent dermatologic manifestations of systemic amyloidosis include enlarged tongue and waxy, smooth shiny papules or nodules [4]. Pitting edema may result from nephrotic syndrome and congestive cardiac failure. Dehydration

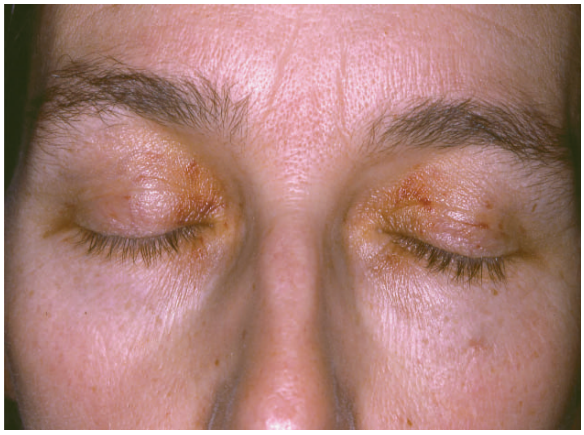

Fig. 16.10 Purpuric lesions of the eyelids

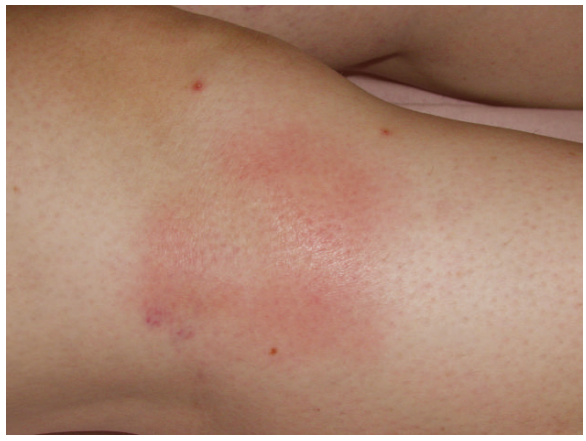

Fig. 16.11 Nodular lesion of panniculitis

and hypovolemia are dangerous, due to the risk of nonreversible acute renal insufficiency and renal venous thrombosis. A monoclonal gammopathy is usually present.

16.2 Skin Changes Which May Be Helpful for the Diagnosis of the Emergency in Three Clinical Situations

16.2.1 Acute Abdominal Syndrome

Panniculitis may be induced by pancreatitis or pancreatic carcinoma. Crops of painful, erythematous, fluctuant nodules appear mainly on the legs or on the trunk [5]. They occasionally drain an oily substance. These nodules are clinically indistinguishable from those related to idiopathic lobular panniculitis (Fig. 16.11).

Eruptive xanthomas are yellow-orange to red-brown papules that are often surrounded by an erythematous halo, which appear in crops on the buttocks, extensor surfaces of the extremities, and flexural creases (Fig. 16.12). They occur in the setting of chylomicronemia and hypertriglyceridemia whatever the origin: genetic or acquired deficiency of lipoprotein lipase in individuals unresponsive to insulin, or familial hyperlipoproteinemia [6]. Other features of hyperlipidemia often noted in patients with eruptive xanthomas include lipemia retinalis, hepatosplenomegaly, and abdominal pain. The abdominal pain may be secondary to intestinal ischemia from increased blood viscosity, stretching

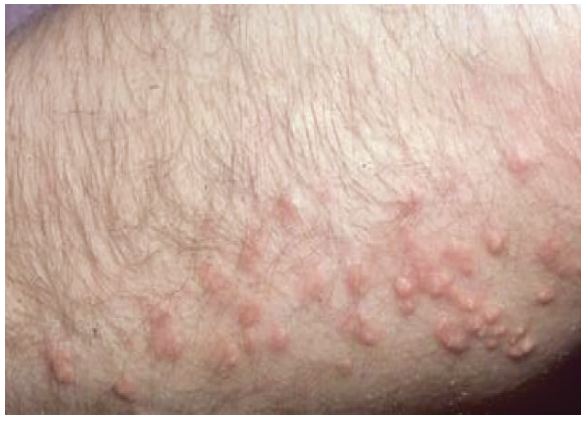

Fig. 16.12 Eruptive xanthomas

of organ capsules by lipid deposition in the liver or spleen, or chronic episodes of pancreatitis.

Malignant atrophic papulosis or *Degos's disease* is a rare disorder characterized by widespread thrombosis of small vessels, not only in the skin but also in the gastrointestinal tract and in the ocular and central nervous system [7]. Clinically, skin lesions consist initially of small, firm papules from 2 to 5 mm in diameter. Secondly, the papules become umbilicated, and a central white, porcelain-like zone of atrophy appears, encircled by an erythematous telangiectatic border (Fig. 16.13). Lesions similar to those of malignant atrophic papulosis have been described in patients with primary or systemic lupus erythematosus-related antiphospholipid syndrome (APS). Usually skin lesions in APS are larger than those observed in malignant

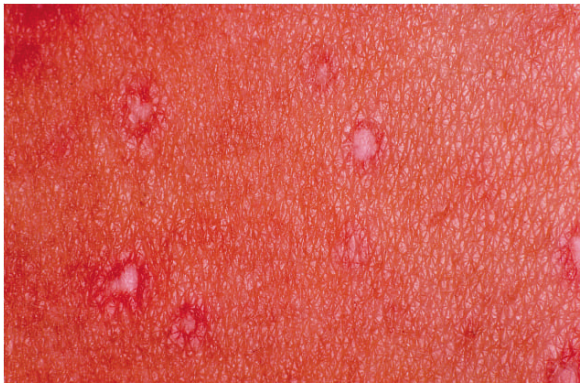

Fig. 16.13 Small atrophic lesions encircled by a telangiectatic border typical of malignant atrophic papulosis

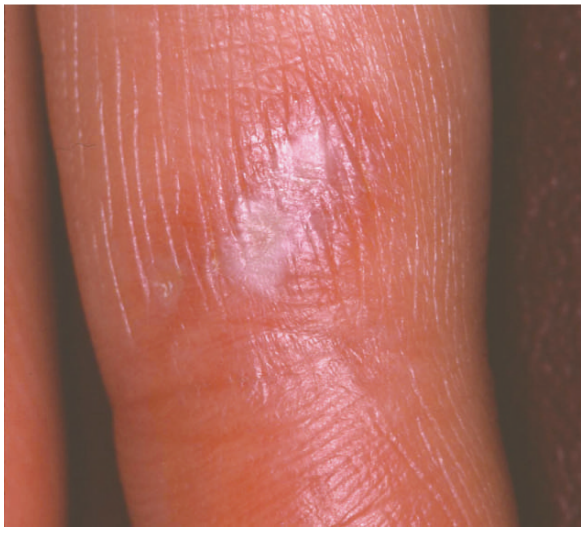

Fig. 16.14 Larger malignant atrophic papulosis-like lesion in antiphospholipid syndrome.

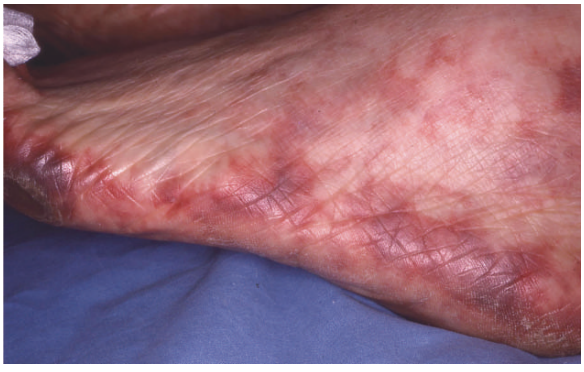

Fig. 16.15 Violaceous livedo reticularis suggestive of cholesterol crystal microembolisation

atrophic papulosis (Fig. 16.14). Acute abdominal syndrome in APS may be related to mesenteric or other arterial thrombosis, or to bilateral adrenal hemorrhages secondary to adrenal venous thrombosis, leading to acute adrenal insufficiency [8].

Palpable purpura is the most frequently observed cutaneous lesion in nearly all systemic vasculitis. Other lesions include wheals which persist for 2 to 3 days unlike ordinary urticaria, red and small-sized nodular lesions that may be surrounded by livedo reticularis, cutaneous necrosis and nonfollicular pustules. These dermatologic manifestations are very useful for the diagnosis of vasculitis, but don't help to identify the type of systemic vasculitis [9].

16.2.2 Cerebrovascular Events (CVE)

Livedo reticularis is associated with CVE in different conditions. Whatever the clinical situation, it is distinguishable from cutis marmorata due to the usual irregularity of the fishnet reticular pattern. When it is painful, violaceous, associated with skin necrosis or purple toes (Fig. 16.15), it is suggestive of cholesterol crystal microembolisms that may be visualized in the eye fundus [10]. The clinical manifestations develop frequently after vascular investigations, surgery or in the weeks after onset of anticoagulant therapy. When livedo reticularis is red, widespread, noninfiltrated, localized not only on the limbs but also on the trunk and/or buttocks [11], it is suggestive of Sneddon's syndrome (Fig. 16.16). In systemic

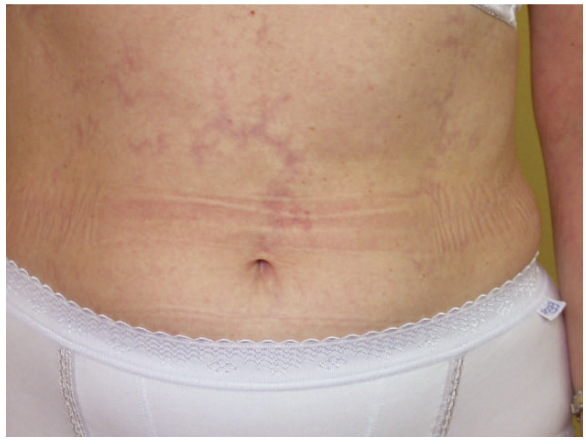

Fig. 16.16 Red, noninfiltrated, widespread livedo reticularis of Sneddon's syndrome

vasculitis, livedo reticularis is usually infiltrated (Fig. 16.17) and associated with palpable purpura. In intravascular lymphomas, livedo reticularis is less extensive, frequently infiltrated, and associated with other cutaneous lesions.

16.2.3 Haemorrhagic Syndrome

Yellow papules on flexural areas, especially on sun-unexposed axillae, are suggestive of an inherited disease of elastic tissue (*Pseudoxanthoma elasticum*), which may lead to the emergency care unit due to intestinal bleeding or early arteriosclerosis, without any other risk factors for early heart disease. Lesions primarily involve flexural areas and scars; they begin as yellow papules (Fig. 16.18) that gradually enlarge and become confluent to form plaques or redundant folds of skin (Fig. 16.19). On the neck, they may be confused with solar elastosis related to skin ageing on sun-exposed areas.

Linear telangiectasia are common on the face of patients with a fair complexion and don't have any signification. In contrast, *round telangiectasia*, localized not only on the cheeks but also in the mouth (lips, tongue…) and on other parts of the body such as on hands and feet are suggestive of hereditary hemorrhagic telangiectasia (Fig. 16.20). When associated with systemic scleroderma, they are usually less numerous.

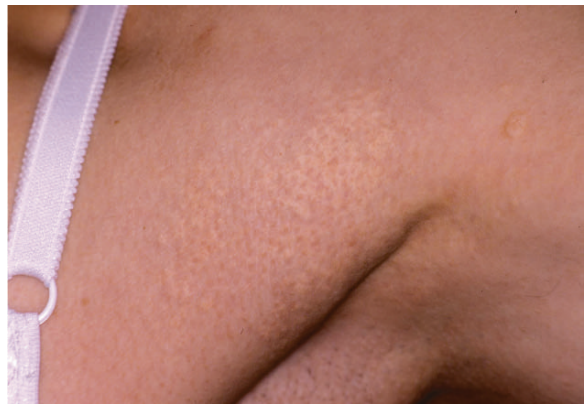

Fig. 16.18 Yellow papules on axillae suggestive of Pseudoxanthoma elasticum

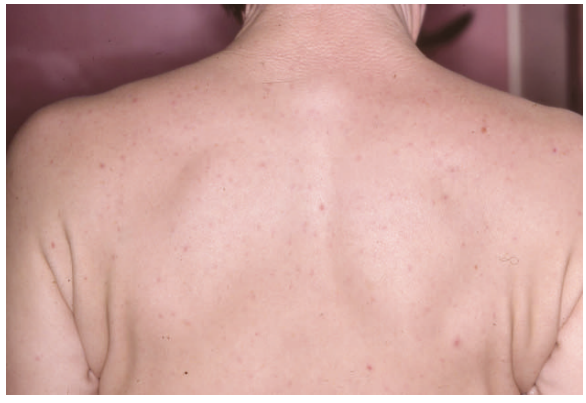

Fig. 16.19 Redundant folds of the skin on axillae also suggestive of Pseudoxanthoma elasticum

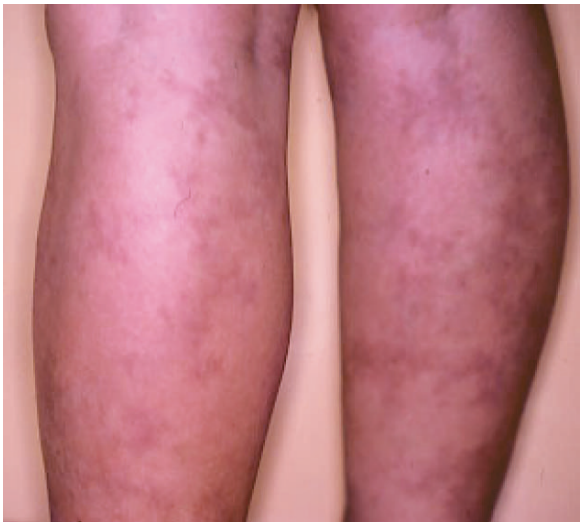

Fig. 16.17 Infiltrated livedo reticularis on the limbs suggestive of vasculitis

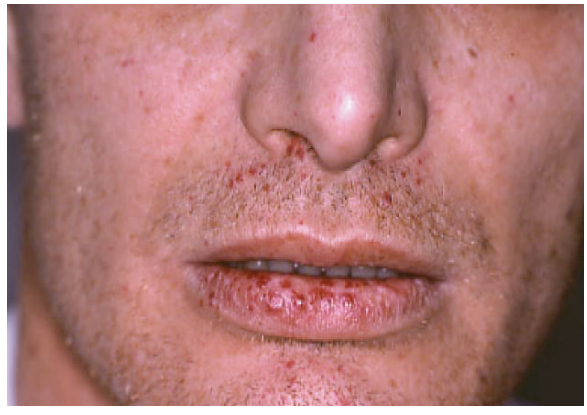

Fig. 16.20 Multiple round telangiectasia in hereditary hemorrhagic telangiectasia

Gastrointestinal bleeding is uncommon in systemic scleroderma while it occurs frequently in patients with *hereditary hemorrhagic telangiectasia*. Those patients may also be seen in emergency due to massive hemoptysis and brain abscesses which are the consequences of the frequent pulmonary arteriovenous fistulae.

The presence of telangiectasia in patients with intestinal bleeding may also be related to *hepatic cirrhosis*. Indeed, patients with chronic liver disease, often have telangietactic changes, mainly over the areas of the body exposed to the light. Palmar erythema and spider angiomas are usually associated. These angiomas, which don't differ from those observed in pregnancy, resemble a spider in that numerous small vessels radiate from a central arteriole that may be flat or elevated (Fig. 16.21). They occur primarily on the upper chest, face and arms.

16.3 Some Nail Abnormalities, Resulting from Internal Disorders, may be Important for the Management of Patients

(1) *Half and half nails* consist of a proximal white half of the nail due to edema of the nail bed and a distinct normal distal portion. It is associated with hypoalbuminemia whatever the cause, cirrhosis and renal failure (Fig. 16.22).

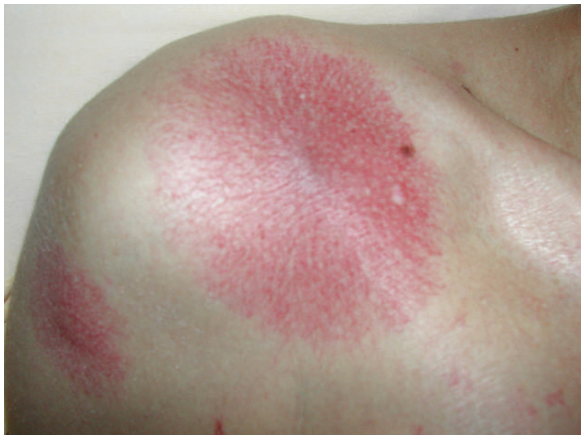

Fig. 16.21 Spider hemangioma in a cirrhotic patient

(2) Multiple *subungual splinter hemorrhages* appear as tiny linear longitudinally oriented, reddish-brown to black, distal subungual lesions that fail to blanch under pressure (Fig. 16.23). They may result from nail dystrophy. When the nail shape is normal, their acute development indicates the existence of an underlying thrombotic or embolic disease with other probable worrying thrombotic events. They have initially been recognized as an important sign of subacute bacterial endocarditis. In fact they can be observed in all thrombotic or embolic conditions, such as Trichinella spiralis infection, hypereosinophilic syndrome, antiphospholipid syndromes, limb aneurysms…

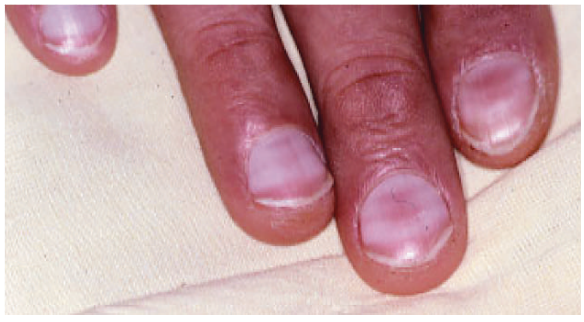

Fig. 16.22 Half and half nails

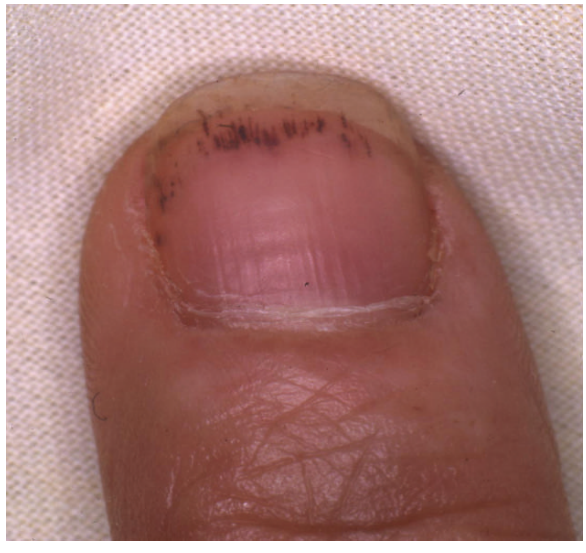

Fig. 16.23 Multiple subungual splinter hemorrhages

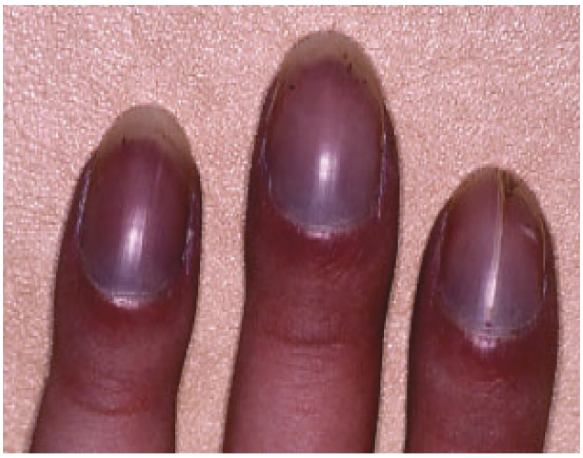

Fig. 16.24 Digital clubbing

(3) *Clubbing* is characterized by an enlargement of distal digits giving them a bulbous appearance (Fig. 16.24). The Lovibond angle, the angle between the proximal nailfold and the nail plate is normally less than 180°. In patients with clubbing, the angle straightens and ultimately exceeds 180°. When clubbing is associated with subperiosteal news bone formation, the term hypertrophic osteoarthropathy is used. Bilateral and symmetric acquired clubbing of the nails may occur in association with all pulmonary and mediastinal diseases, cyanotic cardiovascular diseases, hepatic cirrhosis, and chronic diarrhea. Unilateral and unidigital clubbing is seen in relation to localized vascular lesions, including aneurysm, arteriovenous fistulae.

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Part IV
Specific Context

Emergencies in the Dermatologist's Office 17

Dominique Penso-Assathiany

Core Messages

- Emergency situations can occur even in the dermatologist's private office.
- An emergency can be reviewed for dermatologic conditions: questioning, looking for signs of severity, examining mucous membranes are important.
- Severe vasovagal malaise may occur during benign procedures.
- Material must be easy to use, validity dates must be verified.
- The emergency phone number must be registered and the phone must be easily accessible.
- Although exceptional, emergencies may occur at anytime in our private dermatology offices.
- Some of these emergencies may be dermatologic, i.e. TEN and SJS, DRESS, necrotizing fasciitis, Kawasaki disease, purpura fulminans.
- Others may be the consequence or a complication of our practice (vasovagal syncope, anaphylactic shock) or be independent of the practice but occurring in our office (i.e. seizure or cardiac arrest).
- This chapter will consider all these situations.
- Equipment and prevention will also be studied.
- Our purpose is to recognize these situations at their beginning in order to undertake appropriate emergency procedure.

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17.1 Life-Threatening Dermatologic Diseases:

17.1.1 Cutaneous Adverse Drug Reaction

Toxic epidermal necrotizing (T.E.N.) or Lyell's syndrome and Stevens–Johnson syndrome [1]: Toxic epidermal necrotizing (TEN) and Stevens–Johnson syndrome (SJS) represent different severity levels of this disease. The difference is based on the evaluation of involved body surface area (BSA). They are the more severe of the cutaneous adverse drug reactions (ADR). The mortality is about 30% for TEN. Drugs are nearly always involved, but in about 20% of the cases they are not identified despite very meticulous questioning.

Beginning signs are often very difficult to recognize, but they are very important because it is known that the more rapid the clearance of the responsible drug, the better the prognosis [2]. The condition may begin by isolated fever, sore throat, cough or burning eyes. The cutaneous eruption may be erythematous macules, sometimes with darker purpuric centres that tend to merge. Usually, within 1–3 days, flaccid blisters and a sheet-like epidermal detachment appear, with Nikolsky's sign. Mucous membrane erosions are present, and the diagnosis is no longer difficult (Figs. 17.1–17.5).

The signs that should alert the physician are:

- A rash accompanied by one mucous involvement, even as minimal as a discrete conjunctivitis.
- Bifocal or multifocal involvement is highly suggestive of a severe form of cutaneous ADR.
- Adenomegaly.
- High fever above 38.5°C.
- Very high tenderness of the skin with burn sensation.
- Anxiety.

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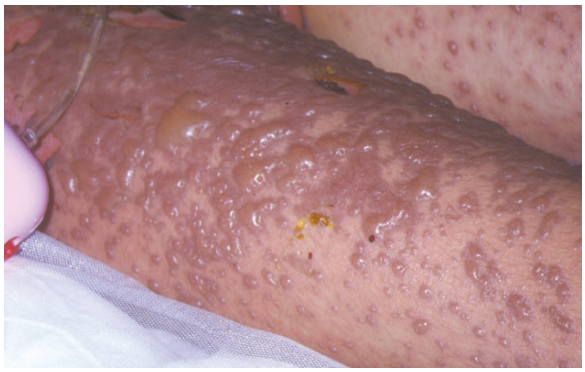

Fig. 17.1 Early lesions of toxic epidermal necrolysis

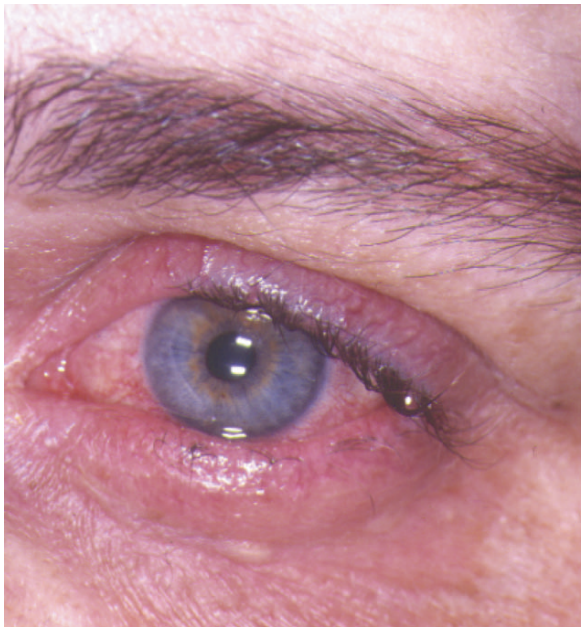

Fig. 17.2 Conjunctivitis: early sign of toxic epidermal necrolysis

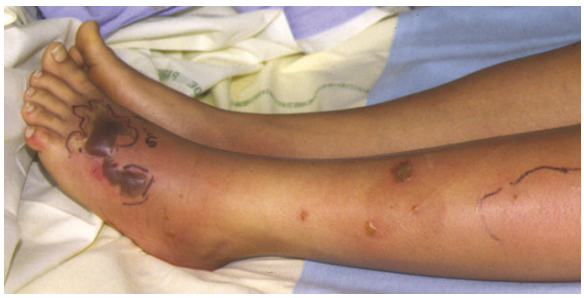

Fig. 17.3 Necrotising fasciitis

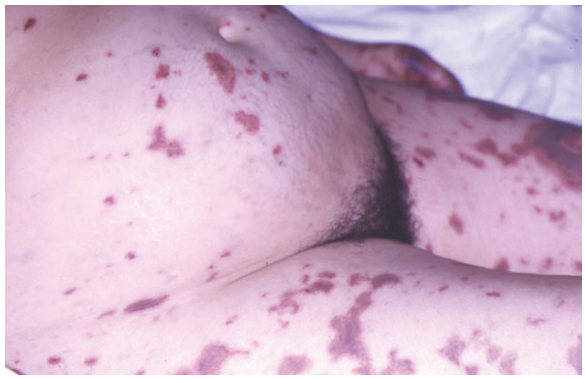

Fig. 17.4 Purpura fulminans

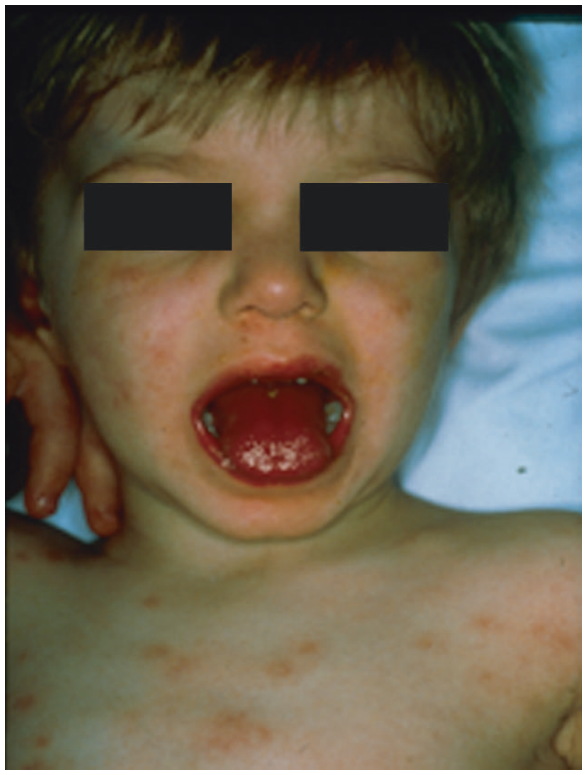

Fig. 17.5 Kawasaki syndrome

- Blisters with Nikolsky sign.
- Delay between introduction of the drug and the first signs longer than expected in a common rash, about 1–3 weeks.
- Recent initiation of a treatment with a drug known to be one of the 'usual suspects' for SJS or TEN, such as carbamazepin, lamotrigin, nevirapin, oxicam and other non-steroidal anti-inflammatory drugs, phenobarbital, phenytoin, sulfamethoxazole, and salazopyrin.

Depending on the initial signs, other diagnoses may be discussed, such as a pharyngitis interpreted as viral or bacterial impairment, infectious conjunctivitis, or chickenpox.

The correct procedure when such a situation is recognized is to phone a specialized unit for burn care or intensive dermatological care. All drugs must be stopped, as quickly as possible. Antalgic drugs may be administered, but no treatment should be undertaken on the blisters except vaseline dressing, awaiting transfer to a specialized unit.

17.2 Drug Eruption with Eosinophilia and Systemic Symptoms (DRESS) Syndrome [3]

This cutaneous ADR is also severe, with mortality about 10%. The delay before onset is often very long between the introduction of the causative drug and the first signs — up to 8 weeks.

Clinical signs are dominated by a very poor general condition, with high fever, important adenomegaly and the presence of erythematous macules quickly becoming a pruritic erythrodermia. The condition starts in the face and the upper trunk and then diffuses to the limbs. Peri-orbital oedema is quite impressive. Even if the vital prognosis is not immediately made, it is very important for the patient to be rapidly referred to a specialized dermatologic unit. Biological perturbations will be associated, such as major hyper-eosinophilia, hyper-basophile lymphocytes, hepatic cytolysis and cholestasis, and renal impairment. All solid organs can be involved, such as liver, kidney, myocardium, lung, and central nervous system.

The culprit drugs are mainly carbamazepine, allopurinol, hydantoin, lamotrigin, sulfonamides, minocycline, non-steroidal anti-inflammatory drugs, nevirapine, calcic inhibitors, methyldopa, terbinafin, neuroleptics, and dapsone.

Suggestive signs are:

- Lichenoid–type erythrodermia
- Fever of more than 38.5°C and large adenomegaly, more than 1 cm, in at least two localisations
- Poor general condition
- Non-mucous involvement
- Drugs known to be inductors
- Very long delay between introduction of the drug and beginning of the ADR

Clinical Criteria of severity of cutaneous adverse drug reaction:

Poor general condition with high fever
Facial oedema
Oedema of lips, eyelids
Mucous erosions in buccal cavity, genitalia
Blisters and Nikolsky sign
Multiple pustulosis on an erythematous skin

Biological criteria of severity of cutaneous drug adverse reaction:

Hyper-eosinophilia above 10% or 1,500 ml^{-1}
Hepatic cytolysis: more than twice the normal, or cholestasis with alkaline phosphatasis more than 1.5-fold the normal
Visceral failure: kidney function, abnormalities of respiratory functions.

17.3 Angioedema [4]

This is an immediate-type hypersensitivity reaction. It corresponds to a profound type of urticaria. Skin localisation is possible but the danger comes from mucous involvement. Unlike the usual urticaria, angioedema is a tender and thick tumefaction of the skin. There is no pruritus; it can be painful. Lips, cheeks, peri-orbital areas and tongue are often involved. Occurrence of dysphonia, hyper-salivation, dysphagia, and signs of involvement of the pharyngeal area must be considered as alert signs because of the risk of glottis oedema. Furthermore, apparition of an angioedema may precede anaphylactic shock. The best approach is to phone the emergency ambulance services; in the absence of signs of gravity such as dysphonia or hyper-salivation, corticosteroids should be injected. Anti-histaminic drugs may be injected afterwards.

In the case of signs of gravity or evolution towards an anaphylactic shock, epinephrine IM must be used. Dosage will be increased from 0.30 to 0.50 mg. It can be repeated every 10–15 min if necessary. An oxygen mask at 10–15 $l\ min^{-1}$ should be fitted while waiting the emergency mobile unit.

Angioedema: signs of gravity:
Dysphonia
Hyper-salivation

Emergency treatment:
Corticosteroids injectable in form without signs of gravity
Oxygen and epinephrine if the situation develops

17.4 Anaphylactic Shock [5] (Cf Chap. 38)

This occurs very quickly, usually less than 1 hour after introduction of the allergen. It is very important to recognize it quickly because of its gravity. Diffuse erythema with palmo-plantar pruritus, urticarial wheals, flush and dizziness are associated. Mucous oedema frequently involves nose, eyes, mouth, lips and tongue. Gastro–enteric signs can induce in error: abdominal pain, especially epigastralgias, nausea and dysphagia. Breathing becomes difficult because of oedema and bronchospasm. Laryngal cough or asthma can occur.

Decrease of arterial pressure by intense vasodilatation is accompanied by tachycardia. Mental confusion or seizure may be consequences of hypoxemia. Dizziness and intense anxiety are always present.

This is a true emergency; one should phone the emergency mobile unit. While awaiting their arrival, the patient must be placed in a supine position, oxygen (10–15 $l\ min^{-1}$) should be administered, and epinephrin injected intramuscularly in deltoid region or in the anterior face of the thigh. Average dosage in an adult is 0.5 mg, in a child 0.01 mg kg^{-1}. In absence of good evolution, another injection can be administered 5–10 min after. In the case of bronchospasm, inhalation of salbutamol should be administered.

Blood pressure, cardiac rate, ventilation and consciousness must be supervised. Intravenous infusion could be installed in order to perfuse macromolecules.

The patient must always be hospitalized, even if the status is good, because of the risk of rapid recurrence.

Signs that should alert to anaphylactic shock:
Distal pruritic oedema and mucous involvement
Respiratory and digestive symptoms
Dizziness and anxiety
Flush phenomenon
Low blood pressure and tachycardia

17.4.1 Cutaneous Infections:

17.4.1.1 Necrotizing Cellulitis

This designation was subdivided in two entities during the French consensus conference [6], which are:

Bacterial and necrotizing dermo-hypodermitis
Necrotizing fasciitis

These two entities refer to two different anatomical entities.

17.4.1.2 Bacterial and Necrotizing Dermo-Hypodermitis:

This condition has a subacute evolution, whereas the second has an acute or suracute evolution.

Necrotizing dermo-hypodermitis looks like a red, tender leg, with fever, looking like an erisypela but certain signs should cause alarm: ever-increasing pain, deep oedema, bullous and purpuric lesions, asthenia. These signs should alarm the dermatologist, and require hospitalisation in order to watch over local and general development and prevent a septic shock.

17.4.1.3 Necrotizing Fasciitis Is an Extreme Emergency

Discordance between poor cutaneous signs and gravity of general sign should alert the dermatologist. The cutaneous lesions can involve inferior members, but also trunk, neck and perineal region. It occurs mostly in adults over 50 years old, but observations have been described in some children during chickenpox. Mellitus diabetes, HIV infection, cancers, malignant haemopathy, immunosupressor treatment are favourizing factors.

Dermatologic signs are: red leg, with acute pain, deep and livid oedema, necrotic and deep plaques, cyanic macules, and sometimes hypoesthesia. Fever is often present and quickly accompanied by shock signs, with low blood pressure, tachycardia, and polypnea.

This is a great emergency, and the patient must be referred to a centre with plastic surgeons trained to this type of surgery, able to perform large debridement.

The diagnosis is essentially clinical and, in the majority of the cases, does not need any imagery.

In both these conditions, the dermatologist must be able to differentiate them from an erisypela, by finding unusual signs, such as livid and deep oedema, significant pain and altered general condition. Blood pressure and cardiac frequency must be looked at.
The emergency mobile unit should be called as early as possible.

17.5 Staphylococcal Scalded Skin Syndrome (SSSS)

This is a blistering, exfoliative dermatosis, caused by the secretion of exotoxin from *Staphylococcus aureus* [7].

It occurs more frequently among children than adults. The risk of death is about 5% in children. It begins like an erythematous rash, with sub-corneal, blistering. It often begins in the flexures. Nikolsky's sign is present. The fever is high and the child is exhausted. The fluid in blisters is usually sterile.

The child must be quickly referred to a specialized unit where a bacterial research will be undertaken. The infecting strain is usually recovered from distant sites. The adapted antibiotic treatment is followed by a dramatic efficacy.

17.6 Purpura Fulminans:

Purpura fulminans is most frequently observed with meningococcal infection; however, it can also occur with other bacteria including groups A and B beta-haemolytic streptococci, *S. pneumoniae*, *H. influenzae*… It occurs more frequently in young children than in adults, and can correspond to the first manifestations of meningococcemia.

It may begin with palpable purpura. Elements are larger than 3 mm in diameter. Some of them may become necrotic; necrosis first involves the extremities. In addition to skin lesions, fever, chills, hypotension, meningo-encephalitis, etc. may be observed. It is very important to perform this diagnosis, because the prognosis depends on the rapidity of starting the treatment. The first act to be performed is an intravenous or, if not possible, intramuscular injection of ceftriaxone (70–100 mg kg^{-1} per day, reconstituted with steril water). This injection will improve the prognosis without compromising the later search for bacteria in the hemocult or in the spinal fluid. Every physician should have ceftriaxone in his office.

Diagnostic criteria [8]:

Haemorrhagic lesions of characteristic appearance
Universal distribution of skin haemorrhages
Maximum diameter of 1 or more skin haemorrhages greater than 2 mm
Poor overall condition
Nuchal rigidity

If two of the above criteria are present, the probability of meningococcemia becomes very significant.

17.7 Kawasaki Disease [9]

Kawasaki disease is a generalized vasculitis occurring in children, essentially boys, younger than 5 years old. It is probably of infectious origin, although no infectious agent has been found. Its danger comes from possible cardiac impairment by the formation of a coronary micro-aneurysm.

The principal clinical signs are:

1. High fever for at least 5 days, despite the antipyretics and antibiotics.
2. Non-pruritic exanthema, beginning in the extremities and involving the trunk in 2 days. Progressively, the macules become confluent and sometimes urticarial. They may also be purpuric or psoriasiform.
3. Painful and red induration of the extremities occurs at day 7. It involves preferentially the dorsum of the hands and feet.
4. Mucous involvement consists of a bilateral conjunctivitis. It involves bulbar conjunctivae rather than palpebral or tarsal conjunctivae. There is no exudates and it is painless. Lips and tongue are also red, with a strawberry tongue and cracking cheilitis. There are no bullae.
5. Lymphadenopathy is often unilateral, with large lymph nodes, 1.5 cm or greater, firm and tender.

Later on, about 3 weeks after the onset, desquamation of the fingers and the toes occurs.

Faced by this high and persisting fever and cutaneo-mucous signs, it is important to evoke the possibility of Kawasaki disease and refer the child to a specialized unit.

Clinical criteria of diagnosis:

Very high fever for more than 5 days despite antipyretics
Polymorphous exanthema
Extremities involvement
Conjunctivitis, cheilitis, and red tongue
Lymphadenopathy
Exclusion of other disease with similar findings

17.8 Non-Dermatologic Emergencies:

17.8.1 False Emergencies: (Chart 17.1)

Although extremely rarely severe, they are frequently upsetting, and need self-control and speaking to the patient calmly.

17.8.1.1 Vasovagal Syncope

Vasovagal syncope is quite a frequent situation in private practice; although one study [10] has observed that 1% of 3,788 patients experienced vasovagal syncope, the occurrence of vasovagal manifestations in patients undergoing a dermatological surgical procedure seems much more frequent. It is independent of the extent of the care being undertaken. It may be consecutive to a local anaesthesia procedure. But it is not an allergic phenomenon. Sometimes it may occur before any procedure of care, or in association with a minimal procedure such as extraction of miliary cyst.

The syncope, defined by a transient loss of consciousness is, however, less frequent than the prodromal syndrome, defined by dizziness, weakness, impairment of vision, nausea, excessive and cold sweating, and pallor. At the physical examination, the pulse rate is slow, accompanied by hyper-ventilation. Blood pressure can be normal, but sometimes it can be low.

Treatment is often very simple [11]. It consists of speaking to the patient in order to reassure, and placing him in a supine position with raised legs. If this does not work, an oxygen mask can be used for a few minutes. Exceptionally, when the patient does not recover, it is possible to administrate atropin 0.25 mg subcutaneously. In this case, phoning an emergency service near the office is recommended, as a prolongation of the condition raises the question of another diagnosis.

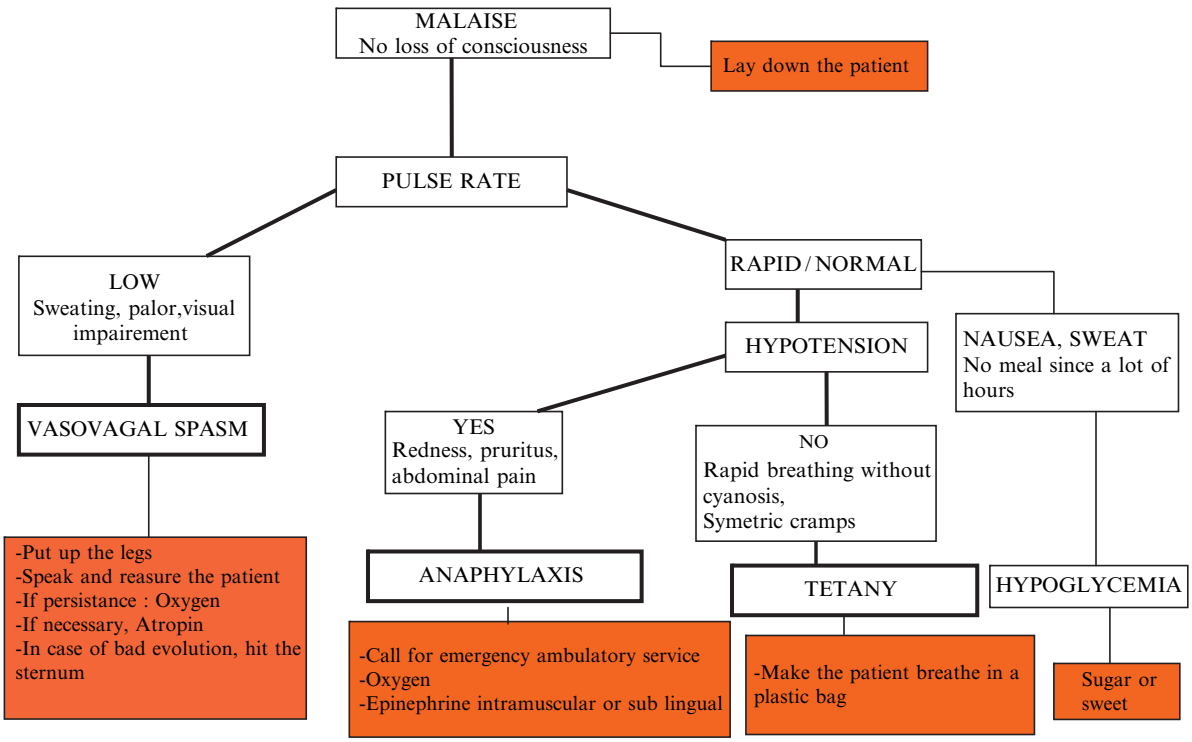

Chart 17.1

17.8.1.2 Tetanic Crisis:

This corresponds to a neuromuscular hyper-excitability. It is manifested first by facial and acral paresthesia, and is followed by painful and uncontrollable symmetric cramping of the arms, legs, and mouth. It is favoured by hyper-ventilation due to anxiety.

The best treatment is to obtain acidification of blood by the way of hypercapnia. This is obtained by breathing into a plastic bag.

Calcium gluconate is very rarely necessary.

17.8.2 True Emergencies: (Chart 17.2)

17.8.2.1 Seizures:

Seizures occur without prodromic signs. The patient falls; tonico-clonal activity occurs. The physician must avoid, if possible, the occurrence of injury. If the patient is lying on the examination bed, the physician must prevent the fall. If not, he must remove all dangerous objects. When the patient is in the post-critical phase, the physician must position a Mayo canula and slowly inject Valium while waiting for the ambulance.

17.8.2.2 Cardiac Arrest: [12]

Cardio-respiratory distress is very uncommon in dermatologic practice, but one may be confronted by this situation without any correlation with dermatologic practice.

Distinction between seizures and vasovagal syncope	
Seizures	Vasovagal syncope
Sudden loss of consciousness	Favouring circumstances
Abrupt fall	Soft fall
Tonico-clonic crisis with cyanosis	Pallor+++
Hypertony during 20 sec	Some bumps
Clonic movements over 30–60 sec	
Progressive recovery and post-critical confusion	Rapid recovery followed by asthenia

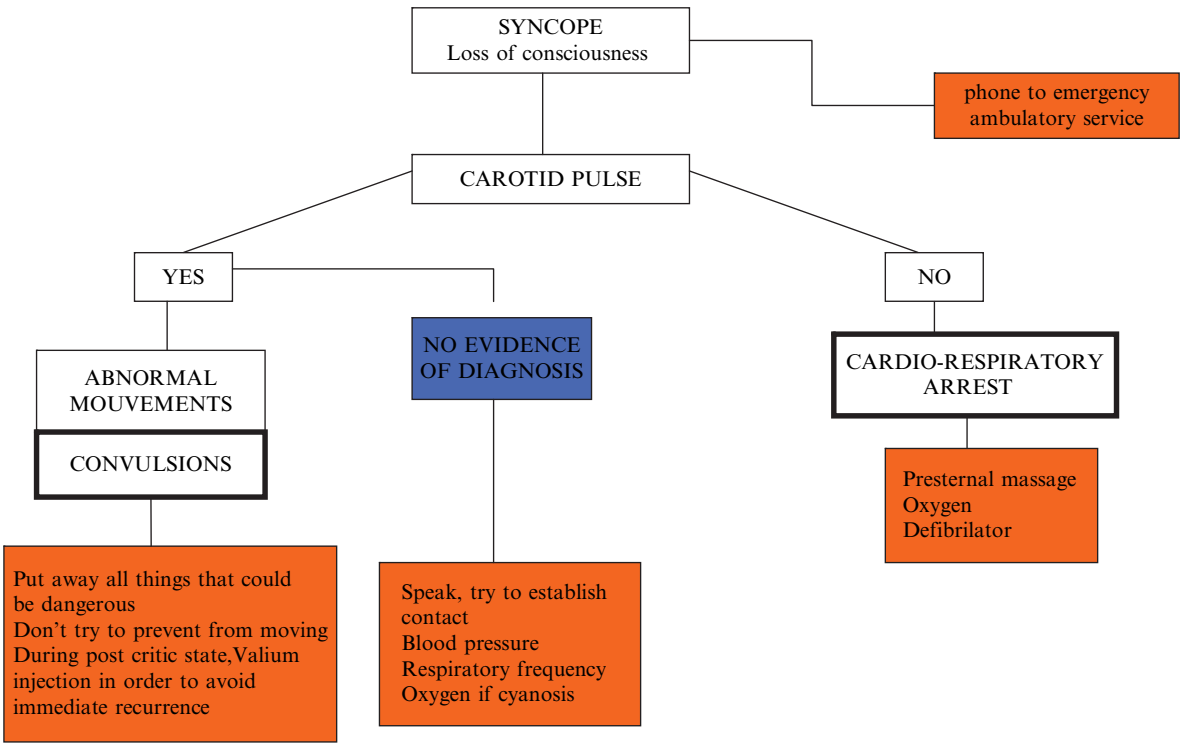

Chart 17.2

The first action is to call for help and then to make sure of cardiac arrest by carotid palpation of the pulse, and tilting the head back in order to free the upper respiratory tracts. The emergency ambulance service must be called and external cardiac massage undertaken. This massage must be performed in front of the sternum, and its purpose is to permit brain oxygenation while waiting for the defibrillator. An oxygen mask will deliver 151 min^{-1}. The defibrillator will recognize the origin of the arrest, very often by ventricular fibrillation, and deliver an electric shock.

17.9 Proposals for Emergency Equipment

17.9.1 Legislation Concerning Office Equipment is Not the Same in All Countries. So the Equipment Proposed Below is What We Consider to Be the Minimum Requirement

The best equipment depends on the type of practice the dermatologist has, and in which type of building his office is situated. It depends also on the proximity of an emergency service.

The above description of incidents must guide equipment modality.

In a study concerning incidents during dermatologic surgery procedures, it was shown [10] that apart from infectious or haemorrhagic incidents, the great majority of them were vasovagal syncope or malaise.

So, the minimum equipment required in a private office of dermatology is:

Accessible telephone
Blood-pressure cuff and stethoscope
Needles and syringes, catheters
Oxygen bottle with capacity of 0.4 m^3
Adult and child masks for oxygen
Insufflators
Injectable drugs:

Corticosteroids already prepared in a syringe
Epinephrine prepared in a kit, without need to keep it in a refrigerator
Atropine
Ceftriaxone

The physician must check the validity date of the drugs. He must also have training for using this material. The need for a semi-automatic or automatic external defibrillator depends on the proximity of the emergency ambulance service and on the structure of the practice. If the dermatologist's office is located in a large multidisciplinary building, the presence of a defibrillator should be considered. The presence of a defibrillator is encouraged in those places where it is expected to be used once every 5 years [13]. So the decision regarding equipment depends on the size of the office and the number of patients being treated.

17.10 Prevention [14]

Many incidents could be avoided by careful questioning about personal history, drugs taken. Before carrying out any procedure, it is recommended to ensure that the patient did not suffer from malaise or syncope during a previous procedure or venous puncture. One should measure the degree of anxiety before performing any procedure on the patient, because it is known that anxiety is a major predictive factor for vasovagal syncope or pre-syncope.

The patient must be comfortable, lying on an examination table; the dermatologist should inform the patient about what is happening (puncture for local anaesthesia for example). He should speak, and have a conversation requiring answers from the patient.

When the patient has to stand up, the physician should make it safe, standing beside him and providing help.

The office should be organized with telephones near the physician, oxygen ready. A suitcase will make it possible to organize the emergency drugs in a single place, easy to find and use.

Carpets should be prohibited and steps are not recommended.

17.11 Conclusion:

Emergencies in the dermatologist's office are very uncommon, but their severity requires that the physician pays attention to atypic signs.

The organization of the private office must ensure the safety of the dermatologic procedures.

The need for equipment to respond to every life-threatening situation depends on the size of the practice, on the number of patients coming to the location, and on the proximity of the emergency service.

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Life-Threatening Dermatoses Occurring During Gestation

18

Kiarash Khosrotehrani

Core Messages

- Pregnancy results in many physiological modifications of the skin including pigmentation and vascular changes.
- Pemphigoid gestationis is a rare auto immune blistering disorder selectively occurring during the third trimester. It is accompanied by an increased risk of foetal growth restriction and preterm labor.
- Impetigo herpetiformis is a pustular eruption resembling pustular psoriasis in many aspects. It is limited to the period of gestation. Maternal hypocalcemia, preterm labor and foetal abnormalities are the main associated risks.
- Viral infections such as parvovirus B19 or chickenpox during gestation may necessitate specific management, due to the potential threat they pose to maternal and foetal health.
- Autoimmune disorders such as lupus erythematosus may present with flares during gestation. Hydroxychloroquine treatment is safe, and should not be interrupted during gestation.

Pregnancy results in a series of physiological changes in skin features and pathology with potential implications for patient care. In particular, the skin is subject to benign modifications that bring numerous questions from pregnant women. These modifications usually include hyperpigmentation, edema, and vascular modifications such as spider angiomas. The objective of this review is to focus on skin conditions during pregnancy that should alert the physician because they are directly or indirectly a reflection of a life-threatening condition for the pregnant woman or the foetus. These conditions can be classified in diseases specific to pregnancy, or ailments that are not specific to gestation but have a particular effect on foetal or maternal health during that period. We will obviously not discuss life-threatening dermatosis that may incidentally occur during gestation.

18.1 Specific Dermatosis of Pregnancy

18.1.1 Pemphigoid Gestationnis

Among the various dermatoses that occur exclusively during gestation, blistering disorders may seriously alter maternal health. *Pemphigoid gestationis* is an autoimmune blistering disease resulting from the deposition of autoantibodies at the dermo–epidermal junction. The frequency of this condition has been estimated at about 1 in 10000 pregnancies [1, 2]. Clinical, histopathological and immunological features of this disease are highly reminiscent of bullous pemphigoid. The cornerstone of the disease is pruritus. It may be isolated or accompanied by urticarial papules and plaques that may give rise to vesicles and bullae. Lesions have been typically described as periombilical; however, they may occur on many parts of the body surface. Histology displays a subepidermal vesicle or blister with a lymphocytic perivascvular infiltrate associated with eosinophils.

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The diagnosis is established by showing the presence of autoantibodies. Direct immunofluorescence demonstrates the deposition of IgG and complement fraction C3 at the dermo–epidermal junction along the basement membrane. In addition, the detection of circulating bullous pemphigoid-type autoantibodies in the patient serum can be obtained by BP180 NC16a ELISA assay. This test allows 96% sensitivity and specificity in establishing the diagnosis of pemphigoid gestationis [3].

The disease occurs during the second or third trimester of gestation. A flare might be observed at delivery, and immediate postpartum occurrence of the disease is not rare. In most cases, disease remission is expected in the postpartum period, even if persistence of the disease for a few months has been reported. Importantly, women with PG may have a disease recurrence during menses, subsequent pregnancies or even after using oestroprogestative contraception. Recurrences of PG in subsequent pregnancies are more severe and at an earlier gestational age [4]. Foetal risks have been associated with pemphigoid gestationnis: neonatal vesicles or blisters may occur in 10% of cases. In addition, foetal growth restriction and premature labor complicate the course of the pregnancy [5]. Differential diagnoses before the onset of blisters are represented by other causes of pruritus during the third trimester of gestation, especially the polymorphic eruptions of pregnancy that may give rise to similar papules and plaques but are not triggered by autoantibodies [6].

Treatment consists of the use of potent topical corticosteroids at initial stages. Applications are tapered, but maintained until delivery and remission [7]. The use of systemic corticosteroids may be necessary if topical steroids fail to bring a remission. A close follow-up is encouraged after delivery (Fig. 18.1).

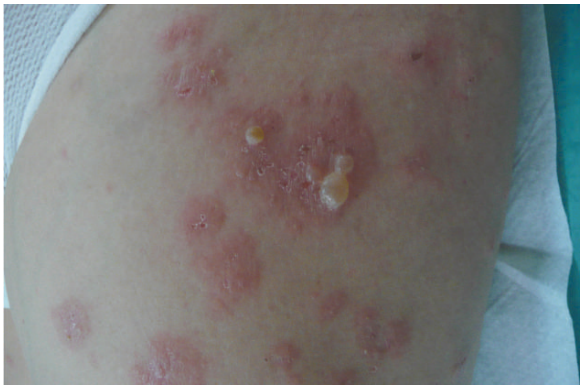

Fig. 18.1 Blisters associated with urticarial plaques on the thighs of a woman within the third trimester of her pregnancy

18.1.2 Impetigo Herpetiformis

Another disorder with similar physiological consequences on maternal health is impetigo herpetiformis (IH) [8, 9]. It is characterized by a pustular eruption associated with high fever and chills. It has been often compared with pustular psoriasis, with similar clinical symptoms such as round, arched, or polycyclic patches covered with small painful grouped pustules in a herpetiform pattern appearing most commonly on thighs, groin and intertriginous areas. The rash may coalesce and spread to the trunk and extremities, although face, hands, and feet are usually not affected. Mucous membranes of the tongue, mouth or oesophagus may be involved. The onset of the disease is sudden, and is accompanied by systemic symptoms such as fever, nausea, vomiting, dehydration and in extreme cases delirium, tetany or cardiac failure. Histology displays spongiform pustules containing neutrophils within the epidermis and a superficial dermal infiltrate of neutrophils and lymphocytes. Pustules are sterile (Fig. 18.2).

A major difference between IH and pustular psoriasis is its mode of evolution. IH occurs in women without a history of psoriasis in the third trimester. Typically the disease ends upon delivery. However, postpartum

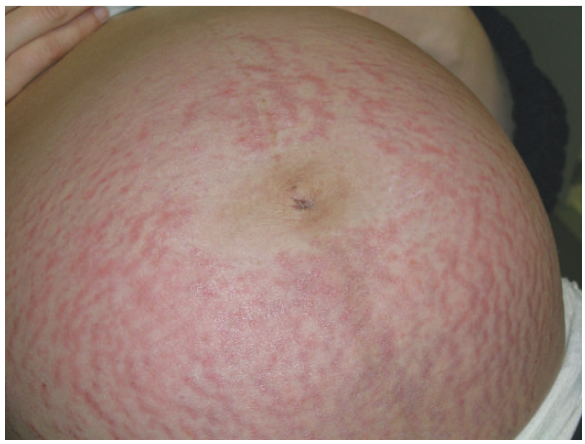

Fig. 18.2 Typical aspect of polymorphic eruption of pregnancy. Erythematous macules papules or vesicles during the third trimester mostly located on stretch marks (Striae gravidarum) of the abdomen but respecting the periumbilical area

onset or persistence has also been described. Recurrences are common in subsequent pregnancies at an earlier gestational age. Oral contraceptive medication or menses may also exacerbate the disease [10].

IH affects both the maternal and foetal prognosis. Maternal complications are mostly due to the systemic symptoms of the generalized eruption, as well as the possibility of an associated severe hypocalcemia. Low phosphate, albumin and vitamin D levels have also been reported. In this disease, foetal health is also affected due to placental insufficiency, infection and premature labour, resulting in an increased rate of stillbirth, foetal abnormalities and neonatal death. Spontaneous mortality of the disease used to be high in the absence of treatment (60–70%).

Differential diagnosis includes generalized pustular psoriasis, and acute generalized exanthematous pustulosis. Therefore, a history of psoriasis or recent onset of therapy should be tracked (Fig. 18.3).

Treatment consists of oral corticosteroids (0.5 mg kg^{-1} per day) that may be associated with PUVA, methotrexate, ciclosporin or oral retinoids in the immediate postpartum period. Potent topical corticosteroid may be attempted for milder diseases, which represent the majority of cases. Correction of fluid and electrolyte abnormalities is also mandatory [8].

18.1.3 Amniotic Fluid Embolism

Although rare, amniotic fluid embolism is a life-threatening disorder with immediate mortality. It is the reported cause of one in every ten maternal deaths [11]. The onset is brutal and unexpected and occurs mostly during delivery, whether natural or by caesarian section. Most characteristic symptoms include a respiratory failure with signs of pulmonary hypertension, a collapse and neurological abnormalities such as confusion, coma or seizures. Skin manifestations are mostly due to coagulation disorders, and include purpuric, ecchymotic or cyanotic patches resulting mostly from disseminated intravascular coagulopathy. Treatment is mostly supportive [12].

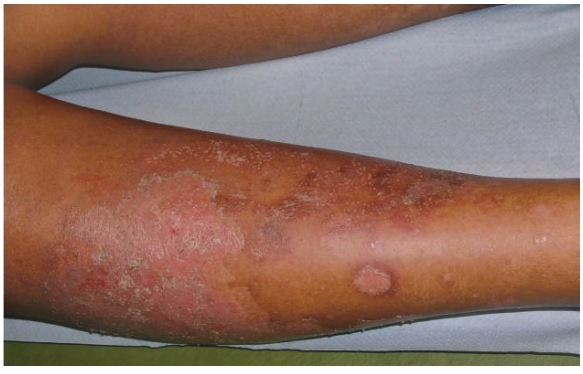

Fig. 18.3 Arciform erythematous pustular eruption resembling pustular psoriasis

18.2 Other Dermatological Conditions with Peculiar Consequences During Gestation

18.2.1 Viral Infections

Like many, pregnant women are exposed to infections. During the gestation period, this may have consequences for the development of the foetus. Among those, rubella, cytomegalovirus, HIV, and toxoplasmosis are well–known, and usually tracked in the early days of gestation with preventive strategies. Most may result in a non specific maculo-papular erythematous exanthema with lymph nodes. In addition to these, primary or secondary syphilis is another infectious disease that is systematically searched for and treated according to the maternal disease stage, to avoid the fetopathy associated with it, in particular after 20 weeks of gestation [13]. *Parvovirus B19* may also cause infection during gestation. The virus can be vertically transmitted to the foetus, with a foetal infection rate of about 30%, resulting for 9% of the infected mothers in foetal anaemia, hydrops, miscarriage, or intrauterine foetal death [14] when it occurs before the 20th week of gestation [15]. The maternal symptoms include fever, arthralgia and a macular erythematous and sometimes purpuric rash that affects extremities (gloves-and-socks syndrome) or less frequently the face (malar rash and flushing). To date there is no preventive or curative strategy against this infection, and close monitoring of the foetus is recommended.

Among other infectious diseases that may have a peculiar course during gestation, herpes virus family members have a special place. *Varicella-zoster infection* during gestation in naïve patients has been reported

as one of the most severe forms of chickenpox. The disease is characterized by an eruption of vesicles, pustules and crust that may involve all body parts. The main notable complication associated with varicella is pneumonia. In fact, mothers, like other adult individuals, are more at risk of developing varicella-associated pneumonia if they are smokers, but also if the infection develops at a later stage of pregnancy and if the cutaneous manifestations of the infection are more severe (more than a hundred lesions) [16]. Such a complication occurs in about 5% of pregnant women with chickenpox. However, antiviral therapy with acyclovir has considerably reduced the level of mortality. The primary risk of maternal chickenpox in early pregnancy is foetal infection, which may result in the congenital varicella syndrome. In the first 20 weeks of pregnancy, the risk of embryopathy after maternal varicella infection is about 2% [17], especially between weeks 13 and 20. However, infection late in pregnancy can also result in congenital varicella that is characterized by limb hypoplasia, cutaneous scarring, chorioretinitis, microphthalmia, Horner's syndrome, cataracts, cortical atrophy, mental retardation, microcephaly and low birth weight [18].

The potential maternal complications of a varicella occurring during gestation have to be treated with antiviral therapy such as intravenous aciclovir or oral valaciclovir. There is no clear indication that antizoster immunoglobulins or antiviral chemotherapy can prevent foetal complications, and a close ultrasound follow-up is highly recommended. Maternal varicella infection between 5 days before and 2 days after delivery poses a substantial risk to the neonate, because of the absence of maternal protective antibody transmitted through the placenta. Neonatal varicella is a severe infection that manifests with skin lesions and pneumonia and has a mortality rate of up to 31% [19]. Therefore, the occurrence of chickenpox lesions in the mother between 5 and 7 days prior, up to 2 days after delivery should trigger an antiviral treatment of the neonate in the form of anti–VZV immunoglobulins and/or acyclovir [20]. Infection with onset more than 7 days before delivery ensures adequate transplacental passage of specific anti–VZV antibody to protect the infant. Unlike primary varicella infection in pregnancy, herpes zoster has not been documented to cause complications unless in the disseminated form.

Genital herpes virus infections, whether primoinfections or recurrences occurring within days before delivery, should also be tracked to avoid the passage to the neonate during vaginal delivery. This could be followed by a severe and life-threatening herpes virus infection of the neonate [21], and necessitates preventive caesarean section (Fig. 18.4).

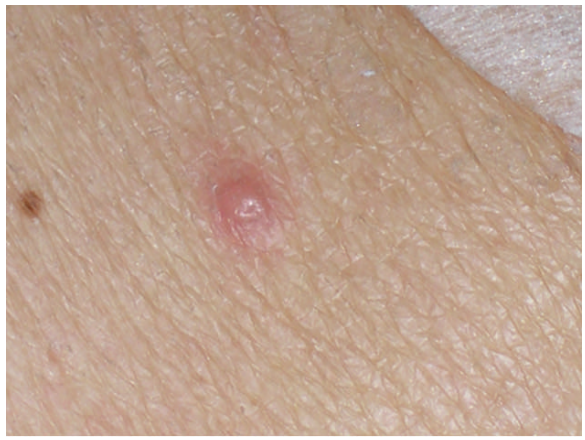

Fig. 18.4 A vesicle in the early stages of chickenpox

18.3 Autoimmune Diseases: Systemic Lupus Erythematosus

Feto–maternal interactions during pregnancy imply the activation of the maternal immune system and its control by a variety of tolerogenic mechanisms. It is believed that these modifications are the cause of the peculiar evolution of several autoimmune disorders during pregnancy. Some of them are not life-threatening, such as thyroiditis. However, in this review we will detail current knowledge on the evolution of systemic lupus erythematosus during gestation. The systemic spread of this disease in flares that may occur during gestation can affect kidney, central nervous or other important systems with potential life-threatening conditions. It is worthy of note that lupus activity has been reported to increase during gestation [22]. Occurrence of lupus flares during pregnancy seems associated with discontinuation of chloroquine treatment, a history of more than three flares prior to pregnancy and increased anti-double-stranded DNA antibodies [23]. Therefore, special attention must be paid to women that have active lupus diseases before gestation. For women with inactive disease, it is highly recommended to continue therapy such as hydroxychloroquine [24]. This treatment has been

shown to prevent flares during gestation, and its safety during gestation has also been thoroughly reported [25, 26]. The two main causes of mortality related to lupus during gestation are renal or neurological disease. Consistently, lupus as well as antiphospholipid syndrome results in an increased risk (15–16 times) of stroke during pregnancy. However, lupus nephritis flares do not seem to be more frequent in pregnant women [27]. In fact, symptoms between lupus nephritis and hypertensive complications of pregnancy are hard to distinguish, and this may explain the discrepancy between various studies of the evolution of lupus nephritis during gestation.

On the other hand, pregnant women affected with lupus may experience severe obstetric complications. Pregnant women with lupus when compared to the general obstetrics population have higher numbers of hospital stay, and higher rates of foetal growth restriction, hypertension and caesarian section [28]. In addition, foetal outcome is also modified by the disease. The presence of lupus anticoagulant and antiphospholipid syndrome as well as lupus activity results in a five-fold increase in stillbirth [29]. Finally, congenital heart block may occur in foetuses and newborns by the transfer of maternal anti SSA antibodies. Altogether, these various conditions reinforce the current guidelines about close monitoring of gestations among lupus patients.

In conclusion, the major physiological changes occurring during gestation in the maternal hormonal and immune system and the very important developmental period during foetal life, emphasise the need to pay close attention to dermatological conditions which may look benign at first sight, but which have the potential to seriously alter maternal and/or foetal health.

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Main Life-Threatening Dermatoses in Neonatal Period and in Infancy

19

Christine Bodemer

Core Messages

- Multiple haemangiomas in neonates with a "beard" distribution must raise the concern of airway involvement.
- Indurated large angioma = immediate evaluation of platelets and coagulation tests.
- Mother's varicella around delivery = intravenous acyclovir for the neonate.
- Keratinization disorders need urgent investigation, not only for evaluation of prognosis but also for future genetic counselling.

Life-threatening dermatoses are rare in neonates (infants less than 4 weeks) and in infants in the first 3 months of life. The most frequent are infectious diseases. The most specific, in this period of life, correspond to developmental abnormalities of the skin, including angiomas, errors in embryonic development, and severe genodermatoses.

19.1 Life-Threatening Cutaneous Infections in Neonates and Infants

Neonatal infections can take a fulminant course, and an immediate work-up is always necessary if there is the slightest suspicion of infection. In most cases the cutaneous lesions consist in bullous, pustular and or vesicular lesions. It is important to underline that rashes are not always related to infectious causes. For instance, urticarial rash or erythematous rash can be observed in auto-inflammatory diseases, and vesiculopustular rash can occur in proliferative diseases such as Langerhans cell histiocytosis.

A systemic congenital or neonatal life-threatening infection can not be diagnosed only on the cutaneous lesions. The general appearance of the infant: colour of the skin (vigour of crying, muscular tone and the quality of feeding) should be carefully analysed. Associated signs are frequent in systemic infections: hepatosplenomegaly, lymph node enlargement, or neurological manifestations. The risk of life-threatening infection is more important in preterm infants with low weight, and particularly in neonates managed in NICU (neonatal intensive care unit).

Aspirated vesicle or pustular fluid, and skin biopsies with cultures can be helpful to confirm the diagnosis of cutaneous infection and to readapt the treatment.

Perinatal history of the child (just before, at, and just after the birth), mother's history, and epidemiologic data are essential for the best management of the child, the prevention of relapses and of epidemics. Infections observed in the neonate period can result from intrauterine but also from postnatal transmission.

19.1.1 Bacterial Infections

(a) *Staphylococcus aureus* and/or *β-haemolytic Streptococci* can be responsible for severe neonatal infections in a septic context. The cutaneous lesions usually occur in the second or third day of life. Cutaneous lesions consist of pustules, but also of macules or papules. *β-haemolytic Streptococci infection* is less frequent in older infants.

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The neonate is particularly susceptible to nosocomial infection with *Staphylococcus aureus*. The most common of these infections is neonatorum impetigo.

Severe toxinic staphylococcal diseases are less frequent in neonates and/or in infants. Indeed, *Staphylococcal scalded skin syndrome* (SSSS) is a toxin-mediated disease related to the diffusion of staphylococcal exfoliative toxins (ET-A or ET-B) from an infected focus (for instance omphalitis, staphylococcal conjunctivitis, etc.). These toxins are able to split the superficial epidermis. The syndrome includes a spectrum of limited to extensive and diffuse manifestation when the toxin enters the blood circulation. A painful redness, tenderness, superficial blistering and detachment characterize it (see chapter NN). *In neonates, and in the first months of life,* maternal antibodies are usually protective, so the disease is most often localized around the infected focus (umbilicus, eyes, nasopharynx and so on). However, SSSS in neonates has been described by Von Rittershain, and a diffuse form is possible with a poor prognosis (Figs. 19.1–19.4).

Although recovery is usual, severe sepsis and severe electrolyte disturbances can lead to death, particularly in the youngest children and in neonates. So it's essential to recognize the epidemic SSSS in newborn nurseries [1]. They have to be informed of the disease, even when the neonate has left and is at home when the first manifestations occur. An identification of the family members or the healthcare workers colonized with toxigenic *Staphylococcus aureus* is a complete part of the best management of the child.

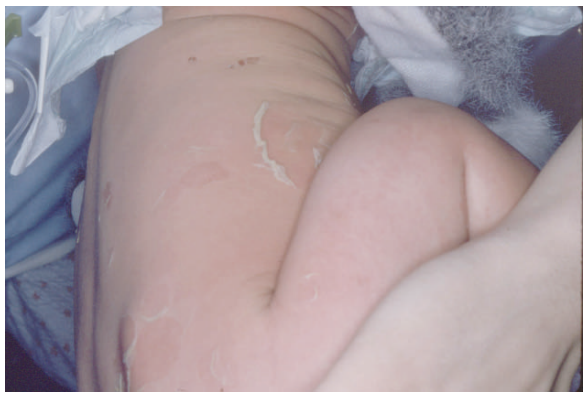

Fig. 19.1 SSSS: Staphylococcal necrolysis with superficial detachment

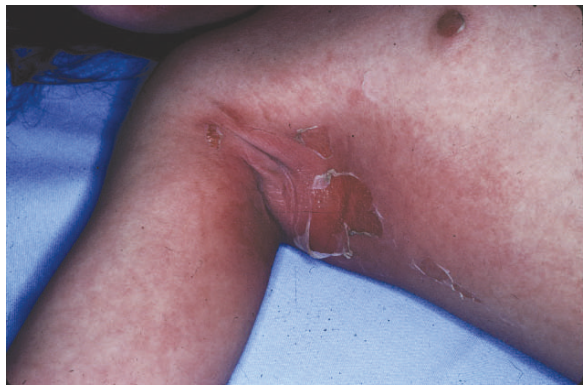

Fig. 19.2 SSSS: Axillary detachment, this topography is a hallmark of staphylococcal toxin

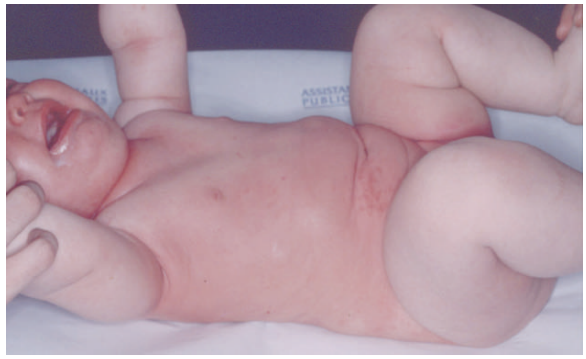

Fig. 19.3 SSSS: Diffuse erythema more marked in the folds

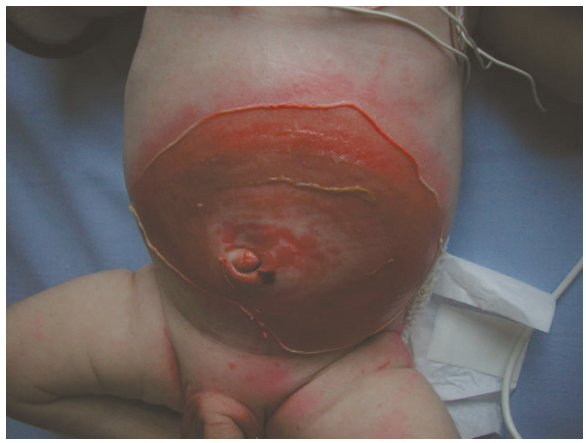

Fig. 19.4 SSSS: Navel infection with staphylococcal necrolysis

Staphylococcal toxic shock syndrome (see chapter: ….) related to the production of the toxin TSST-1 in people lacking protective antibodies at the time of the staphylococcal infection is unusual in children, and

particularly before the age of 1 month. Few cases have been reported in infants, but we have to keep in mind this possibility, even if it remains exceptional in infants.

(b) *Listeria monocytogenes* can be responsible for infections acquired in utero or after birth. The systemic infection is accompanied by grey-white maculopapules with vesicles or pustules. The infection develops several days or weeks after birth. Cultures can isolate the microorganisms, but the laboratory should be informed, as special techniques may be necessary. The best treatment consists of the association of amoxicillin and tobramycin.

19.1.2 Viral Infections

In the neonatal period, *Herpes* and *Varicella* infections can be severe, leading to mortality.

Neonatal herpes is estimated to occur at a rate of 1–2.5 per 5,000 live births. It may be a consequence of intrauterine infection resulting in congenital infection, or the consequence of infection occurring around the time of delivery or in the postnatal period. Postnatal exposure may result from non-genital maternal sites, or from non-maternal sites.

(a) *In the case of intrauterine exposure,* the disease is apparent in the first 2 days of life [2]. Cutaneous lesions consist of characteristic vesicles, sometimes pustules but also in widespread bullae and impressive deep erosions. Aplasia of the skin scalp and diffuse scars has been described. Extracutaneous manifestations are associated with neurological (microcephaly, hydrocephalus, hydranencephaly) and ocular (microphtalmia, choriretinitis) malformations.
(b) *Neonatal infection acquired around delivery* is characterized by the possibility of limited mucocutaneous lesions (skin, eye, mouth), disseminated infection (lung, liver and CNS), or central nervous system infection [3]. Skin lesions are not constant. The average age of onset of symptoms is the first week of life. Because of its high risk of mortality and of severe sequelae, Herpes simplex infection is one of the most feared diseases in the newborn. The best treatment is the immediate introduction of acyclovir intravenously (30 mg kg^{-1} per day). The prognosis remains poor in the *congenital form* related to intrauterine infection: the mortality rates are high and severe impairments are constant (mental retardation, blindness and deafness, etc.). In the other forms of *neonatal herpes* the prognosis is better if acyclovir is introduced early, and particularly in the localized mucocutaneous form. Indeed, deaths are now rare and restricted to the 2% of cases that progress to systemic disease–

Congenital and neonatal varicella [4].

Intrauterine or neonatal exposure to VZV leads to the foetal varicella syndrome, or to the neonatal varicella, or to herpes zoster. If the mother develops varicella between 5 days before and 2 days after delivery, or the infant is between 5 and 10 days of life, the risk of severe neonatal varicella is important. The manifestations may consist of widespread vesicles, sometimes hemorrhagic, respiratory distress, hepatitis or encephalitis. Mortality is now less frequent, since systematic treatment with intravenous acyclovir (20 mg kg^{-1} every 8 h) for a minimum of 8 days and specific supportive therapy.

19.1.3 Fungal Infections

In neonates we can observe three forms of *candida* infections: the congenital systemic form, congenital non-systemic form, and neonatal candidiasis (oral thrush, napkin dermatitis) occurring after 1–2 weeks of life. Congenital forms result from intrauterine infection. The lesions consist in multiple papules and pustules on an erythematous base. They occur on face, neck, trunk, limbs including palms, soles and nails, but the diaper area and the oral cavity are usually spared. Pustules can coalesce, leaving denuded areas. When widespread, they fade within 4–7 days with a desquamative erythroderma pattern [5]. Skin swabs and cultures confirm the diagnosis. Cutaneous candidiasis at birth is not at all diagnostic of severe and systemic disease. Most infants have a favourable outcome, and do not develop systemic disease, due to the rapid efficacy of topical treatment or oral fluconazole.

Widespread congenital systemic candida infections are almost always observed only in premature infants with very low birth weight, or term neonates suffering from an underlying immunodeficiency disorder. The cutaneous lesions can induce an extensive burn-like dermatitis followed by desquamation, but they can also

consist of isolated diaper rash with or without thrush, associated with bad general condition [6]. The same comment can be made in the case of systemic congenital *Aspergillus* infection (materno–foetal transmission at birth or post partum). *Aspergillus* lesions consist in pustules and or necrotic ulceration.

19.2 Vascular Tumours, Hemangiomas

19.2.1 Kasabach–Merritt (KM) Phenomenon (KMP)

KM syndrome has been defined by the occurrence of thrombocytopenia, and a consumption coagulopathy in association with a very rapid enlargement of a vascular tumour, particularly tufted angioma and kaposiform hemangioendothelioma [7]. Vascular tumours associated with KMP are usually observed at birth or early in infancy. KMP has to be suspected when an unusual 'haemangioma' enlarges rapidly with a violaceous, tender, deep dermal and subcutaneous nodular appearance. The nodule or plaque has a particular impressive colour: pink, red, violaceous or red-brown and a woody consistency. Petechiae and ecchymoses related to the thrombocytopenia are inconstant surrounding the tumour or occurring at a distant site. The tumour is usually unique, but may enlarge involving a large area. A haematological evaluation has to be performed as soon as possible, including a platelet count and a fibrinogen level. Platelet counts may be initially an isolated abnormality, with a severe decrease (even less than 3,000) because of platelet trapping. Haemolytic anaemia is frequent, and rapidly D-dimers are detected. Fibrinogen may progressively become undetectable. The diagnosis of KMP is usually made on the association of characteristic clinical presentation and coagulopaphy. A tumour biopsy is performed carefully only when the diagnosis remains confusing with malignant tumours, which have sometimes a transient thrombocytopenia. No single therapy is always effective in all cases of KMP, and in some series mortality is in the range of 20–30% of cases. The monitoring depends on the haematological abnormalities and the risk of bleeding [8]. Platelets transfusion worsens the condition, heparin is ineffective. The aim of the treatments is to reduce the tumour mass, which secondarily improves platelets counts. Oral corticosteroids (2–5 mg kg^{-1} per day), intravenous methylprednisone, and/or vincristine, usually associated with other treatments, are often the first step of the management. Weekly intravenous vincristine cures during 4–12 weeks have been reported to be successful. Other drugs have been tested with variable unpredictable efficacy: aspirin and dipyridamole, pentoxifylline, anti-fibrinolytic agents. Surgical removal or tumour embolization are also discussed. Radiation therapy is nowadays less proposed because of the long-term sequelae (Fig. 19.5).

19.2.2 Life-Threatening Haemangioma

Hemangiomas of infancy are the most common benign tumours in children, characterized by an initial proliferative phase followed by a spontaneous regression. Life-threatening complications are exceptional, but may be observed during the first months of life in the case of airway haemangioma and multi-focal hemangiomatosis.

19.2.3 Airway Haemangioma

Airway haemangioma may occur with or without cutaneous haemangioma**.** They are usually subglottic. This dangerous location has to be suspected when haemangioma occur in a "beard" distribution involving a large segmental distribution: mandibular skin and neck [9]. It consists usually at the beginning of plaque-like haemangioma, and can extend to the preauricular regions, chin, lower lip, and anterior neck. In such cases the risk of associated airway haemangioma is up to 60%, and

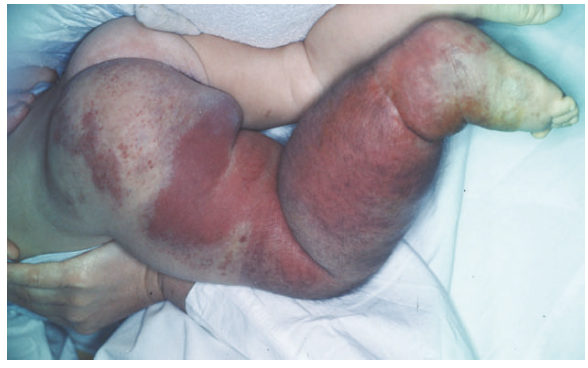

Fig. 19.5 KM: Kasabach–Merritt tumour with rapid enlargement of the angioma. The tumour hard on palpation and violaceous

the babies have to be followed closely, particularly during the first 12 or 16 weeks of life. Symptomatic manifestations of airway involvement consist of a croup-like cough and a progressive biphasic stridor because of obstruction. If symptoms are present, direct endoscopic visualization of the airway is necessary, with a rapid specific management by a specialized team..

Temporary tracheotomy may be necessary to manage extensive airway hemangiomas in an emergency (Fig. 19.6).

19.2.4 Multifocal Hemangiomatosis

Occurring at birth or shortly after, this condition consists of numerous haemangioma (more than five to hundreds), from a few millimeters to centimeters in size. Extracutaneous involvement is possible, principally in liver (2/3 of cases [10]) and less commonly in intestine, lungs, eyes or brain. These haemangiomas usually proliferate and then regress, as with cutaneous haemangiomas, but with a more rapid regression. A complete regression occurs very often by 2 years of age. On the other hand, extracutaneous localizations can lead to life-threatening complications. Mortality is usually related to congestive heart failure following the development of vascular shunts in the liver. Gastrointestinal or intracranial haemorrhage, and consumptive coagulopathy are also rare but severe complications. Management is determined by the specific clinical characteristics of the infant. Because of the variability of extracutaneous involvement (aproximately 20% of cases of cutaneous multifocal haemangioma), and the high variability of complications in the cases of visceral involvement, systematic screening is controversial. All infants with multiple haemangiomas (more than five hemangiomas for some authors) have to be carefully examined with the research of a hepatomegaly, a hepatic murmurbruit, a tachypnea and rales suggesting congestive heart failure, asthenia and bad feeding. A systematic screening can include chest radiography, echocardiogram, abdominal imaging, a complete blood-cell count, coagulation studies and liver-function tests. As cases of hypothyroidism have been reported associated with hepatic hemangiomas, thyroid screening is useful. An explanation would be an abnormal production of 3-iodothyronine deiodinase by haemangioma tissue. Management has to be adapted to the clinical symptoms during follow-up. The goals of the treatments are prevention and best management of the specific complications by specialized teams (Fig. 19.7).

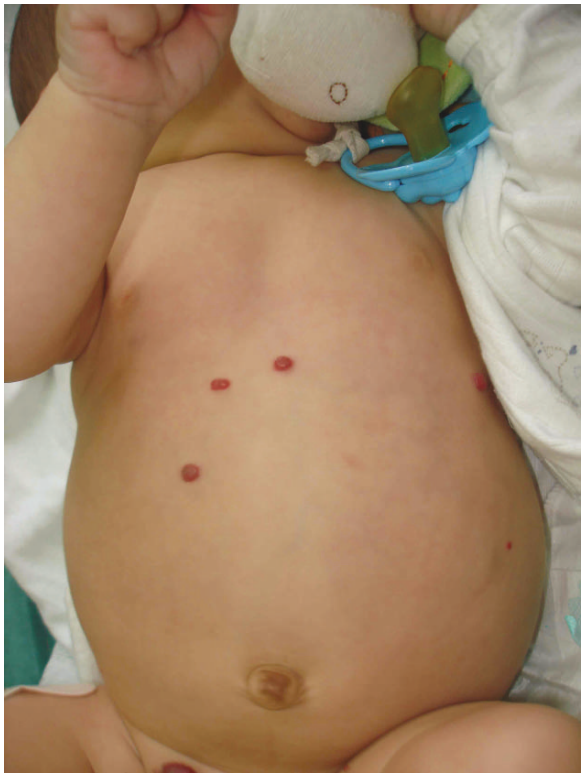

Fig. 19.6 Diffuse neonatal haemangiomas: numerous small hemangiomas with liver enlargement and cardiac failure

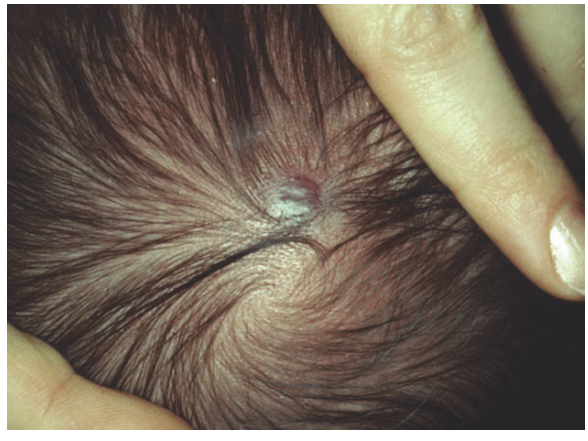

Fig. 19.7 Meningocele: Small congenital midline nodule enlarging when the child is crying

19.3 Developmental Abnormalities of the Skin

Because of the risk of severe infections (meningitis, epidural, subdural or spinal cord abscesses), cutaneous signs of cranial or of occult spinal dysraphism have to be considered as life-threatening in infants. Encephaloceles and meningoencephaloceles contain both meninges and brain tissue with communication with cerebrospinal fluid pathways through bony defect. Most combined defects are located on or near the midline, in the lumbosacrococcygeal or cranial or suboccipital regions.

Cutaneous signs of cranial dysraphism may be minor and overlooked. Lesions consist of a cystic nodule of variable size, in the midline of the scalp. The lesion can increase when the baby cries. Cutaneous signs of spinal dysraphism are numerous: depressed lesions, dermal lesions, dyschromic lesions, polypoid lesions, subcutaneous nodules, etc. [11]. They have to be rapidly recognized, before neurological manifestations, leading as soon as possible to radiological evaluation (high-resolution spinal ultrasonography in the first 3 months of life, magnetic resonance imaging after) and neurological management. Early neurosurgical intervention can prevent deterioration.

19.4 Genodermatoses: Collodion Baby and Severe Hereditary Disorders of Keratinisation (HDK), Epidermolysis Bullosa (EB)

In all these conditions, the risk of severe insensible water losses, thermal instability, and infection is major in newborn infants. Moreover, as neonates have a large skin surface area in proportion to body mass, there is an increased risk of systemic toxicity from topically applied substances. For these reasons the neonate with bullous lesions, severe keratinisation disorders and/or erythroderma should be managed in specialized neonatal intensive care units working closely with paediatric dermatologists. The aim of the management during the first weeks of life is to maintain correct hydration and thermal stability, to minimize infections, and at the same time to organize the etiological investigation of the skin disease. It is very important to collect as soon as possible all the samples necessary for a precise etiological diagnosis, and for a potential future prenatal diagnosis in the case of genetic diseases. Moreover, as some subtypes of HDK, or EB have well-known lethal prognosis in the first weeks of life, better characterisation of the disease is essential to establish the possible different steps of intensive care.

Neonatal bullae and *denuded skin,* with friction-induced blistering are the hallmark of all types and subtypes of hereditary epidermolysis bullosa (EB) (EB simplex (EBS), junctional EB (JEB), and dystrophic EB (DEB)). The possibility of hereditary EB has to be systematically considered in the differential diagnosis of predominant bullae in neonates. Careful handling to minimize blister formation and unnecessary damage is indispensable until the final right etiological diagnosis. Indeed, in the postnatal period, infectious causes of skin blistering (staphylococcal infections+++…) should be excluded. Bullae without skin inflammation, and/or generalized blistering at birth, congenital localized absence of skin, scarring and milia (in DEB forms), high fragility of the skin after minor trauma and intraoral blistering suggest the diagnosis of EB. Skin biopsies and appropriate cultures and Gram stain confirm the diagnosis. Analyse of the inheritance pattern may be helpful for the diagnosis of the type and subtype of EB, but it is not always informative.

In the neonatal period it is very difficult to clearly differentiate clinically the various severe forms of EB, which include JEB–Herlitz, severe forms of EBS–Dowling Meara, and recessive DEB–Hallopeau–Siemens. Skin biopsy (ultrastructural level of blistering, immunohistochemy) and sometimes molecular studies are necessary. JEB–Herlitz is a lethal form in the first months of life, despite an adapted supportive and intense management. Affected children fail to thrive, and become anaemic. Death occurs within the first few months or years after a gradual decline, because of nutritional defect despite supplementation, septicaemia and sometimes sudden death related to an obstruction of the larynx and the trachea.

Collodion baby syndrome is the best illustration of a potential life-threatening keratinisation disorder. The term “collodion baby” corresponds to the presence at birth of a shiny, tight film resembling dried collodion covering the skin. In the development of the condition, the majority of affected infants develop an ichtyosis and particularly an ichtyosiform erythroderma or lamellar ichtyosis. The severity of the subse-

quent ichtyosis cannot be predicted in collodion membrane presentation. The collodion membrane is associated with impaired epidermal barrier function, with the risk of severe hypothermia, dehydration, and metabolic complications. Bacterial sepsis was a classical cause of death of collodion baby in the past. Increased absorption of topical agents can lead to systemic toxicity. Thirty years ago, mortality was estimated at around 30%. Nowadays, if management is organized in a neonatal intensive care unit with close collaboration with an experienced paediatric dermatologist team, the mortality may be reduced to 0%. A collodion baby membrane is generally easily distinguished from the more severe harlequin foetus. *Harlequin foetus* (HF) is characterized by a very upsetting appearance of the neonate covered in thick plate-like scales, which distort surface features and restrict movement. The mortality rate is very high, with stillbirth or early neonatal death. Intensive neonatal treatments for neonates who survive the first day of life may be successful, but with risk of a very severe life-long ichtyosis. An early initiation of systemic retinoid therapy could be crucial to significantly improve an HF patient's prognosis

In all these severe and life-threatening genodermatoses in the neonatal period, medical decisions are very difficult, as the subsequent evolution of the surviving child is usually a life-long severe and painful disease. Parents of the neonate have to be informed of the implications of the condition. As soon as possible, treatment strategies have also to be focussed on providing psychological support to family members.

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Life-Threatening Dermatoses and Emergencies in Dermatology: The Case of the Paediatric Patient

20

Christine Léauté-Labrèze, Franck Boralevi, and Alain Taïeb

Core Messages

- Life-threatening conditions in children include purpura fulminans and other severe infections (endocarditis, ecthyma gangrenosum), scarlatiniform skin rash evoking a toxic shock and acute loss of skin or mucous membranes (drug reaction or post-infectious).
- Chickenpox is the most frequent underlying condition of severe cellulitis in children.
- The presence of a persistent fever of more than 5 days, in association with a polymorphous skin rash, would suggest Kawasaki disease.

There are at the world level major differences in the epidemiology of paediatric skin disorders; we have selected in this chapter some important diagnoses which need urgent or specific treatments in paediatric dermatology.

In children, life-threatening dermatoses can be divided into two major groups:

(1) Life-threatening dermatoses needing urgent treatment and admission to an intensive care unit (Table 20.1)
(2) Dermatoses which are potentially life-threatening in the absence of adequate treatment or delay in diagnosis (Table 20.2)

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20.1 Life-Threatening Dermatoses Needing Urgent Treatment:

20.1.1 Acute Sepsis: (See also Chap. 3)

20.1.1.1 Purpura Fulminans

In children, purpura fulminans is mainly due to *Meningococcus* (B and C), and rarely to *Pneumococcus* or the varicella-zoster virus [1–3]. Some rare cases have been caused by methicillin-sensitive *Staphylococcus aureus* encoding the Panton–Valentine leukocidin [4].

Extensive necrotic purpura is the skin manifestation of intravascular disseminated coagulation. In France, the Health Authority recommends the administration of a third-generation cephalosporin promptly to any child with signs of infection and an ecchymotic purpura (>3 mm of diameter), and then the referral of the patient to the hospital [3]. Children with purpura fulminans should be referred to a paediatric intensive care unit. Management includes antibiotics, fluid resuscitation and catecholamines. Despite intensive management, death occurs in 20–25% of cases. Treatment of cutaneous necrosis and distal ischemia is difficult and still controversial: anti-thrombin, protein C, tissue plasminogen activator and vasodilator infusion have so far not been found efficacious.

20.1.1.2 Ecthyma Gangrenosum

Ecthyma gangrenosum is characterized by necrotic ulcerations surrounded by an erythematous halo [5, 6]. Most lesions are located in the anogenital and axillary areas. Ecthyma gangrenosum is secondary to a Gram-negative bacterial infection: *Pseudomonas*

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Table 20.1 Life-threatening dermatoses needing urgent treatment and admission to an intensive care unit

Acute sepsis:	
Fulminans purpura (*Meningococcus*, *Pneumococcus*, Varicella)	Extensive necrotic purpura, hypotension, intravascular disseminated coagulopathy
Ecthyma gangrenosum (Gram-negative bacteria: *P. aeruginosa*)	Nodular and pustular skin eruption of necrotic evolution, hypotension
Multiple abscesses (*S. aureus*)	Multiple necrotic abscesses, necrotizing pneumopathy (methicillin-resistant S aureus)
Toxic shock (*S. aureus* and *S. pyogenes*)	Scarlet fever-like skin rash, hypotension, vomiting, diarrhea
Anaphylactic reaction	Urticaria (not always present) Hypotension, tachycardia, diarrhea

Table 20.2 Potentially life-threatening dermatoses in absence of adequate treatment or delay in diagnosis

Severe visceral or skin infections:	
Endocarditis (*S. aureus*)	Janeway lesions and Osler's nodes
Primitive ecthyma gangrenosum (gram negative bacteria: *P. aeruginosa, Klebsiella*)	Necrotic ulceration located in the anogenital area.
Dermohypodermitis or cellulitis (*S. aureus* and *S. pyogenes*)	Multifocal necrotizing lesions (*S aureus*) or single extensive cellulitis *(S pyogenes)*
Staphylococcal epidermolysis (*S. aureus*)	Erythroderma and extensive exfoliation
Kaposi Juliusberg pustulosis (herpes)	Widespread vesicular eruption in a patient with pre-existing skin disease (i.e., atopic dermatitis)
Infectious and/or drug reactions:	
TEN/SJS: *M. pneumoniae*, drugs	TEN/SJS: Purpuric macules progressing to blisters and areas of epidermal necrosis with mucosal involvement. Fever and malaise.
DRESS: drugs and viruses (HHV6)	DRESS: eczematous skin rash with lymphadenopathy and fever.
Inflammatory disorders:	
Kawasaki disease:	Prolonged fever, asthenia and in KD, 4 of the following criteria: Non-purulent conjunctival injection, Hand and feet erythema Pharyngitis and cheilitis, Polymorphous skin rash
Autoimmune diseases: Lupus erythematosus, dermatomyositis	Asymmetric cervical lymphadenopathy
Haematologic disorders:	Purpura
Leukemia, lymphoma	Subcutaneous nodules
Macrophagic activation syndrome	Panniculitis

aeruginosa in most cases, and on rare occasions *Klebsiella*. Septicemic ecthyma gangrenosum can be rapidly fatal in young children, and requires aggressive antibiotic therapy. A careful evaluation and long-term follow-up must be done to detect neutropenia, functional abnormalities of granulocytes, or a possible immune deficiency [5, 6].

20.1.1.3 Skin Localisations of a General Sepsis

Multiple abscesses are described in *S. aureus* septicemia. In the case of pulmonary involvement, an infection with a methicillin-resistant *S. aureus* encoding the Panton–Valentine leukocidin should be looked for [7]. Despite antimicrobial treatment, the prognosis is poor.

20.1.2 Toxic Shock Syndrome (See also Chap. 3)

Toxic shock syndrome (TSS) associates three major criteria: fever, scarlatiniform skin rash (Fig. 20.1) frequently associated with mucous membrane hyperhemia, and signs of shock ranging from low blood pressure or dizziness in orthostatic position to car-

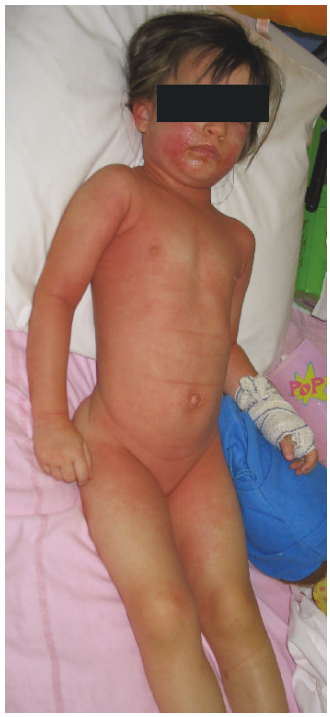

Fig. 20.1 Scarlatiniform skin rash during a toxic shock syndrome in a girl

diovascular failure. Digestive symptoms, such as vomiting or diarrhoea, are frequent. Visceral involvement is variable, including heart, lungs, liver, muscles, kidneys, and the neurological system. The infectious agent of TSS is classically *S. aureus* of the phagic group I, producing a toxin called TSS 1, but the *Streptococcus* species may also be responsible for TSS [8]. In children, the inoculation of the bacteria is often cutaneous (cellulitis, abscess, prurigo, whitlow, chicken pox, skin burn or injury), or less commonly osseous (osteomyelitis).

20.1.3 Anaphylaxis (See also Chap. 6)

Anaphylaxis is rare before adolescence. The most frequent causative agent is food (nuts, peanut and shellfish), then drugs (penicillin) and bee bites. Anaphylaxis develops rapidly and reaches its peak after 5–30 min. At onset, patients may notice itching of the palms and soles, and the genital area; tingling of the soft palate, nausea, vomiting or wheezing are other early symptoms. Hypotension, pruritus, bronchospasm, urticaria, angio-oedema and cardiac arrythmias may be present in various combinations. Management includes fluid resuscitation, adrenalin and antihistamines.

Recently, a study showed that children with extensive skin mastocytosis have an increased risk of developing severe anaphylaxis [9]; thus, information should be given to the adults attending the child, and an emergency set of medication including epinephrine is recommended.

20.2 Dermatoses which are Potentially Life-Threatening in Absence of Adequate Treatment or Delay in Diagnosis

20.2.1 Severe Visceral or Skin Infections (See also Chap. 3)

In paediatrics, severe visceral or skin infections include endocarditis, primitive cutaneous ecthyma gangrenosum and dermohypodermitis or cellulitis.

In a febrile child, cutaneous involvement in *endocarditis* is highly recognizable: splinter haemorrhages under the nails, red, painless skin spots on the palms and soles (Janeway lesions), and red, painful nodes in the pads of the fingers and toes (Osler's nodes) (Fig. 20.2). *S aureus* is responsible for more acute and severe endocarditis than *Streptococcus*.

Primary cutaneous ecthyma gangrenosum is characterized by a solitary necrotic ulceration surrounded by an erythematous halo, frequently located in the anogenital area [5, 6]. The disease is secondary to a local inoculation of Gram-negative bacteria (*Pseudomonas aeruginosa* in most instances). Antibiotics should be rapidly administered to avoid septicemia. As in septicemic ecthyma gangrenosum, a careful evaluation and long-term follow-up must be carred out to detect possible associated immune deficiency.

Severe dermohypodermitis do not spare young children. However, bacteria responsible for such infections have changed with time. The number of dermohypodermitis due to *Haemophilus influenzae* has dramatically decreased because of immunization, whereas dermohypodermitis due to *Streptococcus pyogenes* have increased in number and severity [8]. Actually, cutaneous superinfection of chicken pox is the main cause of severe dermohypodermitis in children under 4 years of age [10, 11]. Bacterial superinfection usually develops 3–4 days after

the onset of chicken pox; this complication should be considered first in patients with varicella remaining abnormally febrile. In addition, the child can also present unusual manifestations, such as major asthenia or a scarlatiniform rash due to the diffusion of bacterial toxins [10, 11]. Usually, two clinical patterns can be differentiated:

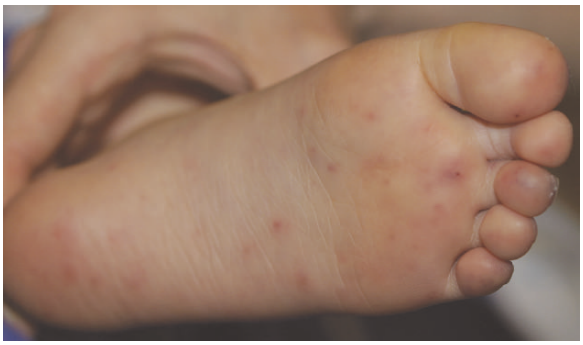

Fig. 20.2 Red, painless skin spots on the soles (Janeway lesions) and red, painful nodes in the pads of the toes (Osler's nodes) in a girl with an endocarditis due to *S. aureus*

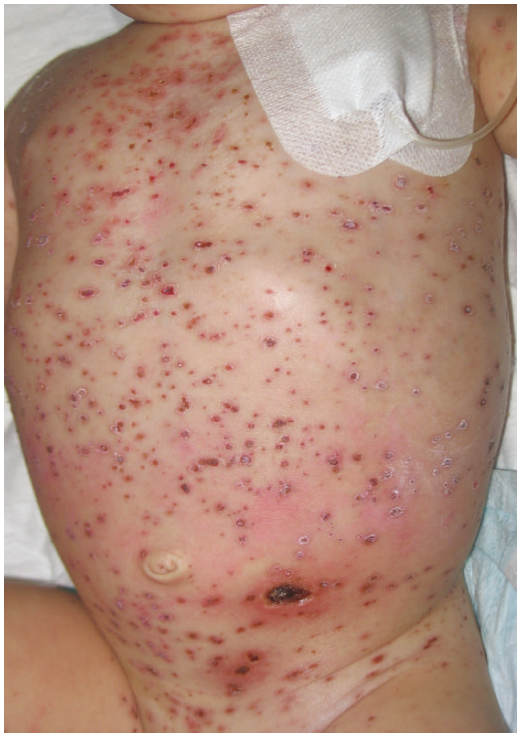

Fig. 20.3 Multifocal painful and necrotizing cutaneous lesions due to a staphylococcal superinfection during a varicella in an infant

(1) Superinfection due to *S. aureus* is characterized by the apparition of widespread painful necrotizing lesions, which vary from 0.5 to 2–3 cm (Fig. 20.3). The major risk is a toxic shock syndrome.
(2) Superinfection due to *S. pyogenes* presents as a single but rapidly extensive cellulitis, with superimposed oozing impetigo evolving into subcutaneous abscess (Fig. 20.4). The most severe complication is necrotizing fasciitis, which should be evoked in the presence of abnormal pain, and extensive cutaneous necrosis associated with signs of shock.

In both cases, an intravenous bi-antibiotherapy is necessary with betalactamins and aminosids, in association with supportive measures.

20.2.2 Staphylococcal Epidermolysis (See also Chap. 5)

Staphylococcal epidermolysis predominantly affects newborn babies and infants. The child develops a dramatic erythroderma, leading within hours to a generalized exfoliation. The exfoliation is the result of the splitting of the stratum granulosum layer of the epidermis caused by staphylococcal epidermolysins secreted by sensitive or methicillin-resistant strains. The histological parallel made with pemphigus foliaceus helped greatly in the characterization of the target for epidermolysins ETA, ETB, ETD, which proved to be desmoglein-1, a desmosome-constitutive pro-

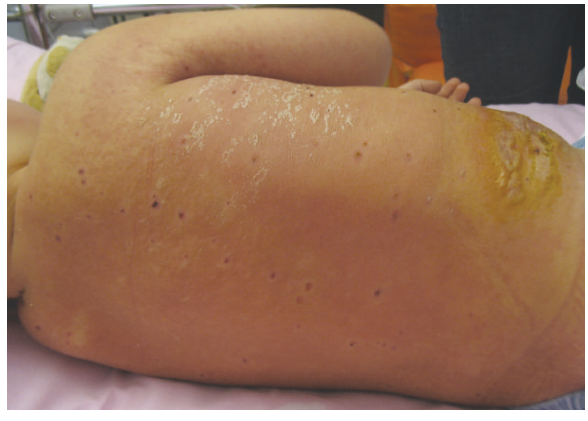

Fig. 20.4 Extensive cellulitis due to *S. pyogenes* complicating a varicella in a 4-year-old child. In addition a scarlatiniform rash is noted due to the diffusion of bacterial toxins

tein. Usually, the evolution is favorable with antibiotics and supportive measures.

20.2.3 Kaposi Juliusberg Pustulosis and Eczema Herpeticum

Kaposi's varicelliform eruption refers to a widespread cutaneous infection with a virus which normally causes localized or mild vesicular eruptions, occurring in a patient with pre-existing skin disease. The great majority of such cases are infections with HSV in patients with atopic dermatitis, for which the term eczema herpeticum is preferable. However, the clinician should remember that HSV could also cause superinfection of several dermatoses disturbing keratinocyte cohesion, such as Darier's disease or epidermolytic ichthyoses, and of course acquired dermatosis such as pemphigus.

Eczema herpeticum is not uncommon in atopic patients. Viscera can be involved, with a subsequent mortality in the absence of treatment (1–9%). Patients with severe or untreated atopic dermatitis are more likely to be affected; in addition, these patients seem to have a significantly higher prevalence of eczematous skin lesions located primarily in the head and neck area, and a higher prevalence at an early age of onset of atopic dermatitis in combination with a chronic–recurrent course until adulthood [12]. Available data do not make it possible to link the use of topical corticosteroids with an increased risk for eczema herpeticum, but there are insufficient data to exclude an association with the use of calcineurin inhibitors. The pathogenesis appears to involve a complex interplay of factors, including demasking of binding sites for the virus through the dermatitis, failure to up-regulate antiviral proteins and a lack of plasmacytoid dendritic cells.

Of eczema herpeticum cases, the majority are primary infections; however, 20% of cases follow ordinary recurrent herpes labialis. Eczema herpeticum manifests as an acute eruption of multiple, pruritic vesicles and pustules in a disseminated pattern involving both eczematous and healthy skin (Fig. 20.5). The incubation period is a few days to 2 weeks. The spread of the HSV from the affected skin areas is the most important direct way of augmenting infection. Scratching of the affected areas is likely to be one of the most important indirect ways of inoculating unaffected skin areas.

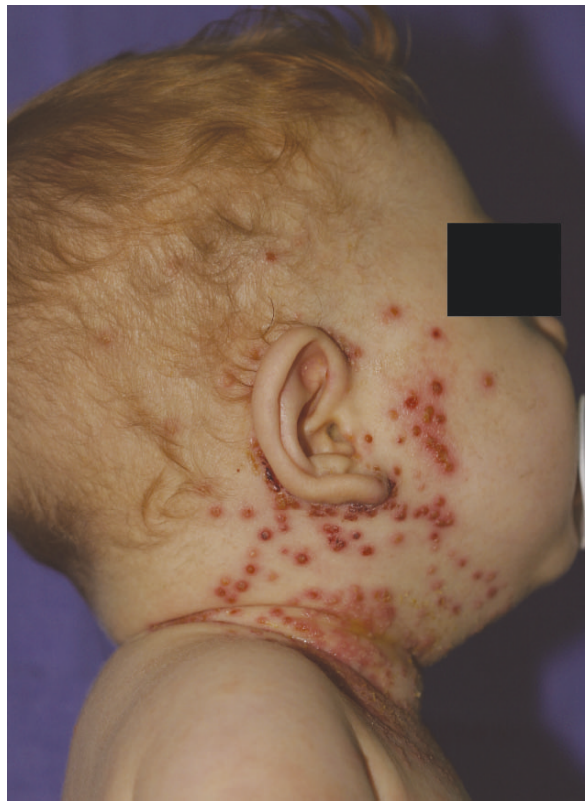

Fig. 20.5 Eczema herpeticum in a 9-month-old infant. The vesicles and pustules frequently involve the head and neck and both eczematous and healthy skin

Systemic symptoms are frequent and characterized by fever, asthenia, and lymphadenopathy.

In an emergency setting, an important diagnostic test is Tzanck's smear. The cytologic sample is obtained by scraping the base of a lesion to discover the presence of koilocytosis. Direct fluorescent staining of such specimens is also a highly sensitive test. PCR is very sensitive, but not routinely performed in all laboratories.

The keystone of EH therapy is prompt systemic antiviral chemotherapy to limit disease duration and prevent further complications. Acyclovir is the treatment of choice for eczema herpeticum. The treatment should be given intravenously in the presence of severity markers (i.e., marked hyperthermia, widespread eruption). Antibiotic therapy may be necessary when secondary bacterial infection occurs, mainly due to *S. aureus*.

The administration of anti-inflammatory therapy, including glucocorticosteroids, in acute eczema

herpeticum is controversial. In spite of unconvincing evidence of aggravation, most clinicians recommend avoidance of topical and systemic glucocorticosteroids during the acute phase of EH. Topical calcineurin inhibitors are contraindicated during the acute phase.

20.2.4 Infectious and/or Drug Reactions (See also Chap. 3)

Toxic epidermal necrolysis/Stevens–Johnson syndrome (TEN/SJS) is a rare disease in children, with a peak incidence in the second decade of life [13–15].

The pathogenesis of the disease remains unknown, but *Mycoplasma pneumoniae* infection and drug intake have been identified as major precipitating factors [14].

SJS/TEN is usually preceded by prodromes, such as respiratory illness or unexplained hyperthermia. All children with TEN/SJS have two or more mucosal sites involved. The extent of skin eruption is highly variable. SJS/TEN has a protracted course of 4–6 weeks, but with adequate management, morbidity and sequelae are minor. However, persistent skin changes are common, including hyper- or hypo-pigmentation. Ophthalmologic complications include adherent pseudo-membranes, corneal ulcerations, and later keratitis sicca, synechias and symblepharon.

Drug reaction with eosinophilia and systemic symptoms (*DRESS)* syndrome in children is close to its adult counterpart, and common causative drugs are antibiotics and anti-convulsivants. Most often, reported cases of infantile DRESS concern children of 5 years or more, with immunodeficiency facilitating viral infections. The hypothesis of the association of a drug and a viral cofactor is more and more admitted. Indeed, numerous cases reported in the literature bring to light a reactivation of the virus HHV6 during the DRESS syndrome, which would be responsible for visceral involvement, chronic evolution of the disease and relapses.

20.2.5 Inflammatory Disorders

Kawasaki disease (KD) is an acute systemic vasculitis that predominantly affects children younger than 5 years of age, with an incidence of 10–15 per 100,000 children in the United States and about 150 per 100,000 in Japan [16]. It is now considered as the predominant cause of acquired heart disease in children living in developed countries, with coronary artery aneurysms or ectasia in about 25% of untreated patients [16]. Even though advances have been made in the understanding of the prolonged self-directed immune response that leads to artery damage, the aetiology of KD is still not known. The potential role of bacterial agents acting as super-antigens and triggering massive activation of the immune system in genetically predisposed children is suggested.

KD is characterized by a wide variety of clinical features (Fig. 20.6). Some of them are considered as diagnostic criteria for typical forms of KD: prolonged fever for at least 5 days, and four of the following criteria: (1) bilateral most often non-purulent conjunctival injection, (2) hand and foot erythema that precedes peeling of the fingers and toes, (3) pharyngitis with strawberry tongue

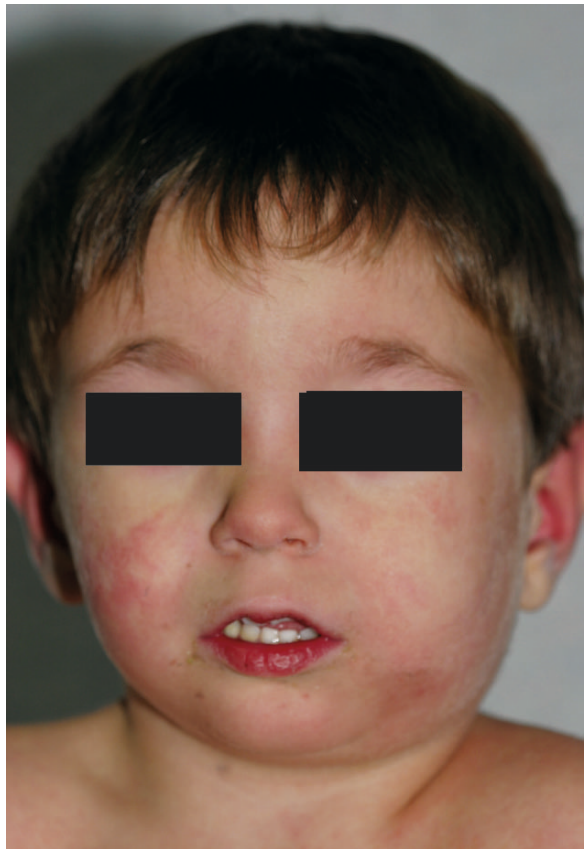

Fig. 20.6 Kawasaki disease in a 3-year-old boy, presenting a bilateral non-purulent conjunctival injection and fissured lips, associated with a maculopapular rash and asymmetric cervical lymphadenopathy

and red and fissured lips, (4) maculopapular or scarlatiniform or urticarial (polymorphous) rash, and (5) asymmetric cervical lymphadenopathy [17]. ECG anomalies or early ultrasound anomalies such as pericardial effusion or coronary dilation have a strong diagnostic value. Since there is no specific biological marker, other findings can be helpful to support the diagnosis of KD, including severe asthenia, early perineal desquamation, erythema at the BCG vaccination site, and anterior uveitis, together with laboratory findings such as elevated erythrocyte sedimentation rate and C-reactive protein, and elevated platelet counts. Atypical forms of KD include incomplete forms, especially in children younger than 1 year, atypical rashes mimicking erythema multiforme or scarlet fever, and patients with preponderant gastrointestinal tract or central nervous system involvement.

Prompt therapy is necessary, to rapidly improve the acute clinical findings and particularly to decrease the risk of coronary artery abnormalities (from 25–35% to about 5% of patients). Following guidelines proposed by the American Heart Association [18] and the Cochrane Database Systematic Reviews [17, 19], acute management of Kawasaki disease should include intravenous immunoglobulin (IVIG) and high-dose aspirin. The recommended therapy during the acute stage of KD should be given within 10 days of onset of fever, and consists of a combination of one single infusion of IVIG, 2 g kg^{-1} over 4–12 h, and oral aspirin at 80 mg kg^{-1} per day in four equally divided doses. Fever remits usually 24–36 h after initiation of the treatment, with improvement of general health and progressive disappearance of the skin rash. Follow-up echocardiograms should be performed by a trained physician at 2 weeks and 2–3 months after initial treatment, or more frequently in doubtful cases. The high-dose aspirin is given until the child is apyretic, and then reduced to an antithrombotic effect-dose of 3–5 mg kg^{-1} as a single daily dose for at least 2 months. During the following months, administration of live virus vaccines should be delayed to avoid an ineffective immunization related to the presence of passively acquired antibodies (IVIG).

About 10% of patients fail to respond to initial treatment with IVIG, with recurrence of the fever or persistent fever beyond 24–48 h after completion of the first infusion. A second course of IVIG is then effective in 75% of cases. In the remaining cases of IVIG-resistant KD, patients may respond to one or two courses of intravenous corticosteroid therapy (prednisolone 1–2 mg kg^{-1} per day for 3 days) or infliximab [17, 20]. Moreover, recent studies have shown that corticosteroids, given in addition with IVIG therapy [21], could be an effective adjuvant therapy in the initial treatment of KD, but further studies are required before we may recommend this combination for the management of all patients with KD.

Autoimmune diseases: in children, the onset of *systemic lupus erythematosus* can be dramatic. Onset is usually over 12 years of age. Only 15% of cases begin before, and the disease is exceptional during the first 2 years of life. Fever, asthenia, weighty fall, muscular pains and often joint pains of sudden onset may be associated with lymphadenopathy and hepatosplenomegaly. About 80% of the patients have mucocutaneous manifestations such as a malar rash, photosensibility, oral ulcerations, cutaneous vasculitis, or a morbilliform skin rash mimicking a viral infection. If a feverish rash persists more than a week in a child, it is necessary to test him for systemic lupus erythematosus markers.

Dermatomyositis also needs to be rapidly diagnosed, since an early treatment may improve the outcome. Cutaneous manifestations of dermatomyositis include a periorbital heliotrope rash, sometimes with associated edema, Gottron's papules overlying the 'kneedle' of the hand or the elbows, knees, and feet. Periungueal erythema with telangiectasia is highly suggestive but not pathognomonic. Skin lesions of dermatomyositis may precede the development of myopathy. Muscle disease affects the proximal muscles; it is generally symmetrical, and provokes fatigue, weakness and sometimes myalgia. Proximal dysphagia reflects the involvement of striated muscle of the pharynx or proximal esophagus. Other systemic features may be seen, such as pulmonary involvement (mostly interstitial pneumonitis and hypoventilation), arthralgias or arthritis, cardiac involvement, vasculitis and calcinosis. The mainstay therapy for dermatomyositis is systemic corticosteroids (starting dose 1–2 mg kg^{-1}). In the absence of response or high dose dependence, intravenous immunoglobulins or immunosuppressive drugs may be used as second lines.

20.2.6 Haematologic Disorders

Leukemia and *lymphoma* are rarely revealed by skin manifestations. The purpura due to thrombocytopenia

is the most frequent; however, the presence of subcutaneous nodules or of a neutrophilic dermatosis is also a possible presentation.. The child should be referred in emergency to a specialized department.

The macrophage activation syndrome is a severe, potentially life-threatening complication of childhood systemic inflammatory disorders [22]; the most frequent underlying disorders are systemic juvenile idiopathic arthritis, systemic lupus erythematosus, Kawasaki disease, and then malignancies (lymphoma or leukemia). In rare cases, the macrophage activation syndrome reveals immune deficiencies (Chediak–Higashi syndrome 1, Griscelli syndrome 2 and X-linked lymphoproliferative syndrome) during a viral infection (mostly EBV infection). Although the clinical features of macrophage activation syndrome have been well documented, early diagnosis can be difficult. The clinical presentation is generally acute, and can be dramatic. Typically, patients become acutely ill, with the sudden onset of non-remitting high fever, hepatosplenomegaly, lymphadenopathy, profound depression of all three blood cell lines (leukopenia, anemia, and thrombocytopenia), and elevated serum liver enzymes. High concentrations of triglycerides and lactate dehydrogenase and low sodium levels are observed consistently. There is usually an abnormal coagulation profile, with prolonged pro-thrombin activity and partial thromboplastin time, hypo-fibrinogenemia, and the presence of fibrin degradation products. As a result, a patient may have purpura, easy bruising, and mucosal bleeding. Other skin manifestations include panniculitis and polymorphous skin rash.

Macrophage activation syndrome is thought to be caused by excessive activation and proliferation of T lymphocytes and macrophages. The first-line treatment is systemic corticosteroids; cyclosporin A has been found effective in patients with corticosteroid-resistant forms.

20.3 When to Worry?

In children, skin manifestations represent a frequent reason for admission in emergency; however, skin involvement is not always proportional to the severity of the underlying disease. For example, anaphylaxis may present with minor skin involvement; on the other hand, viral exanthems are often spectular but mainly benign.

Alarming manifestations in a child are:

- Non-cutaneous clinical signs
  - Signs of shock: hypotension, cardiac failure
  - Badly tolerated fever not responding to antipyretics
  - Abnormal pain
  - Anorexia and severe asthenia
- Cutaneous and mucosal clinical signs
  - Extensive purpura
  - Extensive bullous eruption with mucosal involvement
  - Scarlatiniform rash with associated signs: hypotension, vomiting, diarrhea
  - Necrotizing muco-cutaneous lesions
  - Acute signs of panniculitis

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Extreme Poverty in Industrial Countries

21

Lise Lavillonnière

Core Messages

- Specific diseases of the underprivileged population
  - unemployed isolated or with families, drug addicts, migrants who live in precarious conditions
  - are commonly observed in industrialized countries.
- Lack of hygiene, deficiencies, hostile environment and unbalanced diet increase the prevalence of common dermatosis or create new ones.
- The most frequent are infectious skin diseases, including parasitic, bacterial or common dermatosis worsened by bacterial, mycological or viral infections. Their extreme severity may lead to emergency hospitalisation.
- Neglected wounds received through aggression may be very serious, and may lead to amputation as well as trophic troubles found on such fragile terrain for lack of daily care of diabetes, arteriopathy, neuropathy or another non-detected underlying systemic disease.
- Frequent unrecognized problems:
- Cutaneous abscesses and infections in IV drug users.
- Diffuse scabies (extremely contagious).
- Acute alcoholism may be the mask of another problem.

21.1 Introduction

Skin diseases are frequent among underprivileged persons, who are often ignorant of their rights regarding social and medical protection or who refuse to seek advice from medical structures. Such persons, who are excluded from medical care and live in precarious situations or without any kind of shelter, have diseases linked to their living conditions and/or worsened by them. Such cases, when discovered in humanitarian clinics, often reveal medico-social emergencies: complete deprivation, diseases worsened by clandestinity, alcohol or drug dependencies, serious depression, recent imprisonment or homesickness.

Most such patients are young: men alone often below 40 years of age, women alone with young children [1].

Due to social problems and follow-up difficulties, epidemiological and economical data on cutaneous complications of such precarious situations are sparse. A prospective study on almost 200 patients without social welfare conducted in 1999 found that more than 2/3 of these patients were homeless. Mean age was 37.6 years. The main medical disorders were scabies (56.5 per 100), lice (22.4 per 100) and cutaneous infections (7.2 per 100), related to the patients' poor living conditions [2].

Difficult living conditions, exclusion, psychiatric problems often lead such people to ignore the seriousness of an underlying pathology (tuberculosis or HIV infection in immigrant populations).

Multiple addictions are common (about one third of cases), and may even lead such individuals to be hostile to necessary treatments. The homeless person can live with his 'parasites', his 'ulcers' and yet attend to

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his daily needs. The tramp, impoverished after a long trip arrives in a city, and stops when the condition of his feet prevents him from walking any further.

The passage of a social individual into exclusion is a chaotic process, leading some patients to become resigned and neglecting the care of their bodies: no washing, inadequate food, extreme alcoholism. This leads to a total absence of relational and discursive capacity.

The common ground of such patients is their lifestyle and postponed recourse to the care structure and help. Taking care of such patients is often difficult, as they frequently don't understand the need to track down the possible latent complications of some diseases such as diabetes or HIV infection. It is also difficult to establish a calendar with them when their medical condition needs some follow-up. How can the doctor explain, to a patient who lives from day to day, the need to accept a therapeutical program and carry it out?

21.2.1 Severe Dermatosis

21.2.1.1 Environment-Related Diseases

Caused by Low Temperatures in Winter

Such lesions are due to prolonged exposure to cold, often after consumption of alcohol and postponement of medical attention.

- Frostbites, chilblains located on fingers and toes may be seen in cold and humid circumstances.
- Painful necroses, wounds, gangrene of fingers and toes may lead sometimes to amputation when treated tardily.

Caused by High Temperatures

- Sunstrokes and exposure to heat lead to erythema of the body parts exposed to the sun with phlyctens, wounds, and oedemas, especially on the face.
- Second degree burns due to the handling of gas or spirit stoves or due to sleeping on metro air shafts.

21.2.1.2 Infectious Diseases

Three different situations may become life-threatening: necrotizing fasciitis, infection of diabetic foot and cutaneous complications of drug abuse.

Necrotizing Fasciitis

Caused by streptococcus A, it may be confused at the beginning with an erysipela. But severe cutaneous criteria such as purpura, necrosis, haemorrhagic bullae, and sensitivity troubles, associated to rapid degradation of general conditions, must confirm the diagnosis. Treatment is urgent, and based on antibiotics associated with surgical debridement of all necrotic lesions.

Infection of Diabetic Foot

Diabetic ulcers may be complicated by local abscess, extensive cellulitis, or osteoarthritis. Repeated X-rays are necessary, or MRI. Bone samples are sometimes indicated, to confirm osteitis and choose the correct antibiotics. Arterial insufficiency may be associated, and require amputation.

Cutaneous Complications of Intravenous Drug Abuse (Heroin, Cocaine, Morphine, Buprenorphine) [3, 4]

Parenteral drug abuse is a major risk factor for minor or severe, even life-threatening, cutaneous complications due to lack of asepsy, unsterile equipment etc.

- Local short-term complications: local abscess, cellulitis, necrotizing fasciitis, necrotizing ulcers are due to various species of bacteria (staphylococcus, streptococcus, anaerobes, Gram-negative bacteria) and can occur in the first hours or days. Intra-arterial injections may cause severe cutaneous ischemic necrosis.
- Local delayed complications: pigmentation modifications, scarring, digital retraction, venous insufficiency, ulcers, panniculitis, etc.
- General complications: sepsis, staphylococcal right-side endocarditis, osteo-arthritis, thrombophlebitis

etc. must be always suspected in such patients. Echocardiography must be performed as soon as a staphylococcal sepsis is suspected.

Treatment is based on large-spectrum antibiotics and sometimes surgical excisions in cases of necrotizing fasciitis or necrosis.

Hepatitis B, C and HIV serology must be checked regularly in such patients.

21.2.2 Benign Dermatosis

21.2.2.1 Infectious Diseases

Scabies

Promiscuity in hotels, lack of hygiene and dirty clothes increase the development of parasites: scabies due to acarids is frequent, with generalized nocturnal pruritus.

In the case of eczematous and impetigo-like scabies, specific lesions (fissures, vesicles of the interdigital spaces) are difficult to discover. Secondary impetiginization is frequent in such patients with conditions of social precariousness (Fig. 21.2).

Profuse scabies due to the long proliferation of the parasite on a deficient or immuno-debilitated terrain with the spreading of the scabs on the face or the scalp, sometimes looking like psoriasis with hyperkeratosis of the sole of the feet, can also be found. A clinical diagnosis is difficult in such an atypical form, and the contagiousness is extreme; thus the spreading of epidemic scabies in the healthy population is frequent. The diagnostic relies on parasitological examination and/or dermoscopy.

In the common case, a quick treatment which consists in painting the area with a solution of benzoate of benzyl, or spraying it with pyrethrin is effective among the people living in the same shelter. But how to sterilize the clothes or the bedding is a problem, and the disease will spread again.

- In the case of impetigo-like scabies, an antibiotic treatment taken orally for 6 days (penicillin, or first-generation cephalosporin) is necessary before spreading the scabicide drug. Looking for a proteinuria, especially in small children, is recommended, as streptococcal glomerulonephritis may occur.

In the case of profuse scabies, a local and long treatment is necessary (face, scalp, nails which need to be cut and brushed). An additional oral treatment by invermectin, 150–200 $\propto$g kg^{-1} is also recommended, repeated 15 days after if necessary.

In the case of eczematized scabies, the use of emollient creams (rather than local corticoids) is recommended so that the local treatment is better tolerated. Ivermectin is helpful in such patients.

- In the case of scaling scabies, a long local treatment must be performed along with brushing the nails. A treatment per os is necessary and must be repeated 2 weeks later. This type of scabies requires daily care with scrubbing of the hyperkeratosis with the help of a salicylate Vaseline, followed by frequent spreading of scabicide. The treatment will be better performed in a hospital unit. HIV serology must be performed.
- All the people living in close contact with the patient should also be treated with local and/or oral medication.

Other Parasites

- The discovery of subcutaneous nodes in an African patient suggests looking for onchocercosis.
- Lice infestation is frequent in tramps, and should not be confused with scabies. Pediculosis corporis is characterized by scratching lesions without any specific lesions, and, in contrast with scabies, is predominant in the back but spares hands. Lesions caused by scratching lead to hypo- or hyper-pigmentation lesions (leucomelanodermatosis). The discovery of lice in the clothes confirms the diagnosis. Bacterial complications are frequent. Rarely, *Bartonella quintana* infection can be transmitted by body lice and responsible for fever a few weeks after the initial infection. Treatment of body lice consists of changing the clothes. Sometimes, lice can be found simultaneously on the scalp, the body and external genital organs in the same patient [5].
- Insect bites (fleas, bugs, ticks) increase with heat and contact with dogs. Ticks may carry, through bites, borreliosis with arthropathic and neurological signs, whereas erythema chronicum migrans, an early phase of Lyme's disease, is frequently unrecognized.

21.2.2.2 Bacterial Diseases

Primitive Infections

- Impetigo, often widespread (Fig. 21.1).
- Furunculosis, carbuncles especially on the buttocks and areas where clothes rub.
- Abscesses and phlegmons.

Whitlows, frequent perionyxis.

- Facial or leg erysipelas with streptococci A (β haemolytic) or G group streptococci.
- Humidity and long walks in the rain with inadequate shoes increase the occurrence of bacterial (*Pseudomonas aeruginosa*) and fungal infection of feet.

Dermatosis Secondarily Infected

- Scabies and pediculosis.
- Impetiginized eczema.
- Secondary fungal infection of macerated folds.
- Infected wounds after various injuries and bites.

Mycoses

Such lesions are due to the lack of buccal hygiene (dental abscess, tooth decay), to exposure to humidity and uncomfortable shoes.

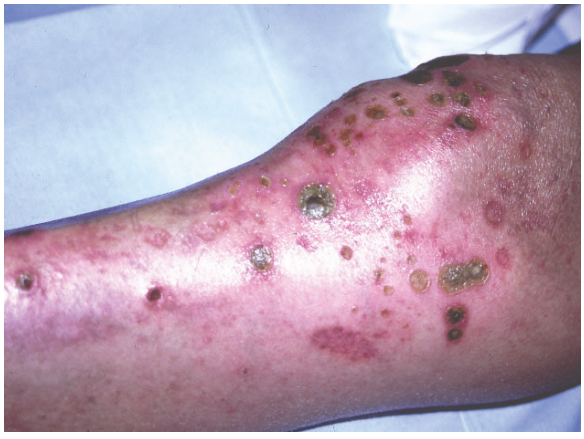

Fig. 21.1 Ecthyma

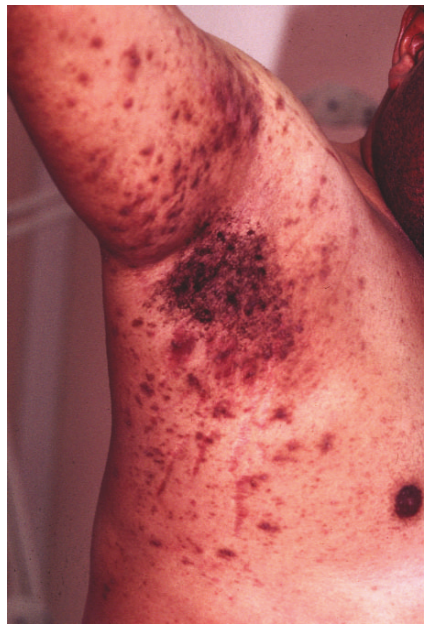

Fig. 21.2 Disseminated scabies

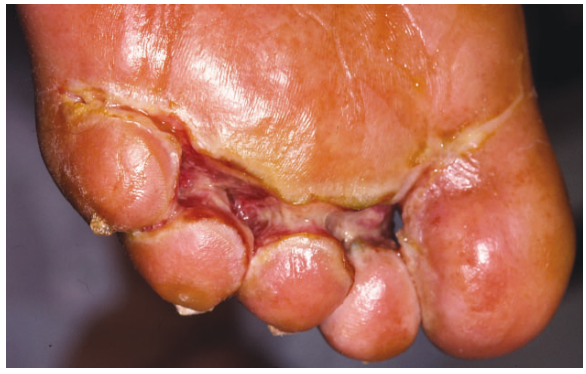

Fig. 21.3 Intertrigo due to gram negative bacilli

- Peri-orificial, genital and buccal candidiasis are caused by *Candida albicans* and *Candida tropicalis*. Such problems suggest diabetes or HIV infection, to be investigated in such a clinical context.
- Dermatophytoses of the inguinal folds, buttocks or between the toes. They are due to *Trichophyton rubrum or T. interdigitale*. They may spread all over the bodies of vagrants. Onchomycosis are frequent and lead to distortion and lysis of the nail (Fig. 21.3).

Tinea capitis due to various species of Trichophyton or Microsporum may be found on young African children.

It presents as unique or multiple, small or large size, alopecic and squamous plaques of the scalp. A mycologic sample must be performed to confirm diagnosis; the siblings and the mother should be closely examined and treated if any doubt. Treatment is based on local antifungal cream or lotion associated with griseofulvin over a period of 6–8 weeks. In case of application of corticosteroids, a bacterial superinfection may occur (kerion).

Folliculitis due to a dermatophyte can involve the beard in vagrants living with their dogs: the disease is transmitted from animal to man.

Semi-deep mycoses are found in Africans. They come from wounds caused by contact with plants. The chromomycoses give rise to prurit, nodes, lymphoedema of the legs.

Viral Dermatosis

- Multiple neglected warts on the body mainly on the feet.
- Acuminated condylomas due to the living conditions and promiscuity.
- Ferocious pruritus due to chronic hepatitis B or C (for drug-addicts).
- Recurrent infected and neglected herpes on the face.
- Profuse herpes zoster in HIV patients.

A HIV serology must be proposed to patients presenting profuse viral dermatosis.

Dermatosis Through Sexually Transmitted Infections

- Genital neglected acuminated condyloma.
- Syphilis, gonococcal urethritis.
- AIDS, sometimes detected through cutaneous lesions accompanied with severe weight loss, lymph nodes, Kaposi sarcoma presenting as dark red angiomatous papules or nodules of the skin or mucous membrane (palate).

21.2.3 Dermatosis Linked to Blows and Wounds

- Bruises on the face, arms and legs received at the time of fights, with large haematoma and which lead to rushing the patient to a hospital (open wounds, broken nose, jaw, eyebrow or torn earlobes).
- Burns produced by tear-gas bombs (often while patient is asleep), with infected wounds on the face, neck and scalp.
- Wounds caused by a knife or broken glass, leading to lesions of the muscles and tendons of the hands and/or wrists.
- Animal bites (dogs of night watchmen in parking lots) at the level of the folds behind the knees or on the hands.
- Infected tattoos when performed with dirty knives or razor blades.

21.2.4 Trophic Troubles of the Upper and Lower Limbs

- Irritative dermatitis due to old and/or inappropriate shoes is frequent in homeless patients, and may be secondarily infected.
- Lower-limb oedema favoured by standing a long time, and worsened by frequent malnutrition and vitamin deficiency.
- Venous insufficiency with venous ulcers, lipodermatosclerosis and oedema.
- Lymphoedema after several occurrences of erysipelas through parasitic obliteration in African patients, leading to investigation for a lymphatic filariasis.
- Raynaud syndrome and sometimes acro-osteolysis with destruction of the fingers, after years of exposure to cold and various traumas.
- Neglected posttraumatic ulcerations or burns.
- ‘Vagrant foot’ with infected calluses, ulcerations, mycosis and bacterial infection with continuous oozing.

21.2.5 Common Dermatosis Modified by the Living Conditions

- Dry eczema and serious skin xerosis in African people living in a temperate climate.
- Chronic contact dermatitis due to jobs performed without protection (dish washing in restaurants, paints, and solvents).

- Troubles of the epidermal differentiation which often appear with a change of living conditions: psoriasis, seborrheic dermatitis, palmo-plantar keratoderma in the case of African patients (a mycosic origin has to be eliminated).
- Neurodermatitis and psychosomatic pruritus created by psychological disorders.
- Alopecia and vitiligo which appear in periods of great stress.
- Pathomimia, especially in the case of young women with lesions on the face and/or the scalp, and prurigo

We sometimes observe neglected or badly treated tumours in migrant African patients with fistulous lesions, or tuberculous ulcerated nodes; lesions of Hansen's disease are unknown on African or Asian patients.

Pigmentation problems with striae, hirsuteness, diffuse pustular acne are found among women from black Africa who spread cortisone-based cocktails of whitening products. This can lead to a condition of hypercorticism with severe arterial hypertension [6, 7].

Hair problems are frequent in African people:

- Pustular folliculitis of the hair line is observed in patients who use coco or castor oil on their hair, which has a tendency to get dry in our climate.
- A frontal cicatricial alopecia may be observed among African women due to specific hair dressing.

21.2.6 Carential Dermatosis

These conditions are found mostly in patients from the African continent, but also in alcoholic and underfed patients.

- Pellagra, due to vitamin PP deficiency secondary to the consumption of either untreated corn or sorghum, found in African patients, gives a dirty brown color to photo-exposed teguments, with very dark hyper-pigmented islands of the neck and the top of the shoulders. Such lesions go along with severe desquamation, skin atrophy, attack of the mucous membranes of the cracked keloid type, and shiny glossitis. This condition is associated with digestive problems (diarrhoea, dysphagia), as well as combined neurological symptoms (dizziness). The treatment is based on administration of vitamin PP 500 mg per day intravenously (Fig. 21.4) [8].
- The shortage of vitamin A leads to a cutaneous xerosis, follicular hyper-keratosis, low night vision: such deficiency is found among alcoholics. A treatment of 50,000 units per day leads to recovery within a few months.
- Alcoholics may also suffer from deficiency in vitamin B6 (pyridoxin) secondary to a lack of hepatic storage, which then leads to a deficiency of PP vitamin. Clinically, a seborrheic peri-orificial dermatitis appears after a few weeks, similar to vitamin B2 and zinc deficiency. A tryptophan dosage helps in establishing the diagnosis, and a quick oral or intravenously supply of vitamin B6 is recommended.
- Vitamin B2 (riboflavin) deficiency is also found in alcoholics. It is characterized by perleche, blepharitis, conjunctivitis and urogenital peri-orificial erythema similar to zinc deficiency.
- Lack of vitamin C is found in undernourished and alcoholic people: glossitis, hypertrophic gingivitis,

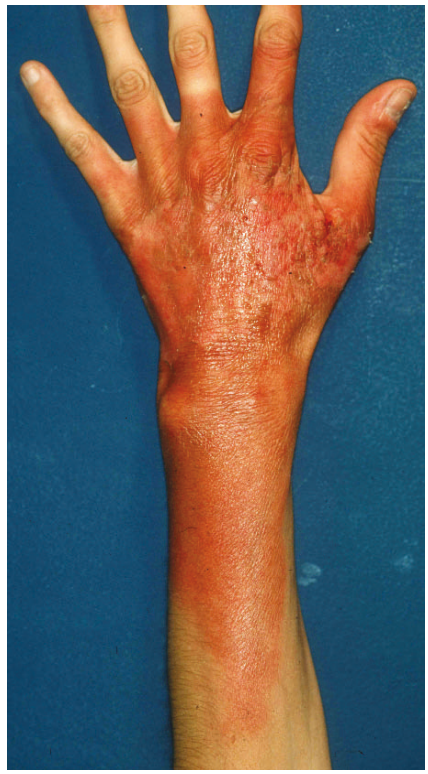

Fig. 21.4 Pellagra (credit to C. Leroux-Villet)

bone lesions, follicular keratosis, ecchymotic purpura and oedema. Daily treatment with 1 or 2 g of vitamin C is quickly efficient [9].

21.3 Conclusion

Promiscuity, violence, drug consumption, psycho-emotional isolation, destruction of social relationships and malnutrition lead to the postponement of medical attention for these patients.

On this fragile terrain, signs of tuberculosis, hepatitis B or C, HIV infection or a serious parasitic infection (in the case of an African patient) may be overlooked.

Poverty is a condition, the result and the cause of exclusion which leads some individuals to lose social relationships, memory and slow self destruction: in fact, when social relationships disintegrate, a modification and lessening of the bodily pattern follows.

We cannot forget that one of the consequences of exclusion is illness: wounds of the soul and wounds of the body are tightly intertwined.

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Life-Threatening Dermatoses and Emergencies in Dermatology in the Specific Context of the Extreme Poverty of the 'Third World'

22

Fatimata Ly

Core Messages

- Infectious diseases are the most frequent life-threatening dermatoses in the context of developing countries, but the life-threatening dermatoses usually seen in the industrialized countries are also reported.
- Numerous factors aggravate the prognosis of life-threatening dermatoses in this context: poor hygiene, poverty, the low rate of accessibility to sanitary structures, the low socio-economic level, and unavailability of some drugs.
- In the context of war, civil conflicts and refugee camps, some dermatoses such as epidemic typhus occur.

Abbreviations: IRIS: Immune reconstitution inflammatory syndrome; HAART: Highly antiretroviral therapy, PAS: Periodic acid Schiff; DHF: Dengue haemorrhagic fever; VHF: Viral haemorrhagic fever; WHO: World health organization; VDRL: Venereal disease laboratory research

22.1 Introduction

The spectrum of life-threatening dermatoses in developing countries differs from those reported for the industrialized countries. Developing countries, also called countries of the 'third World', are all the countries of Africa, Asia and South America [1]. They have some common characteristics: poverty, ignorance, high rate of illiteracy, poor hygiene and low socioeconomic level. Moreover, they are in the tropical or subtropical area. In the context of extreme poverty, infectious dermatoses are the most frequently reported life-threatening dermatoses.

22.2 Public Health Overview

The estimated number of persons living with HIV worldwide in 2007 was 33.2 million [30.6–36.1 million]. *Sub-Saharan Africa* remains the most seriously affected region, with AIDS remaining the leading cause of death there. The estimated number of deaths due to AIDS in 2007 was 2.1 million [1.9–2.4 million] worldwide, of which 76% occurred in sub-Saharan Africa [2].

The life expectancy is over 75 years in developed countries, 64 years in developing countries, and 52 years in the least developed countries. The world's lowest life expectancy at birth, just 40 years, is in Sierra Leone — barely half of the world's highest, in Japan, where it is 79.7 years. At least 18 countries in Africa have a life expectancy at birth of 50 years or less. The probability of a man dying between age 15 and 60 years is 8·3% in Sweden, 82·1% in Zimbabwe, and 90·2% in Lesotho [3].

The inequalities between industrialized countries and developing countries with regard to the number of health workers are very high. For example, the WHO's region of the Americas (mainly USA and Canada) are

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home to 14% of the world's population, bear only 10% of the world's disease burden, have 37% of the global health workforce and spend about 50% of the world's financial resources for health, while sub-Saharan Africa, with about 11% of the world's population, bears over 24% of the global disease burden, is home to only 3% of the global health workforce, and spends less than 1% of the world's financial resources on health [4].

Moreover, in most developing countries, the health workforce is concentrated in the major towns and cities, while rural areas can only boast of about 23% and 38% of the country's doctors and nurses respectively.

The prevalence of skin diseases is relatively high in primary healthcare, between 6% and 14% of the total of visits when all ages are considered together. The mortality of cutaneous infection by severe sepsis secondary to the superinfection of skin lesions of chickenpox is also significant across the world. The other complications of skin infection are the following: invasive bacteraemia secondary to skin infection by ß haemolytic group A streptococcus (GAS), followed eventually by death, at an unexpected rate. Thus in an area of Northern Australia, the incidence of bacteraemia by GAS was 9.3 per 100,000 per year for the whole population, and *Staphylococcus aureus* invasive infection secondary to skin sores/ scabies in 31% of the cases, was reported in the same geographical area [5].

22.3 Life-Threatening Soft Tissues Infections

22.3.1 Bacterial Infections

22.3.1.1 Pyoderma

Pyoderma may be primary or most commonly secondary to scabies or to skin lesions of chickenpox. In tropical areas, the major etiological bacteria are Group A Streptococci (GAS) followed by *Staphylococcus aureus* in tropical less-developed countries. Severe sepsis with a high lethality (up to 21%) occurs in children under 3 months [6]. Treatment is based on macrolides and amoxicillin by the intravenous route [7].

22.3.1.2 Noma

Noma is an opportunistic infection most common in sub-Saharan Africa, which affects children aged 1–4 years. It is promoted by extreme poverty, with chronic malnutrition, unsafe drinking water and poor environmental sanitation, and severe infections (measles, malaria). In adults, the most common risk factor is immuno-suppression by HIV [8]. *Fusobacterium necrophorum* is a trigger organism for noma; non-haemolytic streptococci and *Staphylococcus aureus* are needed to produce noma. The initial manifestation is gingivitis extending to the labio-gingival fold and to the mucosal surface of the cheek and lip. The loss of substance extends rapidly to the skin, with a blue-black discolouration in the affected area and foul-smelling purulent oral discharge. Lesions are often present only on one side of the face. Severe anaemia, hyper-leucocytosis, hypo-albuminemia are present; a low concentration of antioxidant micronutrients in the serum may be found. The management of noma is based on supportive therapy and antibiotics (penicillin G and metronidazole).

22.3.1.3 Erythema Nodosum Leprozum

Infection may be due to mycobacterium leprae: erythema nodosum leprosum (ENL). ENL is a type II reaction occurring in multi-bacillary patients with lepromatous leprosy. It can be life-threatening [9]. Dermatological features are mainly crops of painful nodules with a predilection for the extremities which may ulcerate; there is a severe general malaise with fever and systemic toxaemia. Others organs are frequently involved with inflammation (iritis and iridocyclitis, orchitis, lymphadenitis, arthritis and neuritis). High doses of corticosteroids 20–60 mg may be given for weeks; the specific multiple drug therapy should be continued. Thalidomide may be an alternative to steroids. Another type II reaction of leprosy is the Lucio's phenomenon reported in Mexico [10].

22.3.1.4 Congenital Syphilis

In sub-Saharan Africa, 4–15% of pregnant women are infected with *Treponema pallidum*. Transmission to the foetus results in foetal or infant death or a high rate — 50 to 80% — of disability [11].Clinical manifestations are different in early (the first 2 years) and late

(after the age of 2 years) stages. Dermatologic findings are present in 40% of cases of neonates with congenital syphilis. They include palmoplantar erythema with fine skin peeling, vesicles or bullae (Pemphigus syphiliticus), and purpuric papules. The diagnosis can be established by dark field microscopy of exudates from cutaneous lesions or direct fluorescent antibody testing (FTA). Non-treponemal antibody titre (VDRL test is 4-fold higher than in a mother) is in favour of the diagnosis. The better test is FTA, which detects IgM type antibody. Cerebro-spinal fluid infection and osteochondritis may be present. The best treatment is crystalline penicillin G 50,000 U Kg^{-1} IM or IV daily in two divided doses for a minimum of 10 days.

22.3.1.5 Syphilis Associated with HIV Infection

This is more severe, and potentially life-threatening. The unusual features are the bullous or widespread rash of secondary syphilis, the precocity of neurologic syphilis and the involvement of other organs. Treatment is based on benzathine penicillin 2.4 million given intramuscularly three times at weekly intervals [12].

22.3.1.6 Anthrax

Also called malignant pustule, it is a disease of public health importance caused by *Bacillus anthracis* which affects primarily domestic and wild animals. Humans can be infected, caused by exposure to animals or their products in 90% of cases. Anthrax can be found in agricultural regions of underdeveloped countries where livestock are not immunized. Outbreaks still occurs in endemic areas. In the underdeveloped countries, 20,000–100,000 human cases of cutaneous anthrax occur annually. Cutaneous anthrax is life-threatening only in untreated cases, and the mortality rate is 5–20% [13]. Clinical features occur after 3 days of incubation, with a papular lesion on an exposed area (head, neck or upper extremities) followed by an eschar. During the course of the disease, the red discoloration becomes more intense and dissemination from skin site may occur with systemic manifestations (high fever, tachycardia, and hypotension). Microscopic examination of the Gram-stained smears from the lesions help the diagnosis. The treatment of choice is penicillin G (2 million units every 6 h) by intravenous route for 7–14 days associated with incision and drainage. Ciprofloxacin is an alternative therapy.

22.3.2 Viral Diseases

22.3.2.1 Opportunistic Diseases of the HIV Infection

Kaposi sarcoma (KS) flare during an immune reconstitution inflammatory syndrome (IRIS) can be life-threatening, with a high rate of mortality up to 30% [14]. During the flare of KS, the lesions increase in size and become more nodular (Fig. 22.1). The risk of IRIS-associated KS appears greater during the first 2 months of highly antiretroviral therapy (HAART). Treatment includes liposomal doxorubicin, paclitaxel or external beam radiation, but these drugs are unavailable to most patients in underdeveloped countries (Fig. 22.2).

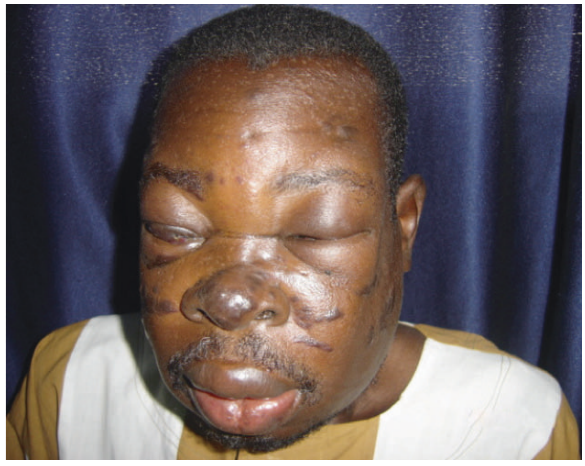

Fig. 22.1 Flare of Kaposi sarcoma in association with IRIS

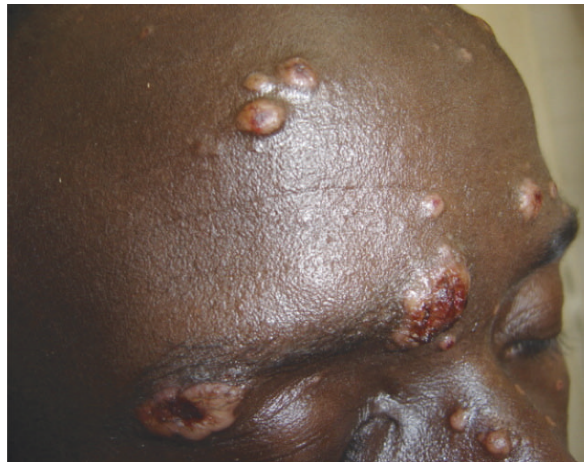

Fig. 22.2 Cutaneous cryptococcosis

22.3.3 Fungal Infection Associated with HIV Infection

22.3.3.1 Cryptococcosis

Cryptococcus neoformans infection occurs in patients infected by HIV, with a prevalence ranging from 4.3% to 16.2% [9]. Disseminated cryptococcosis is by far the most common life-threatening fungal infection in HIV-infected patients at the advanced stage (CD4 Cell count <50 per µl). The typical lesion is an umbilicated papule (Fig. 22.1). There may be a single one or a large number, up to 100, with a preferential localisation on the face; oral nodules and ulcers can occur. Skin lesions may precede cryptococcic meningitis by weeks or months. Diagnosis is made by demonstration of cryptococcal yeast forms with haematoxylin eosin, PAS or methenamine. Cryptococcus neoformans can be also isolated by culture of the skin biopsy specimen. The treatment is based on intravenous Amphotericin B with oral 5 flu cytosine, or fluconazole — not to be used in HIV-infected patients. HAART should be prescribed.

22.3.3.2 Histoplasmosis

Histoplasmosis is due to *Histoplasma capsulatum var capsulatum* (the American variety) or *H. capsulatum var dubosii* (the African variety). Patients infected by HIV with a baseline CD4 <150 per µl have a greater risk of developing histoplasmosis. The most frequent cutaneous finding is molluscum contagiosum-like papules commonly localized on the face Oral mucosa may be involved. In disseminated histoplasmosis, hepatosplenomegaly and lymphadenopathy occur. Treatment is based on intravenous amphotericin B, oral itraconazole or fluconazole for up to 8 weeks, Maintenance therapy with daily oral itraconazole or weekly amphotericin B is given for 1 year or longer [9].

22.3.3.3 Penicilliosis

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei* and is a common opportunistic infection of HIV-infected residents of countries of Southeast Asia and Southern part of China. In a single hospital in Thailand, 1,200 cases were observed in a 7-year period [9]. The skin is involved in more than 60% of the cases, with commonly umbilicated papules. They are localized on the face, upper trunk and extremities. Dissemination to other organs such as lungs and liver is common with fever, weight loss, cough and anaemia. Diagnosis is made by microscopic examination of Wright's stained skin lesion smears, the visualization of the characteristic features on the yeast cells in tissue sections and by culturing the fungus. Without treatment, fatality occurs in all cases; with intravenous amphotericin B (0.6 mg Kg^{-1} per day) for 2 weeks followed by oral itraconazole 200 mg for 10 weeks, the rate of healing is 97.3%.

22.3.3.4 Leishmaniasis

Leishmaniasis is a neglected disease occurring in underdeveloped countries. Only mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis are life-threatening. Muco-cutaneous leishmaniasis is characterized by involvement of both skin and upper respiratory tract, by *Leishmania braziliensis* in South Asia and *Leishmania aethiopica* in Africa. The diagnosis is easy, based on clinical features and epidemiology. The mortality usually results from malnutrition or superinfection by bacteria of pharyngeal obstruction, leading to acute respiratory failure [1]. Cutaneous features of visceral leishmaniasis are variable: hyper-pigmentation on the face, hands and the feet. In African visceral leishmaniasis, numerous hypo-pigmented or hyper-pigmented papules occur. The rate of mortality is high among untreated HIV-infected patients. The treatment is based on pentavalent antimony, amphotericin B and the oral drug miltefosine. The access to these drugs is limited in the context of extreme poverty [15].

22.3.3.5 African Trypanosomiasis

The sleeping sickness is a potentially fatal protozoan infection with central nervous system and cutaneous involvement. Two distinct clinical forms of African Trypanosomiasis are present in sub-Saharan Africa: Gambian trypanosomiasis due to *Trypanosomia brucei gambiense* and Rhodesian trypanosomiasis due to *T. brucei rhodesiense*. They are transmitted by the

bites of tsetse flies (Glossina spp). Humans are the natural host for *Trypanosomia gambiense*, while East African trypanosomias is a zoonosis. During outbreaks, 70% of the population may be involved [11]. Cutaneous features differ according to the stage of disease: trypanosome chancre at the early stage, transient macular or urticarial eruption with systemic involvement including fever, headache arthralgias malaise and dizziness at the second stage. Winterbottom sign (enlargement of lymph nodes along the posterior cervical chain) is characteristic. If the treatment is not started rapidly, the patient will develop the third and final stage of the disease, with fatal involvement of central nervous system. Treatment with melarsoprol B or eflornithine is given by the intravenous route in slowly increasing doses.

22.3.3.6 American Trypanosomiasis

Chagas disease is a neglected disease, found mainly in rural tropical and subtropical areas of Central and South America, with a mortality rate up to 7% [11]. Cutaneous signs (chagoma, widespread and transient morbiliform eruption) and multiple organ involvement are common. Death results from cardiac involvement. The treatment is based on benznidazole 5 mg Kg^{-1} per day for 60 days, or nufirtimox 8–10 mg kg^{-1} per day for 90–120 days.

22.4 Cutaneous Manifestations of Systemic Infections

22.4.1 Meningococcemia

Neisseria meningitidis is a Gram-negative aerobic diplococcus with different serogroups (A, B, C, Y and W-135) transmitted by aerosol or secretions. Epidemics are seen in sub-Saharan Africa, which often is referred to as the 'Meningitidis Belt'. During a major epidemic during the years 1996–1997, more than 250,000 cases of meningococcal disease were reported [16]. Cutaneous findings of meningococcemia occur after the flu-like prodroms, and they include a rash followed by erythema, and petechias localized on wrists, ankles, and axillae. Secondarily, they spread to the whole body except head, palms, and soles. The rash often progresses to the classic purpura. Meningococcemia can rapidly progress to septic shock with hypotension, congestive heart failure, disseminated intravascular coagulation and acute renal failure associated with significant mortality: 30–60% [16]. Treatment has to be instituted rapidly with penicillin; ceftriaxone and cefotaxime are alternatives. The duration of treatment is 5–7 days. Contacts should be treated prophylactically with ceftriaxone or ciprofloxacin. Prevention by immunization is essential for children older than 2 years.

22.4.2 Arboviruses

Dengue viral infection is becoming a major health problem, with a high incidence in some underdeveloped Latin American countries. Epidemics may occur. Cutaneous signs of Dengue Fever are noted in 48% of cases [10]. Acute fever (40–41°C) is observed, with a maculo-papular morbiliform pruriginous eruption followed by ecchymotic, petechial eruption secondarily generalized. Mucous membrane may be involved. Petechiae, ecchymosis and mucosal involvement defining Dengue haemorrhagic fever have a poor prognosis, with a high rate of mortality (10%) Death occurs through shock, with high-fever haemorrhagic phenomena and circulatory failure (Dengue shock syndrome). The treatment is only supportive.

22.4.3 Ebola Fever

This is the most lethal viral haemorrhagic fever, with a high mortality (50–90%). Outbreaks of Ebola fever occur in Gabon, Uganda and in Ivory Coast during the rainy season [17]. Contamination occurs through contact with infected cases. Nosocomial transmission is possible. After an incubation period of 2–21 days, a haemorrhagic syndrome occurs 2 days after the onset, Dermatological findings associate widespread erythematous rash developing into maculo-papular lesions and purpura. Gingival and cunjunctival haemorrhage and epistaxis are also present. Death occurs generally at day 12, with toxic shock. Patients are admitted to the hospital as an emergency, following a disaster-type plan of action [17]. *Rift Valley fever (RVF) and Crimean-*

Congo haemorrhagic fever (CCHF) are both associated with severe haemorrhagic fever and muco-cutaneous manifestations in humans. Rate of mortality is high to 30% for CCHF [18]. Supportive therapy is the mainstay of patient management.

22.4.4 Plague

This severe acute febrile infection in human is caused by *Yersinia pestis* occurs in underdeveloped countries [1], with three forms: bubonic, pneumonic and septicaemic plague. Transmission between wild and commensal rodents and human beings is effected by fleas. After the incubation period (1–6 days) there is sudden onset of malaise, myalgias, backache, tachycardia, high fever and prostration. Untreated bubonic plague progresses to septicaemic plague within 2–6 days. Patients exhibit shock, ecchymoses and small-artery thromboses resulting in digital gangrene; abdominal pain is common. The rate of mortality for septicaemic plague is 100%. The treatment is based on streptomycin for 10 days; alternative therapeutic treatments are chloramphenicol or cycline.

22.4.5 Epidemic Typhus

This is a re-emerging infection due to *Rickettsia prowazekii* reported in refugee camps during civil war [19]. The dermatologic findings appear on the fifth febrile day preceded by chills headache and weakness. The rash consists of pink maculae which become petechial and confluent, first in the axillae then over the trunk and later on the extremities. Complications are gangrene of the fingers and toes, typhus pneumonia and coma. Fatality rate is high, around 15%. The treatment is inexpensive with a single dose of 200 mg of doxycycline.

22.5 Conclusion

United Nations Millennium Development Goals aim at ending extreme poverty by 2015. Until then, the most neglected cutaneous infections of the underdeveloped countries will have a high prevalence. It's a challenge for a dermatologist working in these areas to recognize the dermatologic features of these diseases to reduce the mortality.

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Noxious Spider Bites

23

Batya B. Davidovici and Ronni Wolf

Core Messages

- There are more than 30,000 species of spiders, most of which are venomous but unable to inflict serious bites; most spiders only cause minor effects.
- The effects of medically important spiders are sometimes underestimated; conversely, there is a misattribution of signs and symptoms to alleged spider bites.
- Diagnosis is rarely based on the identification of the spider; immunoassays detecting the spiders' venom are not available.
- Brown spiders (*Loxesceles* spp.) and widow spiders (*Latrodectus* spp.) may inflict life-threatening complications.
- Prompt recognition with subsequent appropriate treatment might prevent severe reactions and improve the prognosis.

Spiders are carnivorous arthropods that ambush or ensnare prey. They play an important role in the ecosystem by consuming other arthropods that frequently transmit human diseases, such as mosquitoes and flies. Spiders usually do not transmit communicable diseases, unless they are secondarily infected by microorganisms. There are more than 30,000 species of spider, most of which are venomous, but they cannot inflict serious bites due to delicate mouthparts and short fangs. The well-known common exceptions are brown spiders (*Loxesceles* spp.) and widow spiders (*Latrodectus* spp.). They are very common, with a worldwide distribution; in addition, their bites may inflict life-threatening complications. This chapter will focus on these ubiquitous spiders. And since brown spider bites may cause serious cutaneous complications, this species will be reviewed more comprehensively.

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23.1 Spiders of the Genus *Loxosceles*:

Spiders of the genus *Loxosceles* have a worldwide distribution. There are more than 100 species described in many countries [1, 2]. The *Loxosceles* females are more venomous and larger than males, which rarely inflict severe envenoming bites. They are dull fawn to dark brown with an even darker brown, distinctive pattern on the dorsal cephalothoraxis looks like a violin with the base at the head end and the neck of the design pointing toward the abdomen. This pattern is consistent only in adult brown recluse spiders, and therefore is commonly misinterpreted. Therefore, for purposes of identification it is more important to examine the eyes. Differing from most spiders, which have eight eyes, recluse spiders have six eyes arranged in pairs (dyads) with one median pair and two lateral pairs. Only a few other spiders have three pairs of eyes arranged this way (e.g., scytodids) [3, 4]. *Loxosceles* spiders are naturally non-aggressive, prefer to retreat when threatened, and bite only in situations in which the spiders are trapped against human skin, such as when tangled up within clothes, or in bedding.

Based on their geographic distribution and the high number of notified bites with considerable morbidity and mortality, *Loxosceles* spiders are considered one of the medically most important groups of spiders in the world [5, 6].

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These spiders build webs, both indoors and outdoors in dark spaces, where encounters with humans are likely. *Loxosceles* species spiders are most abundant and active at night, and since they hibernate in the winter, most bites occur during the warm months of the year. Loxoscelism, the term used to describe lesions and clinical manifestations caused by bites of Loxosceles, was first described in the USA [7]. Presently, it is the most severe form of necrotic araneism in several countries [1, 3, 6, 8–10]. Most bites are benign, but approximately 10% become significant, and in a minority more severe reactions develop, including disseminated intravascular coagulation, haemolysis, renal failure and death.

23.1.1 The Venom:

The mechanism of venom action is incompletely understood; however, it acts by multiple pathways and mediators both directly and by autoimmune responses from lymphocytes and cytokines. The venom is composed of complex proteins and proteolytic enzymes. It is cytotoxic and hemolytic. It contains at least nine components, including enzymes such as hyaluronidase, alkaline phosphatase, esterase, lipase and the most prominent — sphingomyelinidase D2. Sphingomyelinase D activates the complement, attracts polymorphonuclear cells, induces platelet aggregation, liberates proteolytic enzymes, and stimulates the release of cytokines and chemokines including interleukin-8 (IL-8), growth-related oncogene-α, monocyte chemoattractant protein-1, granulocyte-macrophage colony-stimulating factor (GM-CSF) and others. These mediators amplify the inflammatory response responsible for the severe local and systemic reaction to the venom [9–15].

23.1.2 Envenomation:

Envenomation in humans can result in two well-defined clinical variants: cutaneous loxoscelism and viscerocutaneous loxoscelism.

23.1.2.1 Cutaneous Loxoscelism

Cutaneous loxoscelism is more common (67–100% of cases) and mostly has mild features [1, 16, 17]. The bite is initially painless but within several hours burning pain develops. Clinically, it is characterized by edematous erythema, which evolves to a hemorrhagic vesicle often surrounded by an edge of venom-induced vasoconstriction known as 'bulls eye' lesion, and within several days usually results in a dermonecrotic skin lesion. A mixed area of asymmetric erythema, surrounding a ring of blanched skin around the central ischemic lesion, known as red, white and blue sign, appears. In a smaller subset of patients (10–15%) these lesions may evolve to substantial necrosis, eschar and necrotic ulcer, which heal slowly or may even require surgical excision and skin grafting [1, 6, 8, 10]. Pain is the most common symptom. It is related either to ischaemia secondary to vasospasm, or to disruption by the toxin of myelin sheaths on nerve fibers [18].

23.1.2.2 Viscerocutaneous Loxoscelism

Viscerocutaneous loxoscelism, also known as systemic or cutaneous-hemolytic loxoscelism, is less common (0–30%, according to region and species studied). Within 2–4 days after envenomation, a morbiliform rash, fever, chills, nausea, vomiting, malaise, arthralgia and myalgia may occur. Rarely, a more serious form of viscerocutaneous loxoscelism may develop, which is complicated by haematologic disturbances such as hemolytic anaemia, sometimes Coomb's positive and leucocytosis [19–23]. In a retrospective review of 81 patients who were hospitalized for spider bite [24], 24% of the patients developed a disseminated eruption within 2 and 4 days following the bite. The most frequent rash, accounting for 75% of cases, was a macular, papular, or maculopapular disseminated rash. However, a relatively high percent (10%) of pustular eruptions were noted. Interestingly, a report of three cases that developed acute generalized exanthematus pustolosis (AGEP), a rare cutaneous reaction pattern mostly related to medication administration, 24–48 h after a spider bite, was recently published [25].

Less frequently, more severe reactions develop, consisting of thrombocytopenia, jaundice, haematuria, haemoglobinuria, rhabdomyolysis, shock and in some cases, disseminated intravascular coagulation and acute renal failure. These are the main causes of death in Loxosceles envenomation [1, 8, 9, 17, 26].

Recommended laboratory tests include complete blood count, serum glucose, platelet count, LDH, prothrombin time, partial thromboplastin time (interna-

tional normalized ratio), fibrinogen, fibrin split products, renal function tests, and urinalysis [23].

It is suggested that these systemic manifestations may vary depending on the amount of injected venom, time of envenoming, spider factors — such as species, sex and ontogenetic variations — and features of the patients such as age, bite site, concomitant illness, genetic variations and the involvement of different endogenous mediators [1, 17, 27–30]. Severe systemic effects are more common in children [31].

Viscerocutaneous loxoscelism may have a course which is independent of the local reaction [17].

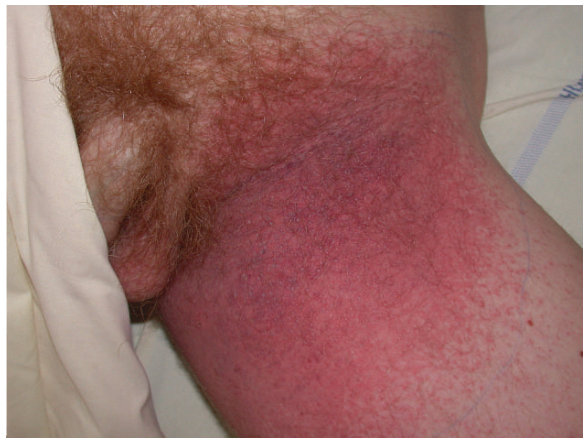

Fig 23.1 Oedematous erythema after spider bite

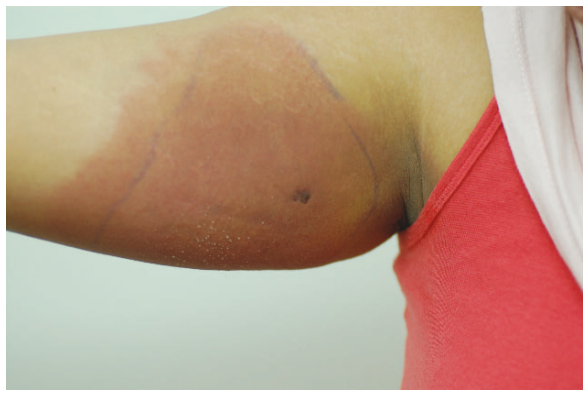

Fig. 23.2 A typical spider bite lesion of the arm

23.1.3 Diagnosis:

A definite diagnosis of spider bite requires the capture of a spider in the act of biting [32]. However, diagnosis of loxoscelism may be difficult as it is rarely based on the identification of the spider. The most frequent bite sites are under the arms, at the waist, or on the lower extremities [30]. Since patients are often bitten while sleeping or dressing and the bite is initially relatively painless, the vast majority cannot give a history of a spider bite, and most cases go unnoticed until the appearance of the local lesion [33]. Mild local reaction begins after a number of hours; however, making the correct diagnosis is still difficult, since the lesion does not present clearly-defined features. There are many documented cases of misdiagnosis by authors misattributing cellulitis, insect bite, chemical burn, fixed drug eruption, or even cutaneous anthrax infection to spider bites [34–36] (Figs. 23.1 and 23.2).

To detect the presence of venom, some immunoassays were studied with potential for future application as diagnostic tests; however, they were not satisfying clinically [1]. Recently, a new enzyme-linked immunosorbent assay (ELISA) designed to detect loxosceles venom was implemented and reported [37]. However, although obviously necessary, no such assay is currently available in clinical practice.

Skin biopsy should not generally be pursued unless other etiologies are considered. The histologic findings of bites, including acute vasculitis, platelet thrombi, and leukocyte infiltrates, are nonspecific [18, 28, 31].

Eventually, the diagnosis is made clinically, based on a combination of history and a recognized pattern of signs and symptoms [38, 39]. Therefore, familiarity with the arthropod fauna and maintaining a high index of suspicion are crucial for making the correct diagnosis.

23.1.4 Treatment:

Controversy exists regarding the treatment of recluse spider bites [4, 5, 8, 10, 16, 18, 33]. Different therapeutic interventions and surgical procedures are used differently in various countries, according to regional experience and envenoming characteristics.

The basic principles for recluse spider bites include rest, ice compresses and elevation of the bites (RICE therapy) [40] to minimize inflammation and venom spread. Limiting patient activity may decrease skin temperature, reducing enzyme activity and gravitational spread. Antihistamines and non-steroidal anti-inflammatory medications are administrated, mainly to relieve pain, pruritus and swelling, but their effect is also unproven.

In addition tetanus prophylaxis is advised. Hospitalization and intravenous fluid therapy may be needed to maintain adequate hydration and to protect renal function.

23.1.4.1 Antibiotics

Oral antibiotics are sometimes given to reduce the incidence of abscess formation and secondary infection in large lesions [9]. Although there are no clinical trials concerning the use of prophylactic antibiotics, the presence of *Clostridium perfringes* in venom and fangs of *L. intermedia* has been demonstrated, and associated to a greater degree of dermonecrosis in animal studies [41]. Moreover, it is known that an infection markedly increases the temperature in the bite site and, thus, the activity of the enzymes responsible for dermonecrosis and local inflammation, which can result in slow evolution and hard-healing lesions [40]. On the other hand, the rate of secondary infections is low [30, 42]; thus, some authors consider antibiotics use inappropriate without established evidence of infection [3, 9, 40].

23.1.4.2 Systemic Corticosteroids

Although there are no sufficient data about the use of systemic corticosteroids in cutaneous or viscerocutaneous loxoscelism, it is evident that corticosteroids do not inactivate the venom or stop its primary actions, and thus they do not prevent the development of cutaneous necrosis. Therefore, they are reserved for severe cases, because they might be helpful in preventing systemic complications [8, 9, 16, 17, 33, 43].

23.1.4.3 Dapsone

Dapsone probably limits the migration and infiltration of neutrophils in the bite site, which is an essential factor for the development of dermonecrotic lesions [3, 16, 40]. Several retrospective clinical studies [3, 4] and experimental trials [44, 45] have shown its beneficial effect in reducing the severity of local and systemic reactions to spider bites and improving patient outcome. A prospective study [46] indicated that pretreatment with dapsone reduced surgical complications. However, these observations were brought into question by two recent studies. A rabbit model, treated with colchicine, dapsone, triamcinolone, and diphenhydramine, showed that none of the agents tested had an effect on eschar size [47]. The second study [48], the largest reported study in humans, showed that dapsone was even associated with longer healing time and a 45% greater risk of scarring. These findings, along with the fact that dapsone is not indicated in systemic cases, and taking into consideration its potential severe side-effects especially in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency [4, 49], should restrain the use of dapsone in the treatment of spider bites.

23.1.4.4 Anti-Venom

In South America, the considerable morbidity and mortality in loxoscelic accidents has led to the development of specific anti-venom by Vellard in 1954 [50]. It has been produced in Brazil since the early 1960s, and to date there are several anti-venoms available in South America. The purpose of this therapy is to neutralize the greatest possible amount of circulating venom, as it is believed that this decreases the risk of local and systemic envenomation. These sera are heterologous immunoglobulins of equine origin, and thus it is not a treatment without risks, such as allergic reactions or delayed serum sickness [9]. In Brazil, serum therapy with anti-arachnidic or anti-loxoscelic sera associated to the corticoids constitutes the most employed intervention [51]. However, there is little evidence to support the effectiveness of this therapy, especially against cutaneous loxoscelism [52]. Yet, Rees et al. [53] observed the reduction of necrotic areas in animal models after the administration of the anti-venom, and in countries where the anti-venom has been introduced, an important reduction of the mortality in children and teenagers has been observed [52]. Although it is known that the majority of the damaging effects of venom in studies in animals occur within 3 h to 6 h after the brown recluse spider bite [33, 52], the importance of antibodies for the neutralization of dermonecrosis was experimentally confirmed [51], even when administered 6–12 h after envenoming. In the viscerocutaneous form, the serum therapy is indicated at any time [42, 50]. Thus, the recommendations for use of serum therapy in loxoscelism depend on the seriousness classification, the time between bite and medical assistance, and the risks and benefits of each case.

23.1.4.5 Surgical Management

Acute excision of the bite site should be avoided, since the inflammatory reaction produced by the venom will inhibit wound healing and produce an inferior clinical result [19, 31]. Most of the lesions resolve without surgery. Surgical management should be postponed until wounds have stabilized with medical management and are no longer progressing (a stable lesion). In cases of permanent tissue loss, with unacceptable scarring, reconstructive plastic surgery may be necessary [1, 8, 9, 50].

23.1.4.6 Other Treatments

Hyperbaric oxygen, vasodilators, colchicines, heparin, nitroglycerin and other treatments have not been subjected to controlled, randomized trials, and thus are with unproven efficacy for loxoscelism.

23.1.5 Prognosis:

It cannot be predicted which bites may progress to a systemic disease or to a large cutaneous necrosis [1, 48]. However, a study on 52 hospitalized patients with necrotic arachnidism confirmed that the patients' age, size of maximal necrosis and comorbidities are predictive of time to complete healing [54]. In another study, no relationship between initial lesion size and long-term outcome was observed [55]. Others have also reported a marked relationship between age of the patient, comorbidities and time to complete healing. In those with a large and deep necrosis, which usually begins within 72 h, ulceration lasted several months before healing [3]. Other prognostic factors were the bite site (duration of hospitalization was significantly longer in patients with severe lesions on the thigh) and the time of presentation to the hospital after the bite, which was directly related to the duration of lesion healing.

In summary, the bite of a recluse spider is typically self-limited and self-healing, without long-term sequels. However, identifying patients with a severe course following a spider bite is important for therapeutic decision-making, as appropriate intervention within the first few days can make a critical difference to the outcome.

23.2 Widow Spiders

Widow spiders *(Latrodectus spp.)* are found throughout the world, with 31 recognized species. There are three recognized species of black widow found in North America: the southern black widow (*L. mactans*), the northern black widow (*L. variolus*), and the western black widow (*L. hesperus*). The southern widow is indigenous to the southeastern United States (US). The northern widow is found primarily in the northeastern US and southeastern Canada, though its ranges overlap that of *L. mactans*. The western widow is found in the western half of the US, as well as in southwestern Canada and much of Mexico. *L. tredecimguttatus* is found in Europe, and *L. curacaviensis* is found in South America [56, 57]. Black (*L. indistinctus*) and brown (*L. geometricus*) widow spiders are found in southern Africa and Madagascar [58, 59]. In Australia and New Zealand, the red-black spider (*L.mactans hasselti*) is a problem [60]. However, most species probably cause a similar clinical syndrome worldwide (excepting *L.geometricus*, which appears to cause much less severe effects) [10]. Females are darker, more venomous, and significantly larger than males. Males also are capable of biting, but rarely inflict severely envenoming bites [61, 62]. Most females are dark gray or black, with red or orange hourglass or geometric patterns, spots, or stripes on their ventral abdomens. *Latrodectus* spiders are most abundant and active during the warmer months. Members of the *Latrodectus* genus are trapping spiders, which spin webs and await their prey. Like the brown recluse, the black widows are naturally non-aggressive, and bite only when provoked. Webs are built in protected areas, outdoors in dark spaces such as barns, trash piles, or around outdoors toilet seats [63]. Widow spiders have more potent venom than most spiders, and prior to the development of anti-venom, 5% of reported bites resulted in fatalities. Bites of the black widow spider are painful, and are usually associated with mild dermatologic manifestations [31]. Local erythema, sweating, and piloerection may appear at the wound site within the first half hour, and urticaria and cyanosis may also occur at the bite site [64]. Systemic toxicity from widow spider bites is caused by α-latrotoxin, a neurotoxic component of *Latrodectus* venom that depolarizes neurons, increases intracellular calcium, and stimulates uncontrolled exocytosis of neurotrans-

mitters and disrupts lipid membranes [65, 66], which causes massive pre-synaptic release of most neurotransmitters, including acetylcholine, norepinephrine, dopamine, and glutamate. Consequently, latrodectism occurs within 30 min to a few hours of the spider bite, and is characterized by pain. The pain can be at the bite site or radiating proximally from distal limb bites, i.e., lower leg pain with burning feet and lower extremity sweating may occur, even after upper extremity bites. Abdomen, back, or chest pain can follow a *Latrodectus* bite. This is usually associated with nonspecific systemic features such as nausea, vomiting, headache, fever, lethargy, and malaise. Sometimes hypertension, hyper-reflexia, regional lymphadenopathy, paresthesias, priapism, ptosis, salivation, tremor and local and regional diaphoresis, may appear. Less common are other autonomic and neurologic effects such as muscle cramps and, rarely, fasciculations [62, 67, 68]. Muscular spasms often begin at the bite site, and spread initially to local lymph nodes, and then to the face and abdomen. The face may be contorted into grimacing expressions, *Facies latrodectismica*, resembling tetanic *Risus sardonicus*. The abdomen may become rigid, mimicking the acute abdomen of appendicitis [69]. Rarely, thoracic myospasm followed by weakness may result in restrictive hypoventilation and respiratory arrest. Latrodectism usually resolves over a 3–7 day period, with few deaths.

In severe cases, the initial laboratory evaluation should include complete blood count and urinalysis to rule out peritonitis and urinary tract infections, and detect proteinuria. Also, measurement of serum creatine phosphokinase and lactic dehydrogenase to detect rhabdomyolysis from muscular spasm and rigidity should be performed. However, laboratory abnormalities are rare [56].

Black widow bite may be misdiagnosed, on the basis of the spectrum of symptoms, as drug withdrawal, appendicitis, meningitis, or tetanus, to name a few [69]. Most of the species of widow spiders can be identified from their characteristic red 'hourglass' marking on the undersides of their abdomen [31].

The local wound care of *Latrodectus* bites should include thorough wound cleansing, ice pack application, oral or parenteral analgesics, and tetanus prophylaxis. Other treatments include oral or parenteral benzodiazepines and intravenous calcium gluconate for muscular spasm and rigidity. *Latrodectus* antivenin is indicated for patients manifesting severe regional or systemic toxicity, and for patients with uncontrolled hypertension, seizures, or respiratory arrest [64, 68, 70, 71]. Usually, one vial of antivenin diluted in 100–250 ml of saline should be infused intravenously over 2 h; this process should be repeated for patients with persistent muscular spasms [68, 70]. However, the dose, route of administration, and infusion time may differ, and so the product information should be consulted before use. In severe envenomations, especially in children, antivenin may be effective in reversing latrodectism up to 90 h after the bite occurs [72]. Symptomatic children, pregnant women, and elderly patients with hypertension or coronary artery disease should be hospitalized and observed for seizure activity, threatened abortion, and myocardial ischemia respectively [68].

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Frostbite Injury Management in Emergency 24

Emmanuel Cauchy, Scrimgeour Carron, Rik Verhellen, and Fontanille Bernard

Core Messages

- Frostbite of the extremities affects two distinct groups of people: an 'at-risk' urban population, mainly the homeless, and persons exposing themselves to an arctic environment, i.e., climbers, polar explorers, etc.
- A localized cold-induced lesion, or frostbite, is defined as tissue injury resulting from the prolonged exposure of flesh to a temperature of less than 0°C.
- Improvement in the quality of textiles and clothing protections diminishes the impact of frostbite, yet it can still develop because of an insidious and painless onset.
- Frostbite injury most often involves the hands and feet, and less often the ears, nose and cheeks.
- Frostbite can result in catastrophic amputations, sometimes quite proximally on the affected limbs of previously healthy young men.
- A new classification of frostbite, based on initial clinical examination, has the advantage of establishing a long-term prognosis early on in the management of frostbite.
- Thrombolytic agents and prostacyclin used in the early phase of treatment of frostbite offer new hope to reduce the risk of amputation and sequelae from frostbite injury.

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24.1 Introduction

Frostbite was historically first described during war-time, and is also well-documented as affecting populations which are victims of forced migration in high-altitude areas. Cold-induced lesions are very often the result of an inability to protect oneself from an adverse environment. These injuries frequently afflict people active in polar environments, such as skiers and mountaineers. The seriousness of the lesion essentially depends upon the severity and the duration of exposure to the cold, and the means the subject has used to protect him or herself.

Over a period of more than 40 years, Chamonix Hospital treated a large amount of patients suffering from frostbite injuries of the extremities. Those with serious lesions were admitted for inpatient care. In those early days, there was no way of diagnosing the severity and risk of amputation at patient admission, and it was felt that a clinical tool to aid in prognosis was needed.

Early establishment of the prognosis for patients with frostbite is hampered by the lack of useful clinical guidelines [1]. Suffering from a lack of clear documentation and randomized protocols, it is difficult to ascertain the best treatment for frostbite. It would be presumptuous to recognize a true effectiveness in existing protocols. The 3–6-week waiting period often necessary to determine the severity of the lesion, and the prospect of amputation alone, causes mental anguish for many patients. Most recent hypotheses regarding the physiopathology of frostbite evoke the possibility of a secondary, progressive phase of necrosis in the first 48 h after the primary phase, where the vasospasm of frozen tissue predominates, further aggravating tissue damage [2]. Current research efforts are focused on this initial phase where vasoactive drugs and potent antioxidant such as prostacyclin [3], and fibrinolytics

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(recombinant tissue plasminogen activator (r-TPA) [4, 5], are administered in the first 48 h. In order to effectively compare treatment regimens, one must develop an accurate clinical tool to be able to compare the different cohorts in the studies. Many authors propose a classification based on the chronological aspect of the frostbite [6–10]. We based our classification on the topographic extent of the frostbite lesion when seen directly after re-warming on a 'one-time' initial extensive topographic of tissue damage. It may be used as a research tool to compare the effectiveness of clinical trial protocols: the different arms of a randomized study could be easily compared to reduce bias by using this simple anatomical classification.

During the last 20 years, guidelines for the management of frostbite have been reviewed based on data from studies validating use of early radio-isotope bone scan criteria [11], a new classification [12], and the use of new drugs and treatment protocols [13]

24.2 Epidemiology

An average of 80 patients with frostbite injuries to the hands and feet are treated at the Chamonix Hospital every year, but the incidence of frostbite in the world is unknown. In Chamonix, the vast majority of patients are mountaineers. As previously mentioned, historically, military personnel have had the greatest risk of injury until recently. However, with the growing incidence of homelessness and rising interest in outdoor cold-weather activities over the last 20 years, a shift over to the civilian population has taken place. These recent changes in demography have prompted investigators to examine risk factors within the civilian population.

A 12-year study on patients treated as inpatients for frostbite injuries in the northern prairies of Saskatchewan, Canada [14] revealed the following predisposing factors: alcohol consumption (46%), psychiatric illness (17%), motricity alterations (19%), and drug misuse (4%). Alcohol consumption is particularly devastating, as it causes heat loss through peripheral vasodilatation and clouds judgement. The victim will fail to recognize the need to seek shelter and warmth, which will further aggravate the injury. The need to amputate injured parts in most studies was closely correlated with the duration of cold exposure rather then the temperature [15]. Studies clearly reveal evidence of the anatomic sites most at risk from frostbite. The feet and the hands account for 90% of injuries reported [16]. Frostbite also affects the face (nose, chin, earlobes, cheeks and lips), buttocks/perineum (from sitting on metal seats) and penis (joggers).

Topographic classification was given by Killian, but the relationship between extent of injury and final outcome was not studied [17].

Earlier studies classified young children and the elderly at high risk from frostbite injury [18]. Although this grouping seems intuitively correct, the published epidemiological studies show that frostbite is in fact uncommon in these age groups, and instead tends to affect adults between the ages of 30 and 49 [19].

24.2.1 Risk Factors

Different risk factors can be distinguished, such as behavioural factors (inadequate clothing and shelter, alcohol and other drugs, psychiatric illness, smoking), mechanical factors (constrictive clothing, contact with heat-conductive material, immobility), environmental factors (wind, altitude or hygrometry) and physiological factors (previous frostbite, genetic susceptibility, dehydration, hypovolemia, acute or chronic hypoxia, hypovolemia, diabetes, vasculitis, Raynaud's phenomenon, vasoconstrictive drugs)

24.2.2 Pathophysiology

The pathophysiological processes underlying frostbite have been studied extensively over the years using both human and animal models. Current opinion is that local cold injury produces a succession of changes which are commonly divided into 'pre-freeze phase', 'freeze–thaw phase', 'vascular stasis phase' and 'progressive or late ischemic phase'. These overlap, and the changes depend on the freezing rate, the duration of freezing, the extent of injury and thawing rate. Mills proposes a more simplified scheme of injury with two phases: the cooling–supercooling–freezing stage; and a vascular stage that includes thawing (re-warming) and post-thaw. As skin cools, cold-induced vaso-constriction is followed

by cold-induced vaso-dilatation. This phenomenon, also known as the 'hunting response', protects extremities from cold injury (at the expense of heat loss). It occurs in 5–10 min cycles [20].

Skin sensation is lost around 10°C. With further cooling, vascular contents become more viscous, there is micro-vascular constriction and trans-endothelial leakage of plasma. Arteriovenous anastomoses may develop with shunting of distal blood. As skin cools further (<0°C), freezing occurs and frostbite starts to develop. The location and speed of ice crystal formation depends on the rate of freezing. Very low ambient temperatures, wind and moisture accelerate this rate.

Unless freezing is very rapid, ice crystals form first in the extra-cellular fluid spaces. Extra-cellular osmotic pressure increases, drawing free water across the cell membrane. This causes intracellular dehydration and hyper-osmolality. As freezing continues, there are extra- and intracellular electrolyte and pH changes, dehydration and destruction of enzymes. Cell volume reduction and possibly direct damage from ice growth occur. Cell membranes are damaged, micro-vascular function is compromised and endothelial cells are injured, with the endothelium separating from the arterial wall lamina. Cartilage, especially epiphyseal cartilage, is very susceptible to freezing injury. This is followed by ultra-structural capillary damage, loss of mitochondria in muscle cells and other intracellular damage [21].

Depending on the method of re-warming, hyperaemia, ischemia, cyanosis, or total circulatory failure develops [22]. Blebs or blisters may appear secondary to vasodilatation, oedema, and stasis coagulation. Platelet and erythrocyte aggregates clog and distort the vessels in viable tissue. Associated injury may cause increased compartment pressures. As is seen in burns, reperfusion injury occurs. This may involve oxygen-free radicals, neutrophil activation, and other inflammatory changes. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and thromboxane A_2 (TXA_2) cause platelet aggregation and thrombosis which results in ischaemia. Robson and Heggers found markedly elevated levels of $PGF_{2\alpha}$ and TXA_2 in frostbite blister fluid [23]. These eicosanoid derivatives have been heavily implicated as mediators of progressive dermal ischemia in burns, frostbite and ischemia/reperfusion injuries.

Depending on the degree of micro vascular damage, one of two processes occurs: either vascular recovery with dissolution of clots, or vascular collapse which results in thrombosis, ischemia, necrosis and gangrene. Refreezing after thawing causes intracellular ice formation, with extensive cell destruction and further release of pro-thrombotic, vaso-constrictive $PGF_{2\alpha}$and TXA_2. A rabbit ear model demonstrated increased tissue survival after a blockade of the arachidonic acid cascade at all levels [24]. The most marked tissue salvage resulted when specific TXA_2 inhibitors were used. This has now been shown to be effective in clinical situations [25].

24.3 Clinical Aspects

Severity of symptoms is usually related to the severity of injury. In our emergency department, we use to describe four phases regarding the time of evolution:

24.3.1 Freezing Phase

Freezing phase (in the field), characterized by cold numbness with accompanying sensory loss. The extremity will feel cold to the touch, and patients often complain that it feels clumsy, like a block of wood. Frozen tissue may appear mottled blue, violacious, yellowish-white or waxy.

24.3.2 Re-Warming Phase

Re-warming phase, when the patient recovers in a warm environment. It is characterized by a well demarcated blue-grey discoloration. Following rapid re-warming, there is an initial hyperaemia, seen even in the most severe cases. This phase lasts 12–24 h, before the arrival of blisters.

24.3.3 Progressive Ischemic Phase

Progressive ischemic phase, characterized by oedema, vesicles and the appearance of blisters. This phase will last 1–3 days (Fig. 24.1).

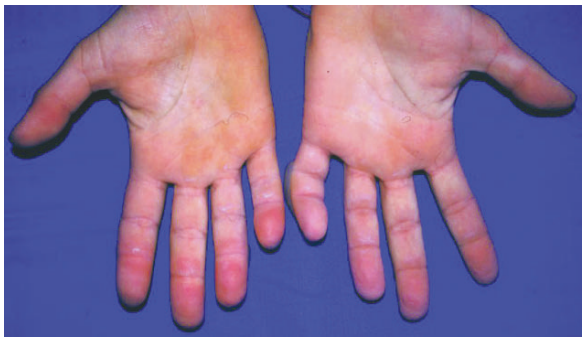


Fig. 24.1

24.3.4 Necrotic and Mummification Phase

Necrotic and mummification phase, seen from days 30 to 45 (Fig. 24.2). The damaged tissue will become dry and dark and crumbly. There is precise demarcation between viable and non-viable tissue.

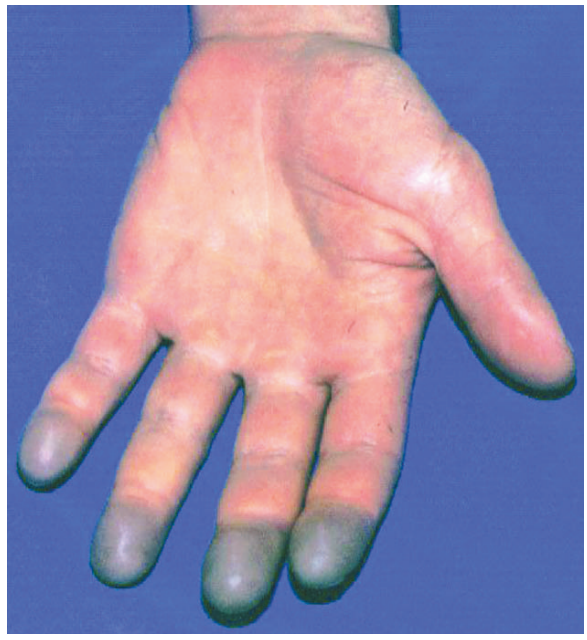


Fig. 24.2

24.4 Classification

Two retrospective studies we conducted have made it possible to classify and stratify frostbite injury. The first looked at the relationship between extent of the initial lesion after re-warming and long-term prognosis. The second looked at isotopic bone scan and its use in determining the level of amputation.

24.4.1 Extent of the 'Initial Lesion'

A study of 80 patients, in 2001, recruited from Chamonix Hospital made it possible to determine a relationship between the extent of the initial lesion and the final outcome. The classification derived from the study is now an invaluable tool, used widely to determine the severity of the frostbite early on in its management.

At day 0, the initial lesion was defined as the level of blue-grey discoloration which extended from the digit extremity towards the base of the limb (i.e., last phalanx, or last two, or up to the metacarpal bones etc.) (Fig. 24.3). This aspect persisted despite the rapid re-warming, and was accompanied by decreased skin sensitivity. The limit of the initial lesion was assessed just after the initial standard treatment protocol for most patients in Chamonix hospital: 38°C bath, intra venous vasodilator (chlorhydrate of buflomedil) and aspirin.

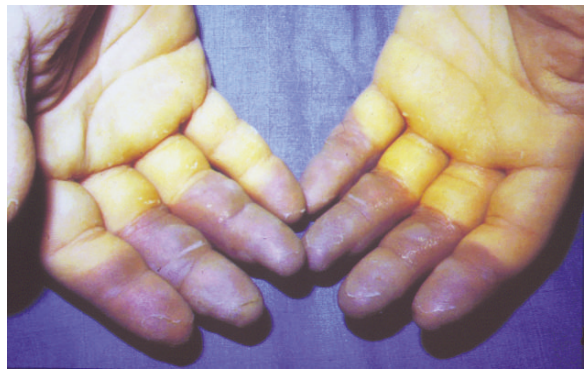
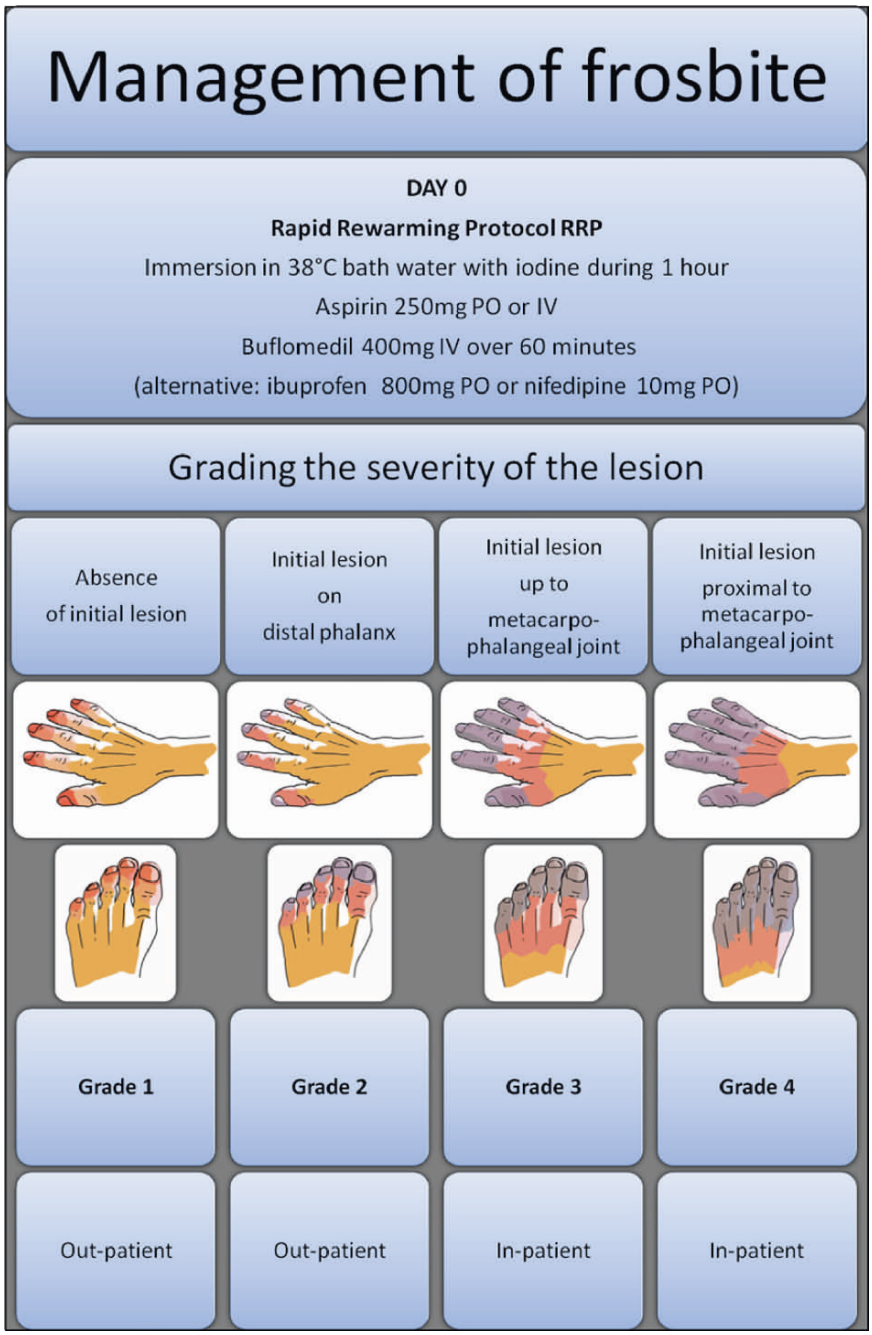


Fig. 24.3

The study consisted of an analysis of the correlation between the level of final bone amputation and the extent of the initial lesion.

The results are presented in Table 24.1. For both hands and feet, when the initial lesions were localized at the distal extremity of the hand or the foot, the probability of an amputation was around zero. The probability of some amount of bone amputation increased progressively, reaching 100% when all the foot or hand fingers were initially involved. By contrast, the specificity of the initial lesion aspect compared to the final outcome was very low, around 30%, indicating that the final amputation level has a low correlation with the

Table 24.1



initial clinical aspect of the lesion. The extent of the initial lesion could be used to predict the risk, but not the level of amputation. To determine the level of amputation, an isotopic bone scan (two-phase bone scanning [99mTc-HMDP]) should be carried out to complete the diagnosis.

24.4.2 Bone Scanning

Previously we have evaluated and published the prognostic value of two-phase 99mTc bone scanning performed on 92 patients who presented severe frostbite of the extremities [11]. The study showed that an initial

bone scan, as early as the third day, has excellent specificity in evaluating the severity of frostbite injury. There was a direct correlation between the uptake limit in the phalanxes and the eventual level of amputation: the probability of an amputation was around 84% in the case of scan images of non-fixation of the radioactive tracer. A second scan, on approximately day 8, was even more sensitive and informative, especially if the initial bone scan showed decreased uptake. A strong correlation was shown between a positive uptake of the radiotracer and the probability of healing (around 99%). (Fig. 24.4)

Bone scanning plays an essential medico-legal part too. A surgeon can justify the level of amputation used to treat severe frostbite by correlating it to the initial bone scan result.

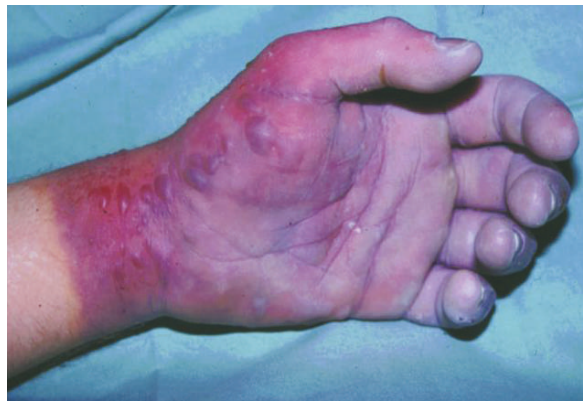


Fig. 24.4

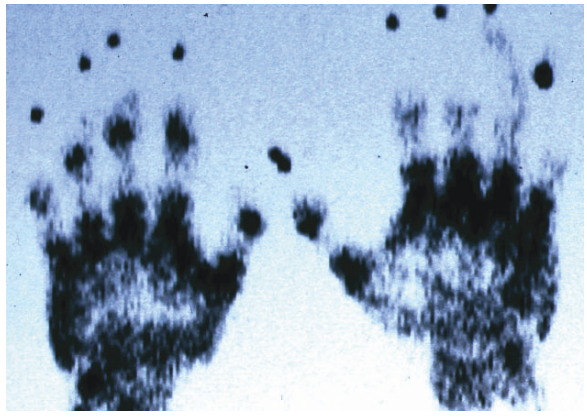


Fig. 24.5

24.4.3 Other Imaging Aids to Diagnosis

In addition to physical examination findings and bone scanning, several diagnostic tests have been used to help predict the severity and prognosis of the frostbite injury (plain radiographs, thermography, angiography, laser Doppler imager, digital plethysmography, MRI/MRA [26] (Fig. 24.5))

24.4.4 New Classification

Classically, frostbite has been described by its clinical presentation. Initially it was often difficult to predict the extent of frostbite injury. Taking into account these new results, a new classification was devised based on clinical criteria alone. Anyone without any specific knowledge of the management of frostbite can determine very early on the risk of amputation. A simple complementary examination with a strong positive predictive value for the frostbite level amputation completes the picture. This new classification can be used immediately after the re-warming of the limbs, and can aid the clinician to make a management plan and to give his patient an idea of the prognosis. Four levels of severity are proposed. The main advantage of this classification compared to previous systems is the immediate knowledge of prognosis: previous classifications needed 15 days of observation before they could predict outcome. With our system, by day 2 the exact level of amputation is known.

24.5 Treatment

Treatment of frostbite can be divided into three phases: pre-thaw field-care phase, immediate hospital-care phase, and post-thaw phase.

24.5.1 In the Field

If caught out in the field and there is a possibility of onset of frostbite, one should move out of the wind and seek shelter. One must avoid compression of the limbs

proximally, which can be caused by a tight backpack or climbing harness. Tight shoes must be avoided for the same reason. One should drink warm fluids, remove boots, remove wet gloves and socks and replace them by dry ones. Warm the cold extremity by placing it in a companion's armpit or groin area to seek warmth for a short time, put your boots back on, and take aspirin (500 mg) or buflomedil (300 mg) or ibuprofen (800 mg) to improve the circulation (if not contraindicated). Aspirin is less beneficial, as it prolongs blockade of all prostaglandin synthesis that are beneficial for wound healing. Buflomedil has a vasoactive effect on tissue microcirculation; it increases tissue perfusion. Ibuprofen is also indicated, as it provides systemic anti-prostaglandin activity that limits the cascade of inflammatory damage.

Do not rub the affected part, or apply direct heat. If feeling returns, one can continue to walk. If there is no return of sensation, go to the nearest warm shelter (hut or base camp) and seek medical treatment. If at high altitude, oxygen should be given. According to numerous studies, field re-warming should only be attempted if there is no further risk of refreezing. Tissue which is thawed and then refrozen almost always dies. Consequently, the decision to thaw the frostbitten tissue in the field commits the provider to a course of action which may involve pain control, maintaining warm-water baths at a constant temperature, and protecting tissue from further injury during re-warming and eventual transport. In base camp, rapid re-warming should be carried out over 60 min in a 38°C bath; however, it is not recommended that the patient walk on the feet once re-warmed.

24.5.2 Emergency Room Care

Always look for hypothermia and/or associated injury. Treat life-threatening emergencies first; hypothermia should be corrected to a core temperature of 34°C before frostbite management is attempted. 'Rapid Re-warming Protocol' (RRP) involves:

- Re-warming whirlpool water bath of 38–40°C with a mild antibacterial agent such as iodine or chlorhexidine. The time period recommended for re-warming is up to 1 hour [27]. Re-warming should continue until a red/purple colour appears and the extremity becomes mobile. Active motion during the re-warming period is beneficial, but care should be taken to prevent the extremity from touching the sides of the whirlpool.
- Medical treatment: During the bath, an IV dose of 400 mg of buflomedil is given over an hour, along with an injection of 250 mg of aspirin. In countries where buflomedil does not exist, we suggest the use of 800 mg of ibuprofen with aspirin. Intravenous fluid resuscitation is not usually required during this phase.

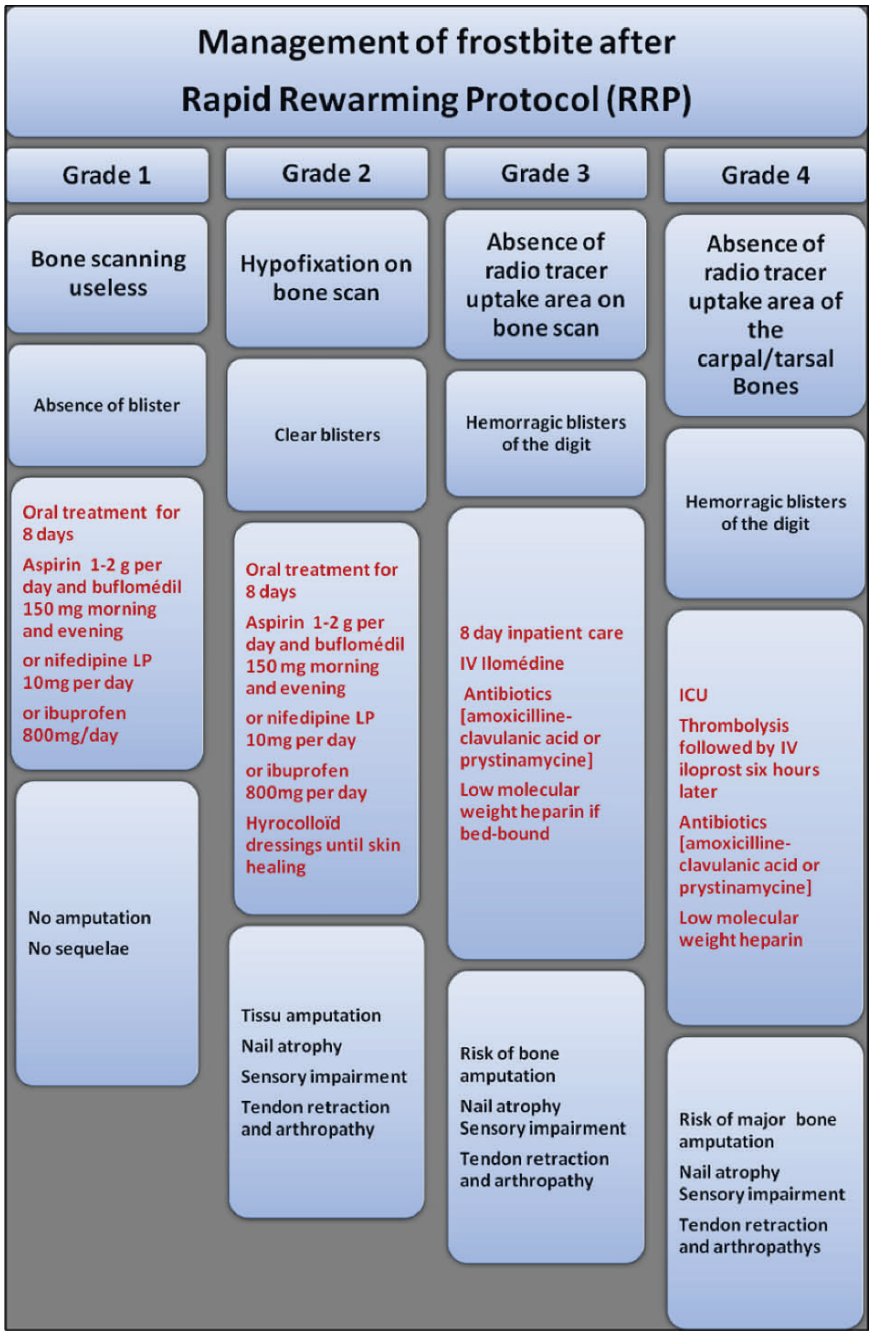
After the bath, an evaluation of the initial lesion should be done to determine the degree of severity and decide the treatment protocol (Table 24.2)

- Grades 1 and 2: Taking into account the low risk of amputation, lesions of Grade 1 (Fig. 24.6) or 2 (Fig. 24.7) do not need inpatient care, or isotopic bone scan. A treatment of aspirin, and vasodilators orally during 8–21 days, associated with local treatment (dressings), is sufficient in most of the cases.
- Grade 3 (Fig. 24.3) is correlated with an important risk of amputation, so cases should be admitted immediately for specific treatment. Low molecular weight heparin is used in cases of severe foot frostbite. Iloprost is given intravenously (prostacycline analogue) (up to 50 µg per day) for 5–7 days. Iloprost intravenous is relatively well-tolerated and has few secondary effects. It should be started 6 h after the first dose of aspirin. Systemic broad-spectrum antibiotics are usually given prophylactically for foot frostbite, because of a high risk of secondary infection (amoxicilin + clavulanic acid).

An isotope bone-scan performed on day 2 will determine more precisely the extent of the frozen lesions, and make it possible to ascertain the level of bone amputation. In the case of a positive result, the surgical intervention should be planned after the second bone scan at day 8 (stabilisation of the frostbite bone lesions).

- Grade 4 (Fig. 24.8) is associated with near-certain need for amputation, as well as a high risk of major complications (deep vein thrombosis, sepsis, septic shock and death). The same treatment as Grade 3 by intravenous route should be started immediately after rapid re-warming protocol, associated with intensive local treatments. The use of more aggressive treatments such as thrombolytic [rtPA (30 to 5 mg] or iloprost (up to 50 µg per day)] must be discussed on a case-to-case basis. Use of thrombolysis should be restricted to patients with severe Grade 4

Table 24.2



frostbite, because of the important risk of hemorragic side-effects. However since these patients run a high risk of disability due to amputation, use of this radical treatment must be discussed.

Despite proper intense early treatment, early amputation is often required, as sepsis complicates infection of necrotic tissues. In such an instance, the level of amputation can be guided by isotope bone-scan at day 2 and 8. These major complications are more likely on those patients with a fragile terrain, i.e., malnourished, with renal or hepatic impairment or other systemic illness. The surgical technique of amputation depends on the surgeon (i.e., amputation in 'one-step', 'two-steps'

or with salvage flap transfer, etc.). Most surgeons agree that early amputation limits the length of inpatient hospital care, the duration of wound dressing and the re-constructive surgery delay. However if there is no need for urgent surgery (no septic complications), the best attitude is to let the body demarcate the limit between viable and necrotic tissue and to amputate secondarily (Figs. 24.9 and 24.10).

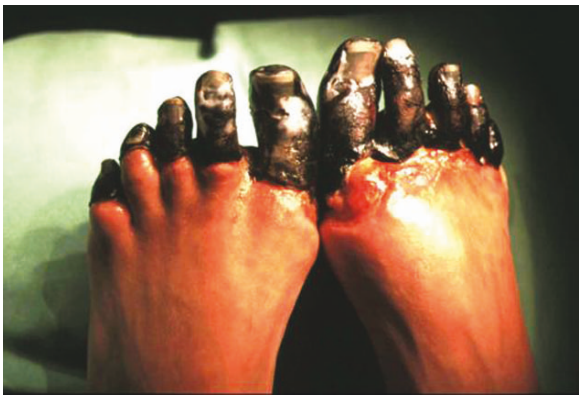


Fig. 24.6

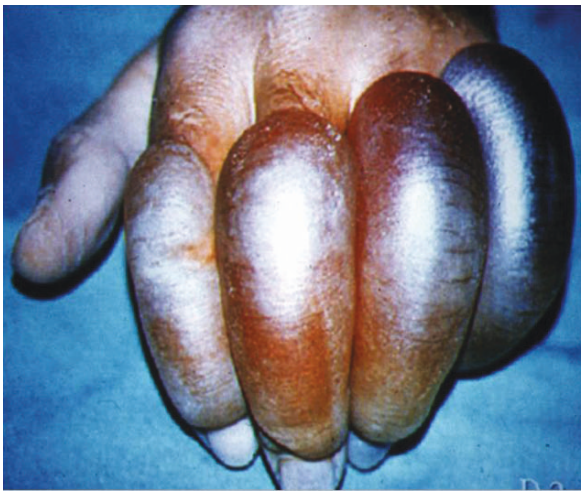


Fig. 24.7

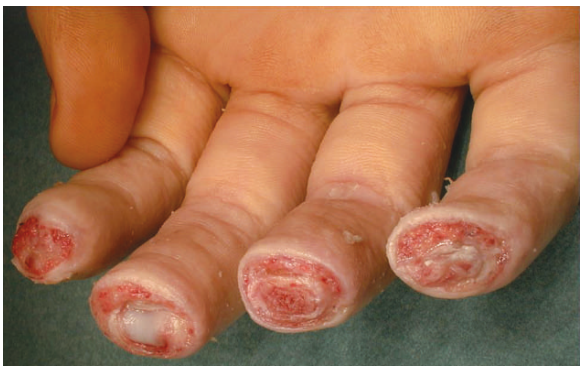


Fig. 24.8

24.5.3 Post-Thaw Care

Blisters appear after 12–24 h. They can be filled with clear fluid, milk-like fluid or can be hemorrhagic. Blisters should be left alone for the first 3–5 days, as they tend to enlarge and debriding them will only result in the need for further debridement at a later stage. It is recommended to drain leaving the roof of the blisters intact, to cover them with dressings and to debride them properly after 3–5 days once they have attained their maximal size. Dressings used should be changed daily. The use of hydrocolloids containing silver sulfadiazine reduces the risk of infection. Padding should be put between the patients' toes if they are affected

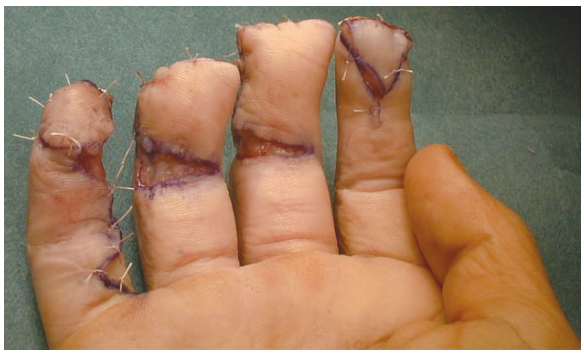


Fig. 24.9

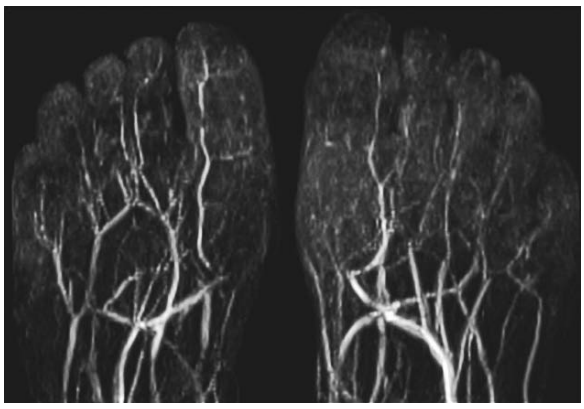


Fig. 24.10

There is no need to use re-warming foot/hand baths apart from the one carried out on day 0 to re-warm the frozen limbs.

Tetanus vaccination status must be reviewed. Anti-tetanus toxoid should be given if vaccination is not up to date. Analgesia must be given during this phase. Opiates are sometimes required, especially during the daily wound dressing.

Thawing and reperfusion are often accompanied by intense pain. A throbbing pain begins 2–3 days after re-warming and may persist for weeks or months, even after the tissue becomes demarcated. A residual tingling sensation beginning after 1 week has also been described. This is probably due to an ischemic neuritis [25]. A variation in onset of symptoms exists, with some victims never noticing pain (e.g., diabetics with previous neuropathic damage). In victims without tissue loss, symptoms usually subside within 1 month, whereas with tissue loss symptoms may exceed 6 months. In all cases, symptoms are exacerbated by a warm environment. Other sensory deficits include spontaneous burning and electric current-like sensations. Usually frostbite victims experience some degree of sensory loss for at least 4 years after injury, some maybe indefinitely.

24.6 Adjunct Therapies

More recent studies have assessed the role of adjunctive therapies in the treatment of frostbite. These include surgical lumbar sympathectomy, intra-arterial reserpine, brachial plexus blocade, oral nifedipine, hyperbaric oxygen, low-molecular weight dextrans and thrombolytic agents [28]. Many have only been tested in animal models, and further randomized trials in humans are needed.

Hyperbaric oxygen therapy (HBO). The role of HBO therapy in frostbite has had mixed acceptance amongst authors. Several animal studies have demonstrated it to be of no benefit [29], yet two recent studies in humans have yielded excellent results [30]. HBO increases the deformability of erythrocytes, diminishes oedema formation in burned and post-ischemic tissues and has a bacteriostatic effect [30]. It also may act as an antioxidant [31]. Its role in frostbite therapy warrants further investigation, as it is a relatively safe and inexpensive treatment.

Sympathectomy. The role of sympathectomy, either surgical or chemical, has yielded mixed results. Early sympathectomy, performed within the first few hours of injury, actually increases oedema formation and leads to increased tissue destruction. However, if performed 24–48 h after thawing it will hasten resolution of oedema and decrease tissue loss. Sympathectomy certainly has a role in preventing some long-term sequelae of frostbite such as pain (often due to vasospasm), paresthesias and hyperhidrosis [28].

Vasodilators. Intra-arterial reserpine has been shown experimentally and clinically to be of use in frostbite [25]. Reserpine appeared to be of use in preventing vasospasm, but it did not retard progression of tissue loss. The use of pentoxifylline, a methyl-xanthine derived phosphodiesterase inhibitor, has yielded some promising results in human trials. It increases blood flow to the affected extremity, decreases platelet hyperactivity and helps normalize the prostacyclin to TXA_2 ratio. It has been clinically proven to enhance tissue survival.

24.7 Prevention of Frostbites

Here are some simple measures to reduce the risk of frostbite: wearing multiple-layer protective clothing, adequate nutrition and hydration, staying dry, wearing mittens rather then gloves, avoiding constriction of body parts with clothing, avoiding tight-fitting boots, using aspirin prophylactically. It is essential to be proactive in detecting frostbite where weather conditions are extremely cold. The insidious onset of frostbite means that unless one looks out for it frequently it can be missed and detected too late.

24.8 Conclusion

A rise in homelessness and increase in outdoor cold weather activities have caused the incidence of frostbite amongst the civilian population to rise over the last 15 years. A proper knowledge of frostbite management is no longer reserved to military doctors; civilian medical practitioners may be confronted with this pathology too, and knowing how to manage frostbite is therefore crucial to both the military and civilian medical practitioner.

Although it remains a potentially disastrous injury associated with high morbidity, frostbite can now be treated effectively to ensure minimal loss of tissue and function. With adequate preventive measures, the risk of frostbite injury can be reduced. Research over the past 15 years has led to a new understanding of the pathophysiology of cold injury. Understanding of the role of inflammatory mediators, such as $PGF_{2\alpha}$ and TXA_2, has led to new active medical regimes such as the use of ibuprofen, prostacycline analogues and thrombolytic agents. Improved imaging assessment using MRI, MRA and technetium scintigraphy, coupled with further research into the use of adjunct therapies, should herald further advancement in the treatment of frostbite.

The efficiency of radical medical treatments of frostbite (thrombolysis and intravenous prostacycline analogues), when they are used within the first 24 h on grade 3 and grade 4, should encourage medical practitioners to treat such patients as medical emergencies, and to refer them as early as possible to a centre where the treatment can be initiated.

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Photodermatoses*

25

M.-T. Leccia and J.-C. Beani

Core Messages

- Photosensitive disorders include idiopathic photodermatoses and photo-toxic and photo-allergic diseases related to identified photosensitizing molecules (also called chromophores).
- Severe acute cutaneous reactions (from diffuse erythema to large bullous) are mainly observed with photo-toxic reactions caused by external agents (systemic or topically applied) which lower the threshold for abnormal UVR responses. Extensive burns have been particularly reported after therapeutic phototherapy or cosmetic use of psoralens for tanning.
- Various photo-toxic and photo-allergic clinical reactions have been described with systemic drugs, especially with quinolones and propionic acid derivatives.
- Diagnosing photosensitive disorders first depends on clinical examination with precise interrogation concerning possible sun exposure, and research of photosensitizing drugs.

Photo-allergic and photo-toxic reactions
Drug-induced photosensitivity reactions refer to the development of cutaneous disease on sun-exposed areas as a result of the combined effects of a drug (systemic medications and topically applied compounds) and light (mostly spectrum within the UVA and visible light range or UVB range). Photo-toxic reactions are significantly more common than photo-allergic reactions, and mostly resemble exaggerated sunburn. Severe photo-toxic reactions are observed with systemic medication and extensive cutaneous ultraviolet exposure, typically with psoralens and UVA irradiations. Photo-allergic reactions appear only in a minority of individuals, and resemble allergic contact dermatitis on sun-exposed areas and may expand beyond the site of topical application. Photo-allergic reactions are classical T-cell-mediated or delayed-type hypersensitivity reactions of the skin in response to a photo-allergen to which a subject was sensitized in the past.

Photosensitive disorders correspond to abnormal reactions of human skin exposed to ultraviolet radiations (UVR) or visible light, consecutive to the activation of specific molecules abnormally present in the skin called photosensitizing molecules or chromophores [1]. Clinical patterns are called photodermatoses. In some cases the chromophores can be identified, and correspond to endogenous molecules (metabolic photodermatoses or endogenous photosensitisations) or exogenous molecules from an internal source (medications) or topical applications (medications, cosmetics, plants, etc.). In other cases called idiopathic photodermatoses (some of which may correspond to autoimmune photodermatoses), chromophores are still unknown. The main idiopathic photodermatoses include polymorphic light

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* The only life-threatening photodermatoses concern phototoxic reactions with psoralens.

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eruption, solar urticaria, chronic actinic dermatitis, actinic prurigo and hydroa vacciniforme.

As we'll see below, few photodermatoses are life-threatening, and most severe reactions are observed with photosensitisations provided by oral or topical drug intake.

History and physical examination are essential steps in the diagnosis of photodermatoses. They can be completed by biopsies and light testing using a solar simulator a long time after the acute clinical reaction [2]. In the context of a severe acute photodermatose, clinical aspects and research of photosensitizing drugs are keys to diagnosis.

25.1 Endogenous Photodermatoses

Pellagra, pellagroides erythemas and cutaneous porphyrias are the main metabolic photodermatoses. In pellagroides erythemas and cutaneous porphyria tarda, photo-toxic burning can represent an immediate discomfort of the skin exposed to UVR or visible light, in the absence of visible signs. Also sometimes acute skin inflammation and blistering can be present. However, the severity of these diseases is not related to cutaneous involvement but to other organ involvement independent of UVR. Erythropoietic protoporphyria may exhibit immediate erythema and urticaria, but its bad prognosis is related to scars and mutilations of the face and the hands following chronic UV-induced blistering.

25.2 Exogenous Photodermatoses

Severe photosensitive disorders are usually observed with photo-toxic reactions caused by external agents, either systemic or topically applied, which lower the threshold for abnormal UVR responses. Most photosensitisations implicate reactive oxygen species that are photo-generated, especially superoxide anion ($O_{2\_}{}^{\circ}$) and singlet oxygen ($^1O_2$). Erythema is the usual aspect of exogenous photo-toxic reactions. The erythemal reaction can start a few minutes or hours after UVR exposure. It is exclusively localized on photo-exposed areas containing the active chromophore (all photo-exposed areas for systemic absorption versus localized areas with topical applications). Variable intensity of reactions can be observed; the most severe are bullous reactions. Symptoms consist in burning and tingling without itching.

25.2.1 Phototherapies

Generalized erythema with possible extensive burns has been reported consecutive to therapeutic phototherapy or to intentional cosmetic use of psoralens for tanning. Psoralens are photo-active chemicals that form adducts with DNA on UV exposure that suppress keratinocyte proliferation [3]. The mechanism of injury in PUVA burns may be a direct DNA damage in the basal cell layer of the epidermis. Photosensitivity can persist for up to 72 h after treatment, as psoralen-DNA monoadducts remain in the skin far longer than free psoralens. Depending on the individual susceptibility to UV radiation, several predictable side effects of PUVA are known ranging from erythema to blister formation [4]. Psoralen concentration and UVA dose are two critical parameters associated with severe acute photo-toxic events. Herr et al. described in a 10-year follow-up study *(with 17,000 annual PUVA-therapies)* ten severe burns (incidence 0.05%) [5]. For six patients, mistakes were related to medical personnel (UV over-dosage). Three patients had been sunbathing just after PUVA sessions. Three patients needed hospitalization and burn nursing during 3–21 days. No adverse effects were reported after a few months except hyper-pigmentations. Burns are also described with cosmetic use of psoralens. Braye et al. described 14 severe photo-toxic burns in young women, related to misuse of photosensitizing agents, with nine hospitalisations (11 + 3 days) [6]. Lok and colleagues reported, between 1982 and 1990, 20 patients who were hospitalized for burns because of misuse of psoralens for cosmetic reasons [7]. All patients had a skin erythema on 90% of the skin and cutaneous bullae on 22% of the skin. Most cases healed spontaneously without grafting. However, one severe case was described with balneo-PUVA, with death by septicaemia [8]. Direct contact effects or effects of aerosolized bergamot (5-MOP) aromatherapy oil, with secondary UVA exposure by staying outdoors or in tanning salon, were also described [9, 10]. Photo-toxic erythema is also the main effect of UVB phototherapy [11]. These reactions can be increased by concomitant use of medications. Emergency departments and physicians should all be aware of the

possibility that patients may present with burns which are secondary to psoralens abuse [12, 13]. In all cases, general principles in burn management should be observed. Patients with significant burns may develop secondary bacterial infections which can become rapidly life-threatening. Skin grafting is barely required among the patients who burn with no deeper than second degree. Prognosis is probably first related to surface area involved with burns, rather than depth of burn injury. Some authors also suggest that healing is poor in elderly patients in the life-threatening cases. Concomitant intake of photosensitive drugs must systematically be suspected (anti-inflammatory non-steroid molecules (AINS), phenothiazines, calcic inhibitors) [11, 14].

25.2.2 Photo-toxic Reactions

Acute photo-toxic reactions have been described with different drugs such as tetracycline class of antibiotics, AINS and psychotic medications [15–17] (Fig. 25.5). Most brutal photo-toxic reactions were however observed with quinolones. Large bullous or very painful phlyctenal detachments may appear and persist several weeks after the acute accident. Secondary, pigment anomalies can develop, such as hyper-pigmentation or vitiliginous de-pigmentation. The photo-toxic risk varies with molecules and has been established as followed: fluroxacine > lomefloxacine, perfloxacine > ciprofloxacine > enoxacine, norfloxacine, ofloxacine [18–21].
Particular photo-toxic effects have been described with other drugs:

- Persistent photo-sensibility with quinine [22] or fenofibrate [23].
- Different photodermatoses (erythema, discoid lupus, pseudo-porphyries, dyschromies) with voriconazole (anti-fungic drug) [24, 25]; we recently described two immuno-suppressed patients treated with voriconazole who developed multiple solar keratoses and invasive epidermoid carcinomas in a context of photo-sensibility related to the introduction of this anti-fungic drug. Most pre-epitheliomatous lesions and some carcinomas regressed with the stop of treatment.
- Photo-distributed papulo-pustulosis eruptions with EGFR inhibitors [26].
- Patients treated by 5-fluorouracil, methotrexate or taxans can develop severe photo-recall reactions, with fluoride redness and burning and erosion of photo-damaged skin with modest UVR exposure [27, 28].

Photo-recall reactions appear with administration of specific medications (5-FU, methotrexate, taxans) in patients who were exposed to UV radiation some days or weeks before drug administration.

25.2.3 Photo-Allergic Reactions

Severe photo-allergic disorders such as delayed hypersensitivity reactions or immediate hypersensitive reactions mediated by IgE in response to UVR are less frequent. Mechanisms of photo-allergy implicate the induction of cellular hypersensitivity by an immune reactive photo-antigen [29]. Photo-allergic reactions are independent of drug and UV doses. Clinical aspect is usually an eczematous eruption that can affect exposed and non-exposed skin. Severity is linked to intensity of the reaction and to development of the ondition, since cutaneous manifestations can persist for months, even years. Most severe cases of both photo-toxic and photo-allergic reactions have been described with propionic acid derivatives such as ketoprofen [30–32] (Figs. 25.2, 25.3, 25.4). Photochemical and photo-biological studies have shown that the ketoprofen molecule absorbs UVB and short UVA radiations, leading to the formation of diphenylketone derivate responsible for photo-allergic reactions. This explains cross-reactivity with molecules such as fenofibrate, oxybenzone, or tiaprofenic acid, very similar structurally [33, 34]. Eruptions mimicking erythema multiforme can be seen with these drugs [35]. Photo-allergic contact dermatitis due to diclofenac has also been reported [36]. Hypersensitivity syndrome with fever, hepatic cytolysis and eosinophilia has been observed with sulfasalazopyridine [37].

Severe photo-allergic reactions have been also described with plants such as frullania, compositae or lime [38, 39] (Fig. 25.1).

25.3 Idiopathic Photodermatoses

Idiopathic, autoimmune photodermatoses can greatly affect life because of the severity and chronicity of skin eruptions, but usually without vital consequences.

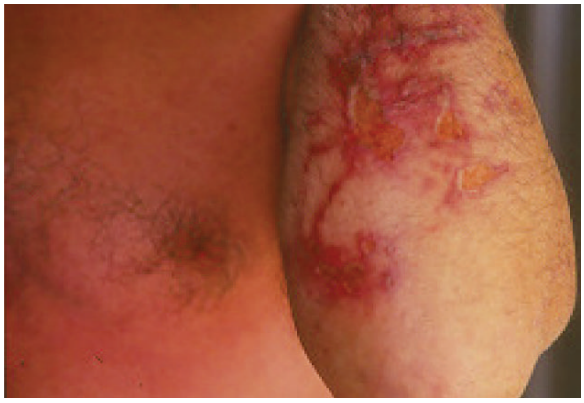


Fig. 25.1 Phyto-photodermatosis

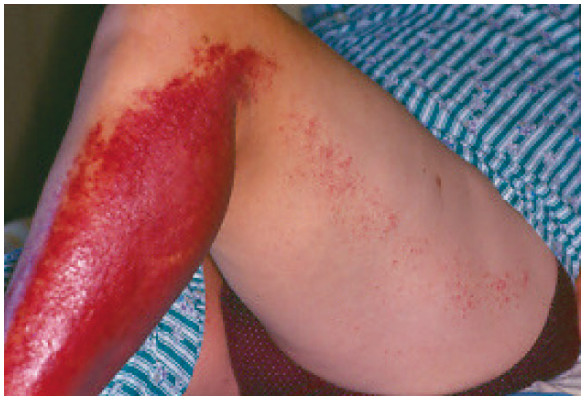
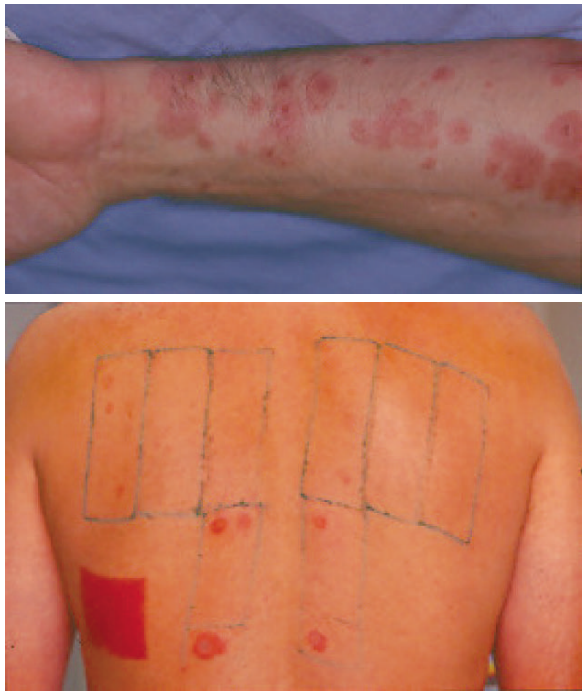


Fig. 25.2 Eczematous contact photo-allergy to ketoprofen gel



Figs. 25.3, 25.4 Erythema-multiforme-like eruption following photo-allergic contact dermatitis to ketoprofen gel and positive photopatch tests

The most frequent idiopathic polymorphous eruptions are benign and never life-threatening.

Solar urticaria is rare (less than 2% of all photodermatoses) and affects predominantly Japanese women between 20 and 40 years old. Eruptions are thought to be linked to a unknown chromophore leading to the development of a hyper-sensibility mediated by IgE, with two types individualized today [40]. Papulous eruptions are associated with very uncomfortable sensations of burning and itching. The severity of solar urticaria is linked to the action spectrum, usually concerning UVB, UVA and visible light and explaining skin reactions in everyday life and the difficulty of preventing and treating eruptions [41]. Exceptional reactions such as anaphylaxy and vasculitis have been described [42, 43].

Hydroa vacciniforme (HV) is a rare childhood disorder mainly induced by UVA. Umbilicated blisters occur on exposed areas, especially on the face, leading to scars with important cosmetic disorders. Typical hydroa vacciniforme have to be distinguished from severe HV-like eruptions that are associated with systemic complications, and especially Epstein–Barr virus (EBV)-associated NK/T-cell lymphoproliferative disorders with possible fatal outcome [44].

Chronic actinic dermatitis is a rare disease occurring mainly in elderly men [45]. It can occur as eczema in exposed areas in the summer only, with no cutaneous sign in wintertime. Severe forms consist of diffuse photosensitivity with sparing of light-shielded areas, and may progress to erythroderma. Some forms may follow photo-allergic or allergic contact dermatitis, oral drug photosensitivity and occasionally polymorphic light eruption. Other forms are associated with atopic dermatitis [46, 47]. In addition, contact dermatitis allergic to various airborne or topical allergens exists [38, 48]. Severe clinical patterns are associated with lymphomatous malignant transformation. Skin biopsy shows a dense dermal lymphocytic dermatitis, with atypical cerebriform lymphocytic cells identical

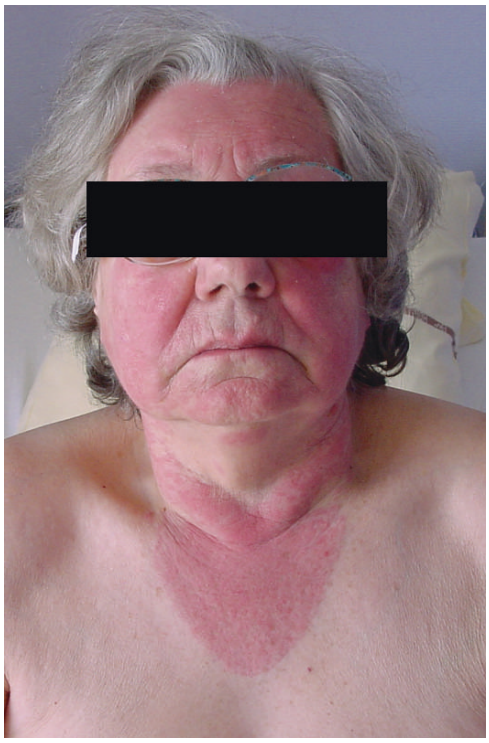


Fig. 25.5 Photo-toxicity to phenothiazine

to those found in cutaneous T cell lymphoma. UV testing is essential to make a definite diagnosis of chronic actinic dermatitis, most patients presenting abnormal threshold responses to UVR.

Sweet's syndrome is a neutrophilic dermatosis which frequently affects photo-exposed areas, without clear UV induction or aggravation. However, two cases of photosensitive Sweet's syndrome have recently been described, with no associated diseases and with benign evolution [49].

Systemic diseases like erythematous lupus or dermatomyositis usually present photo-aggraved cutaneous eruptions.

Deleterious effects of UVR in photosensitive genodermatoses such as xeroderma pigmentosum, trichotiodystrophy or Rothmund–Thompson syndrome are characterized by cutaneous cancer induction without life-threatening acute effects.

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26 Life-Threatening Dermatoses and Emergencies in Migrants and Patients Coming Back from a Tropical or Subtropical Country

Eric Caumes

Core Messages

- Skin and soft-tissue infections are the most common travel-associated dermatoses.
- Acute urticaria or localised inflammatory oedema with blood eosinophilia orients towards a helminthic infection.
- Febrile exanthema may be observed during systemic bacterial infections, arboviral diseases, haemorrhagic viral fever and drug adverse reactions.
- Environmental diseases may be related to arthropod-induced or marine life dermatitis and envenomations.

Dermatoses are a leading cause of health problems in travellers. They cover a large spectrum of exotic and cosmopolitan infections, as well as environmental diseases which include life-threatening diseases.

26.1 Epidemiological Overview

Dermatoses are considered as one of the three most common causes of health problems in returning travellers. Three studies have helped to identify the spectrum of skin diseases in travellers [1–3]. Overall, the most common skin diseases were insect bites (with or without secondary infection), skin and soft-tissue infections, cutaneous larva migrans, scabies, myiasis, tungiasis, urticaria, febrile rash and allergic reactions. Taken together, these studies show that the leading dermatoses in returning travellers are infections and environmental skin diseases. In the largest series to date, the only death related to a skin disease was related to cutaneous abscesses [2].

26.2 Emergencies Related to Infections

26.2.1 Bacterial Infections

26.2.1.1 Skin and Soft-Tissue Infections

The clinical spectrum of skin and soft-tissue infections (SSTI) ranges from impetigo and ecthyma to erysipelas, abscess, and necrotizing cellulitis [1–3].

S. aureus and *Streptococcus* species are the most frequently involved bacteria. Insect bite is the portal of entry in 28.6–63% of the cases diagnosed as SSTI [1, 3].

SSTI may be life-threatening in two circumstances. The involved bacteria may produce toxins (toxic strep syndrome, toxic staph syndrome, staphylococcal scalded skin syndrome) with systemic consequences (see the corresponding chapter 13). Apart from local complications (necrotizing cellulitis, myositis) the lesions can be the portal of entry of systemic infection that may appear as signs of systemic inflammatory response syndrome, sepsis and lastly septic shock (see the corresponding chapters 6 and 7).

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26.2.1.2 Rickettsioses and Scrub Typhus

Rickettsioses and scrub typhus are zoonotic bacterial infections transmitted to humans by arthropods. African tick bite fever, Mediterranean spotted fever, Rocky Mountain spotted fever, murine typhus and scrub typhus are the most frequently described in travellers [4]. Most patients present with a benign febrile illness accompanied by headache, myalgia and cutaneous eruption (rash in addition to inoculation eschar) (Fig. 26.1). Severe complications and fatalities are occasionally seen. Diagnosis usually relies on clinical grounds, and serological analysis only provides a retrospective diagnosis. When available, PCR performed on a skin biopsy of the eschar allows a rapid and highly sensitive diagnosis, with determination of most species. Pre sumptive therapy with doxycycline is recommended whenever a case of rickettsiosis is suspected [4].

26.2.1.3 Other Systemic Bacterial Infections

Meningococcemia may be observed in this setting, but its incidence in travellers is estimated to be similar to that of persons living in Western countries. This disease is certainly one of the most frightening ones (see the corresponding chapters 5 and 32). Potentially life-threatening 'travel diseases' such as typhoid fever, rat-bite fever, leptospirosis, trench fever may present with febrile rash (see the corresponding chapters 13 and 39).

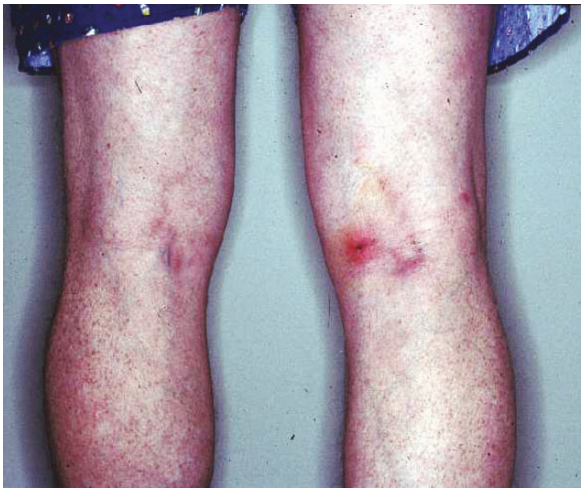

Fig. 26.1 Inoculation eschar during African tick bite fever

26.2.2 Parasitic Infections

26.2.2.1 African Trypanosomiasis

African trypanosomiasis (also known as sleeping sickness) is a parasitic infection transmitted by the bite of *tse-tse* flies (glossina) which may affect travellers participating in organized photographic or hunting safaris. West African trypanosomiasis is due to *Trypanosoma brucei gambiense*, whereas East African trypanosomiasis is due to *T. brucei rhodesiense*. This disease is divided into three stages, only the first two being associated with cutaneous manifestations.

Trypanosomal chancre (first stage) occurs at the inoculation site, with a frequency up to 70% [5]. It appears 5–10 days after the infective bite, and the lesion consists of a circumscribed inflammatory nodule, ulcer or plaque (Fig. 26.2). At this stage, diagnosis is easily made by identification of trypanosomes in the smear from the chancre.

Haemo-lymphatic dissemination of the parasite (second stage) is classically associated with fever, lymphadenopathy, and cutaneous lesions known as

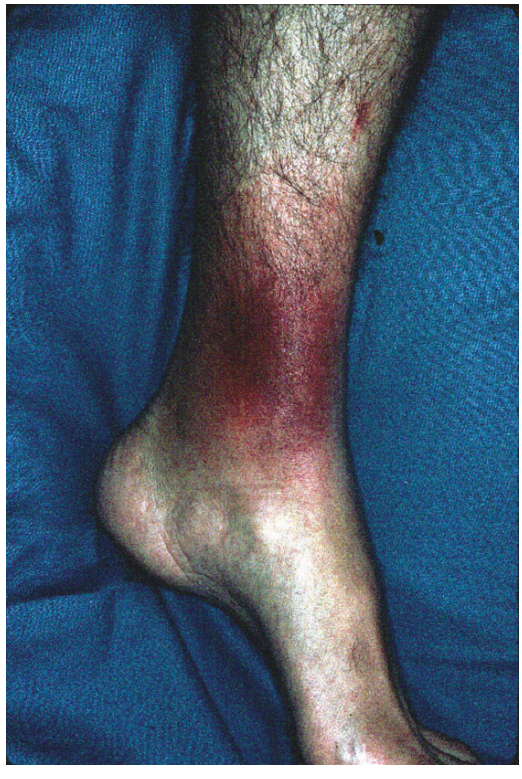

Fig. 26.2 Trypanosomal chancre during African trypanosomiasis

trypanides. Trypanides are reported in less than 10% of cases. The eruption is an evanescent macular erythematous rash with polycyclic urticarial plaques, occurring on the trunk or the proximal parts of the limbs [6]. At this stage, peripheral blood smear or lymph node fluid aspirate specimen allows isolation of the trypanososomes, and specific serological testing allows indirect diagnosis.

Involvement of the CNS is the hallmark of the third stage. It is of more rapid onset in East African trypanosomiasis. It has to be systematically ruled out by lumbar puncture and CSF examination because it has prognostic and therapeutic consequences [5].

26.2.2.2 Invasive Phase of Helminthic Diseases

Acute urticaria is a typical skin manifestation of the acute (or invasive) phase of any helminthic disease. The most common helminthic disease that gives rise to such manifestations in travellers is schistosomiasis [7]. However, a similar clinical picture has been described during other invasive phases of helminthic diseases (Table 26.1).

Diagnosis should be considered for any traveller with a history of corresponding exposure in an area of endemicity. Clinicians should be aware of the associated risk of neurological and myocardial involvement, which needs early treatment with corticosteroids to prevent irreversible damage [8].

26.2.2.3 Gnathostomiasis

Gnathostomiasis is a food-borne parasitic zoonosis infection caused by ingestion of uncooked food (mainly raw freshwater fish) infected with the nematode larval third stage of the helminth *Gnathostoma spp*. Gnathostomiasis is endemic in Southeast Asia (particularly Thailand) and Central and South America (particularly in Mexico).

Table 26.1 Infectious causes of urticaria in travellers and migrants

Hepatitis A infection
Invasive phase of schistosomiasis, ascariasis, hookworm, trichinellosis, strongyloidiasis, gnathostomiasis and fascioliasis
Rupture of cyst during hydatidosis
Toxocariasis

The most common clinical presentation of gnathostomiasis is the cutaneous form. Typical cutaneous manifestations are recurrent subcutaneous swelling, creeping eruption and oedema of the extremities [8]. These lesions provide an opportunity to diagnose gnathostomiasis before the occurrence of a life-threatening event such as severe neurologic complications later in the course of the disease.

26.2.2.4 Filariasis

Cases of filariasis such as loiasis and onchocerciasis have been reported in travellers returning from Africa [3]. These diseases are not life-threatening in themselves. However, patients with loiasis may be exposed to life-threatening adverse reactions related to diethylcarbamazine and to a lesser extent ivermectin if exposed inadvertently to the corresponding treatment.

26.2.3 Viral Infections

26.2.3.1 Dengue

Dengue is the most common cause of arboviral disease in the world, and the most frequent arboviral disease reported after travel to tropical and subtropical countries [10]. Dengue virus is transmitted by mosquitoes (*Aedes aegypti*, *A. albopictus)*. Dengue hemorrhagic fever has been reported in travellers returning from Southeast Asia, the South Pacific, the Caribbean, and Latin America.

Typical presentation of classic dengue fever includes the sudden onset of fever, headache, retro-orbital pain, fatigue, musculoskeletal symptoms (arthralgia and myalgia) and a macular or papular rash. Other dermatological signs include pruritus, flushed facies, and haemorrhagic manifestations such as petechiae and purpura. Most patients present with classic dengue fever with a benign febrile illness, but dengue hemorrhagic fever and dengue shock syndrome must be systematically ruled out.

Diagnosis of dengue virus infection is based on serological test and/or PCR. Diagnosis of dengue hemorrhagic fever is made on the association of hemorrhagic manifestations, a low platelet count ($<100{,}000\,mm^{-3}$) and evidence of plasma leakage [10].

Aspirin and non-steroidal anti-inflammatory drugs which can increase bleeding should be avoided. Dengue hemorrhagic fever and dengue shock syndrome require intensive care treatment.

26.2.3.2 Chikungunya

Chikungunya virus outbreaks have been reported in Africa and Asia, and more recently in the Indian Ocean. Transmission to humans occurs through bites of Aedes (mainly *A. aegypti* and *A. albopictus*) mosquitoes. Since 2005 (emergence in the islands of the south-western Indian Ocean and re-emergence in India), chikungunya cases have been extensively reported in travellers returning from these areas [11, 12]. Skin manifestations occur during the first week of the disease in more than 75% of the patients. They consist in a generalized erythematous macular or maculopapular exanthema located on the abdomen, thorax, back and limbs with fever [12]. Lakes of normal skin and pruritus of the skin or a burning sensation are common (Fig. 26.3). Initial facial flushing or palms and soles involvement may be observed. The erythema follows the onset of fever, lasts 3–7 days and disappears without scaling. But the main complaint of chikungunya infection is acute arthralgia related to arthritis and tenosynovitis that may persist for months [11].

Diagnosis is based on serological test and/or PCR. Paracetamol, which can aggravate hepatitis, should be prescribed cautiously. Fatalities (encephalitis, hepatitis, myocarditis) have been described.

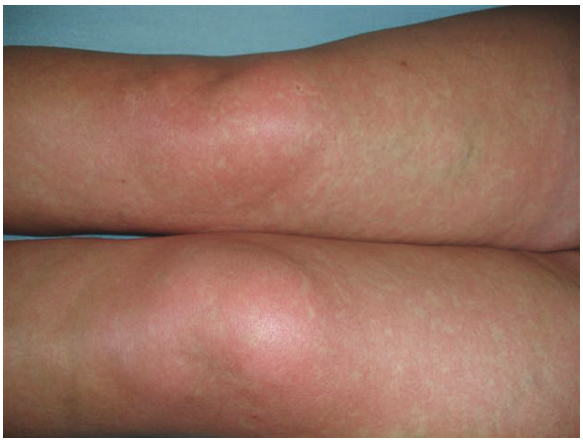

Fig. 26.3 Exanthema of Chikungunya infection

26.2.3.3 Other Arboviruses

Other arboviral infections may present with fever and rash (Table 26.2): West Nile virus in North America, Africa and southern Europe, the Ross River and Barmah Forest viruses in the South Pacific, O'nyong-nyong and Sindbis viruses in tropical Africa, and Mayaro virus in South America [13]. Fatalities (encephalitis, hemorrhagic forms) have been described.

26.2.3.4 Viral Haemorrhagic Fevers

Viral haemorrhagic fevers (VHF) are potentially life-threatening diseases, which in addition carry the risk of transmission to healthcare workers (HCW). This must be born in mind by every physician examining a traveller with fever and haemorrhagic signs coming back from an endemic country (Table 26.3).

However, there are many other causes for haemorrhagic fever (Table 26.4). Some of them have to be ruled out first, because they are more frequent and may call for an urgent, efficient and specific treatment [14]. The most common tropical viral disease with haemorrhagic signs is dengue fever which has not been associated with HCW transmission [15]. Even in cases of VHF, the risk of transmission to HCW reaches zero when

Table 26.2 Causes of fever and maculopapular rash in travellers and migrants

Dengue, other arboviral infections (West Nile, Ross River, Barmah Forest, O'nyong-nyong, Sindbis, Mayaro)
Measles, rubella, Epstein–Barr virus, HIV and cytomegalovirus primary infection
Viral hemorrhagic fever (see Table 26.3)
Rickettsial infections
Meningococcemia (purpura), typhoid fever, rat-bite fever, leptospirosis, trench fever, brucellosis, *Mycoplasma pneumoniae* infection, syphilis
African trypanosomiasis, trichinellosis, toxoplasmosis
Adverse drug reaction

Table 26.3 Causes of viral haemorrhagic fever

Arboviroses	Anthropozoonoses
Dengue	Arenaviroses: Lassa*, Junin, etc.
Yellow fever	Filoviroses: Ebola*, Marburg*
Chikungunya	Hantaviroses: hemorrhagic fever with nephritis
Crimea–Congo*	
Rift Valley	

*with potential transmission to health care workers

Table 26.4 Infectious causes of fever and haemorrhagic signs in travellers and migrants

Yellow fever
Haemorrhagic dengue fever, haemorrhagic form of other arbovirus
Fulminant viral hepatitis (HAV, HEV, HSV)
Infectious mononucleosis
Any severe sepsis (Gram-negative bacilli, Gram-positive rods)
Meningococcemia
Ictero haemorrhagic leptospirosis
Yersinia pestis
Tularemia
Enteric fever
Trench fever
Rocky Mountain spotted fever and other rickettsioses
Q fever
Severe malaria

the standard precautions are taken, as has been shown in the outbreaks of Lassa fever in Africa [16] as well as in the case of Crimea–Congo fever imported into France [17]. In addition, no human case of aerial transmission has been described during the outbreaks of Lassa fever, which is the main VHF described to date [16].

26.2.4 Mycoses

Mycoses do not usually carry life-threatening consequences, with the exception of the immunosuppressed traveller (see the corresponding chapter 14).

26.3 Emergencies Related to Environmental Diseases

26.3.1 Arthropod-Related Dermatoses

Apart from bacterial super-infection (described above) the other life-threatening predominant features carried by arthropods are severe allergic reactions and envenomations (see the corresponding chapters 32 and 33).

26.3.2 Marine Life Dermatitis

The dangers of marine environment include sea urchins and other echinoderms, shark and Moray eel bites, stone, scorpion, or lion-fish stings, sea-leech burns, and coral cuts and scratches (see the corresponding chapter). Stonefish (*Synanceja verrucosa*) and cnidarians like jellyfish, anemones, and corals may be responsible for severe immediate life-threatening envenomations.

26.4 Hypersensitivity Reaction to Drugs

Adverse drug reactions can be associated with malaria prophylaxis in travellers [18]. It must always be considered in the differential diagnosis of urticaria and exanthema in travellers (see the corresponding chapters 38 and 39).

26.5 Conclusion

Whatever the skin presentation, the alarm signs are fever and signs suggestive of systemic inflammatory response syndrome, sepsis and septic shock. In this setting, the travel history must be understood, with focus on possible epidemiologic exposures and countries visited. This provides a good orientation, and together with the clinical examination and the laboratory results allows the diagnosis to be reached. Such diseases usually call for urgent treatment before the results of diagnostic procedures such as serologies, skin biopsy and cultures are available. In this setting, PCR (when available) and direct examination of skin smears may provide the best diagnostic clues.

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Telemedicine in Skin Emergencies

27

Jim Muir, Terri M. Campbell, and H. Peter Soyer

Core Messages

- Tele-dermatology has comparable diagnostic accuracy to face-to-face consultation.
- Skin emergencies need rapid turnaround.
- Tele-dermatology can reduce patient morbidity from skin emergencies.
- Tele-dermatology is cost effective in skin emergencies.
- Tele-dermatology is an under-utilised service, particularly for skin emergencies.
- The technical requirements for tele-dermatology may be limited to a digital camera and effective telecommunication.
- Most dermatological investigation and treatment can be carried out easily by medical practitioners and medical staff in A and E units.

27.1 Introduction

Telemedicine refers to the diagnosis and treatment of patients via long-distance transmission of medical information. In its earliest applications, telemedicine utilized radio and telephone, while refinement of communication technologies in addition to the advent of the internet has given strength to its modern-day diagnostic capabilities [1–3]. The visual nature of dermatology lends itself perfectly to digital lesion imaging and therefore remote consultation. Indeed, various studies have demonstrated the value of tele-dermatology both as a diagnostic tool [4–7] and as a support network through second opinion [7, 8]. Recently, we have also seen the establishment of readily accessible online consultation services such as the *telederm.org and Tele-Derm National* projects which aim to provide a tele-consultation platform for health-care providers to discuss challenging or unusual cases for diagnosis [9]. These sites also provide educational services. In the light of technological advances it would be expected that other similar forums become increasingly popular in the future; however, despite its practical suitability there has been a rather limited uptake of tele-dermatology in standard health services [10]. One area specifically in which tele-dermatology would have a considerable impact is that of skin emergencies, which is discussed in detail below.

27.2 Skin Emergencies

Specialist dermatology advice has been available via telemedicine for many years [4, 11] via store-and-forward or real-time conferencing. The degree of accuracy has been demonstrated to be comparable with that of face-to-face consultation [7, 12–16], and is combined with a high degree of patient and physician acceptability around the world [16–18].

The vast majority of dermatological consultations are for non-urgent conditions, where a prolonged turnaround time between case submission and receipt of diagnostic and management advice would have no major detrimental effect on patient outcome. This, however, is not the case when dealing with skin emergencies. Early diagnosis and treatment is crucial to optimising outcomes for skin emergencies [19] such as toxic epidermal necrolysis, staphylococcal scalded

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skin syndrome, exfoliative dermatitis, pustular psoriasis, the various autoimmune blistering disorders, vasculitis etc. Skin emergencies are rare and so are seen infrequently, even in specialist dermatology clinics. Most doctors are unlikely to have the experience or training to diagnose and manage these conditions without assistance from a dermatologist. Unfortunately, there is a worldwide shortage of dermatologists; even in developed countries such as Australia and the USA, many people live hundreds of miles from a dermatology service.

The crucial step in an effective skin emergency telemedicine service [SETS] is the provision of accurate diagnosis and management advice within a short period of time, ideally within 30 min of submitting a case. The response would need to provide the referring doctor with a differential diagnosis in addition to the investigation and management plan that can be carried out by a practitioner without specialist dermatology training.

Even in urban areas, but especially in rural and remote regions, a timely face-to-face consultation with a specialist dermatologist for a patient with a skin emergency can be very difficult to obtain. A properly established SETS should be able to overcome the twin barriers of isolation and undersupply of dermatologists when dealing with skin emergencies.

27.3 How it Could be Done

At the moment, a rapid diagnostic turnaround is not routinely available. Effective SETS would require the following characteristics;

- Around the clock availability.
- A response time of less than 30 minutes from case submission
- User friendly. Submission of cases should be able to be done with basic photographic and computer skills.
- Provision of simple proformas for history and examination details.
- Provision of tutorials on biopsy techniques, treatments etc.
- Availability of telephone, e-mail and video-conferencing contact with the advising dermatologist.
- Integration with other telemedicine services such as paediatrics, general medicine etc.

Provided the service is effectively established according to the above model, a typical consultation for a patient needing SETS would be as follows;

1. Patient presents with a skin emergency.
2. The treating doctor takes a history and performs an examination.
3. Representative digital images of the patient are taken.
4. The history and examination proformas and digital images are submitted via e-mail to the SETS.
5. The dermatologist staffing the SETS is notified by text message or page that a case has been submitted.
6. The dermatologist immediately views the submitted material, formulates a diagnosis and management plan and communicates this to the referring doctor. This may be done via e-mail, telephone or video-conference.
7. The treating doctor carries out the management plan as indicated by the specialist.

This model relies on the referring doctor having certain skills. These include basic photographic and computer skills, the ability to perform a directed skin history-taking, examination and possibly biopsy. These requirements necessitate the need for content-specific online tutorials to be made available. The proforma (Table 27.1) is also significant for the referring doctor, so as to ensure the crucial history-taking and examination is performed. For instance, a thorough drug history and examination of mucosa is needed for management of TEN, in which case the referring practitioner could be guided by the proforma.

27.4 Would such a Service be Practical?

When one considers the long list of dermatological emergencies, it becomes apparent that they are potentially as diagnosable with a good digital image and apposite history as they would be with a face-to-face consultation. Furthermore, the required investigations and interventions are well within the skills of any trained doctor. Use of such a service would reduce delayed diagnosis and treatment, and would significantly improve patient outcomes in areas where no specialist dermatology consultation is available at all.

The technical requirements of a tele-dermatology service may be limited to a digital camera and an effective telecommunication service. As such, the equipment needed is already available in most "western-style" hospitals, which will help minimise the associated costs. Cost effectiveness is likely when one considers the savings that would be generated from possible earlier diagnosis and treatment, lack of travel costs and improved patient outcomes.

On a personal level, the doctors utilising such a service would be intimately involved in the diagnosis and management of their patient, and so would obtain enormous educational value.

27.5 Limitations of SETS

The benefits of using SETS as an adjunct to standard patient care have been outlined above; however, it is necessary to also address the limitations of such a facility. The level of diagnostic accuracy provided by

Table 27.1 Patient history

Patient ID number: …….. DOB: …… Sex: M/F
History of presenting complaint
Duration: ……
Site of onset: ……
Progression: ……
Morphology: ……
Areas of involvement (e.g. mucosa, scalp, nails, palms and soles) ……
……
……
Associated symptoms (e.g. itch, fever, arthralgia, malaise)
……
……
Results of any investigations (e.g. blood/urine tests, biopsies, X-rays)
……
……
Treatment to date
……
……
General medical history
Medical (including personal history of skin disease and significant family history)
……
……
……
Surgical: ……
……
……
Drug: including prescribed, non-prescribed, OTC (over the counter drug), natural, intermittent and regular, also alcohol/ tobacco/ illicit drugs, and chronology
……
……
……
Occupation/pastimes ……
……
Exposure to animals ……
Overseas travel
……
Please attach images showing the extent of the eruption, i.e., we need to know where it isn't as well as where it is. Good quality close-ups are essential. If any pathology present, please send images. They need to be clearly labelled as to site and patient. If possible, send images that do not allow patient identification.

the tele-dermatologists is incumbent on the transmission of quality images, which may be difficult to obtain in certain regions of the body. In addition, the electronic examination of the images may impair the clarity of fine detail such as micro-vesiculation and pustulation, which is why specialist training in such analysis would be advantageous. Despite such issues, it remains clear that SETS has the potential to play a significant role in the future of emergency skin disease diagnosis and treatment.

To demonstrate the benefits of SETS, three cases are outlined below. These are all fictional, and designed to give realistic illustrations of how properly functioning SETS could be integrated into medical practice, especially in the accident and emergency departments/rural and remote areas without ready access to dermatologists.

Case 1

A 14-month-old child presents to a remote area practitioner with a 24-h history of a progressive, widespread erythema and fragile blisters (Fig. 27.1). He is febrile. He had been placed on carbamazepine for epilepsy 3 months earlier. The treating doctor is concerned that the child has Stevens–Johnson syndrome (SJS).

Images and history are submitted to the SETS, and the dermatologist is notified of the consult by a text to her mobile phone. After viewing the history and images, she contacts the treating doctor via phone. Questioning establishes that the child has no evidence of oral/genital mucosal inflammation and that the skin seems to be very tender, as the child screams when touched. His left eye shows some minor purulent discharge, but the right is clear. His mother states that the left eye has been runny for a week or so.

A provisional diagnosis of staphylococcal scalded skin syndrome [SSSS] is made. The child is treated with antibiotics, analgesia, fluid support etc. Input from a paediatrician is obtained via telephone hookup. Swabs of the eye confirm the presence of staphylococcus. At the dermatologist's suggestion, blister roof is snipped and submitted for histology. This confirms SSSS rather then TEN/SJS. The carbamazepine is not ceased.

This is a good example of the utility of SETS. The local doctor quite rightly considered the possibility of drug eruption to explain the sudden onset of a widespread blistering eruption in a young child. However, with expert guidance by a SETS dermatologist, this diagnosis could be effectively excluded by careful, directed history-taking and examination. The child was thus saved both from misdiagnosis and ineffective treatment, without the need to travel and within an hour of submission of the request for help.

Case 2

A woman in her sixties presents with a rash to a junior doctor relieving in a remote rural area (Fig. 27.2). The rash has been present for 3 days and is asymptomatic.

Images and history are submitted to SETS, and the dermatologist contacts the referring doctor. A provisional diagnosis of leucocytoclastic vasculitis is made. Further history reveals that the patient had penicillin prescribed recently for a sore throat. These are the only likely triggers identified. On advice from the derma-

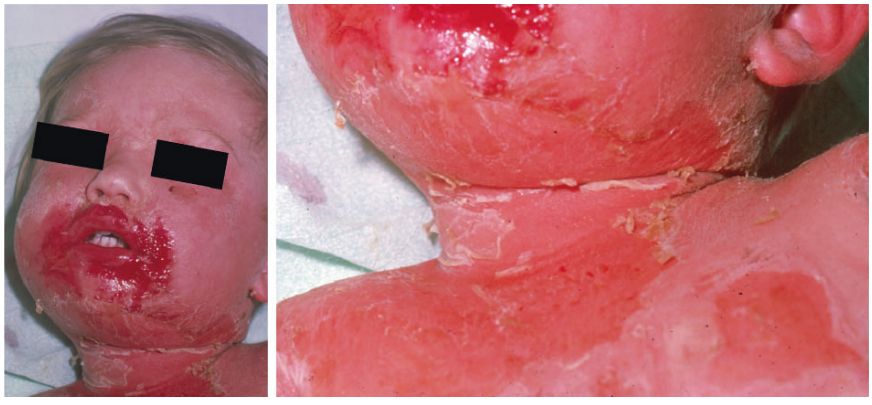

Fig. 27.1 Images of erythema and fragile blisters submitted and used for staphylococcal scalded skin syndrome diagnosis

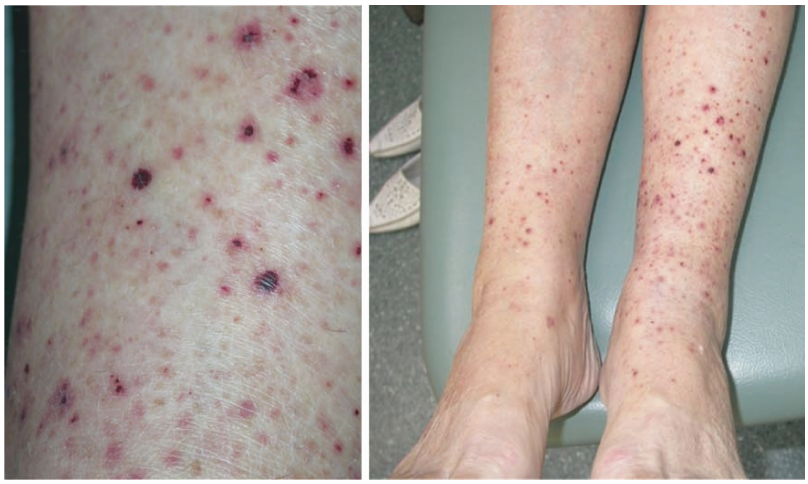

Fig. 27.2 Images of the rash submitted and used for leucocytoclastic vasculitis diagnosis

tologist the patient's urine is checked, and found to be free of blood and protein. Blood pressure and renal function tests are within normal limits. Systems review reveals no symptoms referable to any system.

Skin biopsy is performed, and a variety of investigations are ordered to try to determine a cause. As the patient is not unwell, there is no evidence of renal involvement and the rash is neither progressive nor ulcerating, it is felt she can be managed locally and with no intervention other then support stockings.

Histology is reported a few days later as "leucocytoclastic vasculitis". Streptococcal serology is consistent with a recent infection. At review 1 week later, the rash has largely resolved. It is felt that the likely trigger is the recent streptococcal infection, but that the penicillin cannot be excluded and thus should be avoided.

This case illustrates how SETS can be used to support isolated practitioners, especially important with inexperienced doctors practicing far from specialist support. This patient was managed without the need to travel, and achieved the same outcome as with a face-to-face consultation with a dermatologist.

Case 3

A man presents to an urban accident and emergency unit with an acute, widespread blistering eruption over his trunk and limbs. His oral, ocular and genital mucosa are severely involved with inflammation and widespread erosion (Fig. 27.3). There is no dermatologist on site. Images and clinical details are forwarded to SETS. The dermatologist makes the diagnosis of toxic epidermal necrolysis [TEN] and calls the treating doctors within 15 min of the case being submitted. Guided questioning reveals that the patient was commenced on allopurinol for hyper-uricaemia 3 weeks earlier. This agent is identified as the likely trigger and ceased. Transfer to a burns unit is organised.

The incidence of TEN is between 0.4 and 1.2 cases per million per year [20]; thus, even very experienced accident and emergency staff are unlikely to have encountered a case. This can result in misdiagnosis and inappropriate treatment. Immediate review of the clinical images and history by an experienced dermatologist allows accurate diagnosis and appropriate management with no needless delay. TEN carries a mortality rate of between 30% and 50% [21]. The crucial steps in managing TEN are identification and removal of the trigger [22] and supportive care in a burns unit whilst the epithelium regenerates [23]. Discussion of the role of specific medical interventions in TEN is beyond the scope of this chapter.

27.6 Conclusion

In this age of technological advance, the possible applications of telemedicine are continually expanding. Within dermatology, provision of a skin emergency telemedicine service (SETS) will enable accurate and rapid diagnostic and treatment advice for both true and pseudo-dermatological emergencies. The implementation of

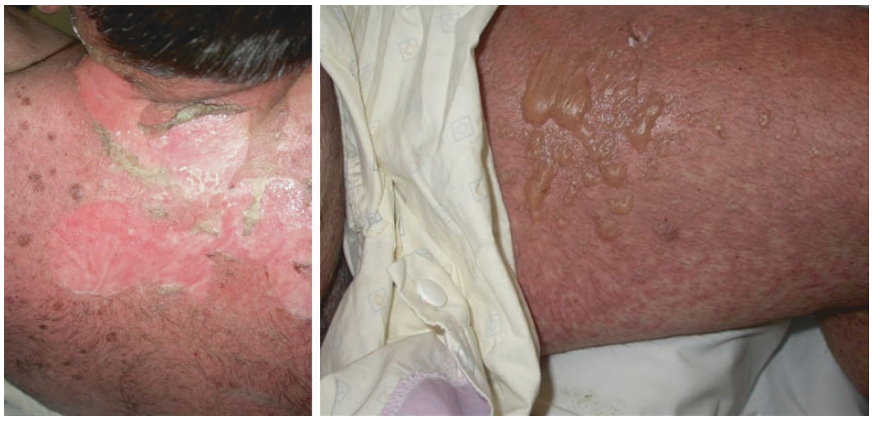

Fig. 27.3 Images of the blistering eruption submitted and used for toxic epidermal necrolysis diagnosis

this service would generate improved patient outcomes, but in order to be effective the service must be utilized by the medical community as a whole.

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Skin Diseases in Bioterrorism

28

John A. Ebner and Kenneth J. Tomecki

Core Messages

- These catastrophic illnesses often have distinct cutaneous findings when encountered in natural conditions, yet when disseminated as a bio-weapon, cutaneous findings may be infrequent and unhelpful.
- Anthrax illness is caused by the spores, not by the living bacterium.
- Weaponized anthrax will likely manifest as a pulmonary disease with few cutaneous findings.
- Haemorrhagic mediastinitis is the hallmark of pulmonary anthrax.
- Post-exposure prophylaxis and treatment for all forms of anthrax must continue for a full 60 days.
- Primary dissemination and spread of smallpox occurs via respiratory droplets, yet fomites like bedding or infected clothing may also spread the virus.
- Smallpox exanthem begins on the face and extremities, and progresses inward to involve the trunk.
- All suspected and confirmed cases of smallpox require strict negative-pressure isolation, respiratory precautions, and universal precautions.
- *Francisella tularensis* is a highly infectious organism, able to cause disease in humans from infection by as few as ten colony-forming units.
- Isolation is not recommended for tularemia patients, as there is no evidence that person-to-person transmission exists.
- Primary pulmonary plague has a mortality rate approaching 100% if not treated in the first 24 h of symptoms.
- Respiratory precautions are indicated for all cases of suspected pulmonar plague until excluded, or after 48 h of therapy in confirmed cases.
- All viral agents cause clinical illness associated with high fever, myalgia, prostration, petechiae, haemorrhage and shock.
- All viral haemorrhagic fever (VHF) patients should be initiated on ribavirin pending viral identification.
- VHF patients are highly contagious, and require stringent universal precautions, barrier protection, and negative pressure isolation.

Throughout human history, conflict has continually bred new ways to reveal man's inhumanity to man. During the mid-fourteenth century, the Tartar forces of Kipchak khan Janibeg laid siege to the port city of Kaffa on the Crimean peninsula of the Black Sea. During the long siege of this city, the Tartar forces were overcome by the plague. In a last-ditch effort to capture the city, Janibeg launched the plague-infested bodies of his dead soldiers into Kaffa [1]. In 1754, during the French–Indian War, British soldiers apparently distributed smallpox-laden blankets to the Native Americans. The Germans developed anthrax, glanders, cholera, and wheat fungus for use against the Allied forces during World War I. Then, in the 1930s, the Japanese, under the direction of General Shiro Ishii, started a biological warfare program in Manchuria, China. They exposed Chinese prisoners to plague, anthrax, and syphilis, causing the deaths of more than 10,000 people [1].

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During World War II, the United States began its own biological warfare program to act in retaliation against a possible Nazi-initiated biological attack. By 1969, the US military had developed a massive biological arsenal, including the means to inflict anthrax, botulism, tularemia, brucellosis, and Q fever among others. In addition, the United States possessed fungal pathogens that could cause devastating crop failure and catastrophic famine. Given the recent events of September 11, 2001 and the subsequent dissemination of anthrax spores via the United States Postal Service, there is a tremendous amount of international public health concern regarding the use of biological agents for terrorism. The most catastrophic and likely agents for use have prominent cutaneous manifestations when encountered under natural conditions. However, when disseminated as an aerosol, the manifestations are likely to appear quite different. Dermatologists are likely to be on the front lines in recognition and diagnosis of these diseases, and should therefore familiarize themselves with the presentation and treatment of these entities as well as how to limit spread of the disease, keeping in mind that several of these are directly contagious to caregivers [2].

28.1 Anthrax

28.1.1 Bacteriology and Pathogenesis

The spores of anthrax are fastidious, and naturally remain viable for decades in the soil. These endospores resist gamma radiation, heat, cold, drying and some disinfectants [3]. The actual route of transmission is via the spores which germinate into vegetative bacilli upon exposure to the nutrient-rich environment of tissue or blood in animals or humans [4,3]. The anthrax bacilli are large, Gram-positive, aerobic bacteria whose virulence factors, encoded in two separate plasmids, include a polyglutamyl capsule to resist phagocytosis and separate exotoxins (Edema toxin and Lethal toxin) [5]. Both of these toxins possess protective antigen (PA), which allows the bacterium to bind and enter host cells [5]. The edema factor causes severe edema at the inoculation site by inhibition of neutrophil function and monocyte production of TNF and IL-6 [6]. The lethal factor inhibits intracellular signaling and stimulates TNFα and IL-1β from macrophages, resulting in death [4]. Infection commences after inoculation of the endospore into abraded skin (cutaneous anthrax), through GI mucosa (gastrointestinal anthrax) or inhalation into the lungs (inhalation anthrax). Spores are phagocytized by macrophages and routed to the regional lymph node [7]. While inside the macrophage, germination of the spore into the vegetative form occurs. Germination and multiplication within macrophages may be delayed by as much as 60 days in the mediastinal lymph nodes [4]. For this reason, all antibiotic prophylaxis for suspected inhalation exposure should be given for 60 days [8]. A septicemia eventually results as the bacilli are released by macrophages, but the polyglutamyl capsule resists phagocytosis, resulting in an absence of immune response [4]. The World Health Organization estimates that the release of 50 kg of aerosolized anthrax released upwind of a population of a half million people would likely kill 95,000 and incapacitate another 125,000 [9]. The median lethal dose for inhalation anthrax, a value extrapolated from primate data, is estimated at 2,500–55,000 spores [10].

28.1.2 Epidemiology

Anthrax is believed by many to be responsible for the fifth and sixth plagues of animals and humans described in the Book of Exodus in the Bible [11]. The bacteria is found throughout the world, but is more common in the rural arid to semi-arid regions of Africa, Asia and the Middle East, where herding of cattle, sheep and goats and processing animal skins is common [7,12]. In natural conditions, humans acquire infection via contact with infected animals or contaminated animal products like wool, hair, animal hides or ivory tusks. This route of exposure and infection usually results in the cutaneous form of anthrax. Infrequently, gastrointestinal disease may occur after consumption of poorly cooked meats. Inhalation anthrax (Woolsorter's disease) has been found associated with conditions where enclosed factory spaces allow inhalation of aerosolized spores [4]. The accidental release of "weaponized anthrax" from a Soviet bio-weapons lab in 1979, the production and deployment of anthrax-laden missiles by Iraq and the dissemination of anthrax via the United States Postal Service have all spotlighted anthrax as a viable candidate for use as a bio-weapon [6,13].

28.1.3 Clinical Features

Inhalation anthrax: the hallmark of inhalation disease is biphasic, in that the initial phase occurs after a 1- to 6-day incubation period and features vague symptoms, including mild fever, malaise, myalgia, a non-productive cough and some chest or abdominal pain [4]. The second phase begins roughly 2 to 3 days later with the abrupt onset of dyspnea, fever, cyanosis and diaphoresis. Stridor can result from extrinsic compression of the trachea by mediastinal lymphadenopathy. Haemorrhagic mediastinitis occurs with regularity, and is the hallmark of pulmonary anthrax. Patients can become obtunded with nuchal rigidity, signaling a progression to anthrax meningitis. This second stage is rapidly progressive, with shock and death occurring within 24–36 h [14]. Mortality rates for inhalation anthrax approach 100%.

Cutaneous anthrax: 95% of the naturally occurring anthrax is of the cutaneous type, and 80–90% of these cases resolve in a few weeks without complication. However, some 10–20% of cases may progress and lead to death. Incubation for cutaneous anthrax is commonly 2–7 days. The progression of cutaneous anthrax begins as a non-tender pruritic macule/papule, which converts to a vesicle or bulla in 24–48 h, teeming with anthrax bacilli. A yellowish, non-pitting, gelatinous edema surrounds the lesion, which progresses to form an ulcer with the characteristic central black eschar [4] (Fig. 28.1). Anthrax lesions can be solitary or multiple, but are commonly localized to one or a few body regions. Progression to ulceroglandular disease can occur, heralded by tender regional lymphadenopathy, fatigue, chills and fever in addition to the skin findings [15].

Gastrointestinal anthrax results in nausea, vomiting, abdominal pain and severe bloody diarrhea roughly 2–5 days after ingestion of contaminated, undercooked meats containing the spores. The findings often mimic an acute abdomen and haemorrhagic mesenteric lymphadenitis. Mortality is greater than 50% for gastrointestinal anthrax [4].

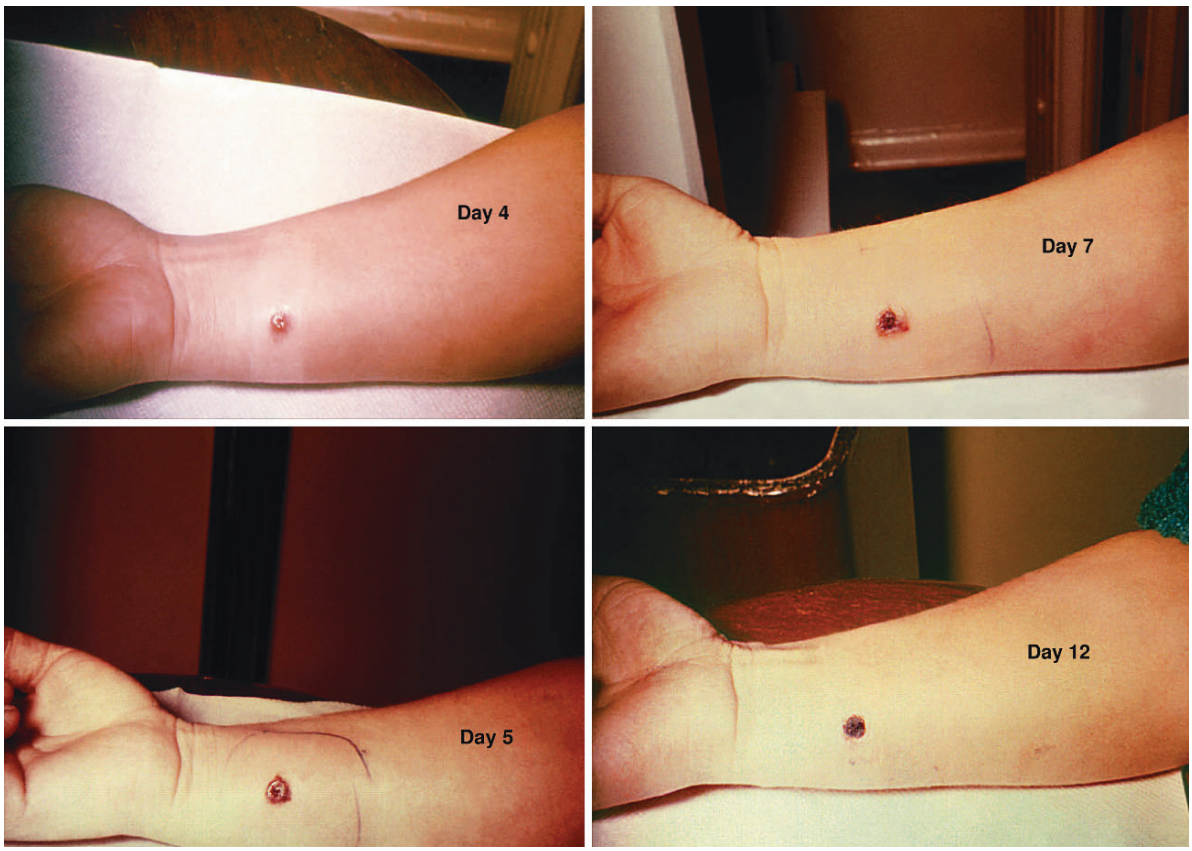

Fig. 28.1 Cutaneous anthrax, Courtesy of Public Health Image Library (PHIL), CDC

Anthrax meningitis occurs after anthrax bacteraemia, and mostly after inhalation anthrax has been established. It is far less commonly seen in association with the cutaneous and gastrointestinal forms [4]. Mortality is near 100%, but rapid use of empiric antibiotics has been showed to increase survival chances [6].

When anthrax is used as a bio-weapon, the spores will more likely result in mediastinal and systemic infections after inhalation of the spores [7]. Spores, measuring < 5 μm in diameter are deposited in the alveoli, and germinate inside alveolar macrophages which are then transported to the nodes of the mediastinum. The use of nasal swabs to confirm anthrax exposure is a valuable epidemiologic tool for assessing the area of potential exposure in an outbreak. However, swabs should not be used to rule out anthrax disease in any patient, as swabs obtained more than 48 h after exposure are not useful and often falsely negative [7]. Inhalation anthrax may show subtle radiographic changes in early disease, making the separation from more banal viral or bacterial infections difficult. However, as disease progresses, pleural effusions and mediastinal widening are commonly seen on chest radiographs and CT scans [7].

28.1.4 Diagnosis

28.1.4.1 Eschar and Ulceration

The differential diagnosis of a cutaneous eschar or ulceration can be wide and varied. Following the progression of the painless, pruritic papule of early anthrax, the ensuing anthrax eschar or ulceration may resemble several entities. A staphylococcal furuncle, ecthyma gangrenosum, orf/milker's nodule, tularemia, cutaneous leishmaniasis, heparin or coumadin skin necrosis, and staphylococcal or streptococcal ecthyma can all resemble, closely, the appearance of cutaneous anthrax [15]. When entertaining a diagnosis of anthrax, one should contact the local Department of Health for additional instructions before doing any diagnostic testing. In the United States, this information is available from the Centers for Disease Control and Prevention at www.cdc.phppo. All laboratories should receive preemptive notification to expect samples suspected of harboring the anthrax bacilli or spores [15]. Laboratory investigations of cutaneous anthrax should include a swab for Gram stain and culture of the vesicle fluid. Additionally, a punch biopsy specimen for formalin-fixed processing should be taken, along with a second punch biopsy for further bacterial and fungal staining and culture. This tissue biopsy should be placed in sterile, non-bacteriostatic saline or a standard bacterial culturette [15]. It is important to note that cutaneous ulcers and eschars become sterile within 24–48 h after instituting appropriate antimicrobial therapy, so culturing should be performed prior to initiating therapy. In addition to tissue sampling, drawing blood for anthrax serologies and PCR analysis should be performed. It is critical to contact the appropriate local Health Department for instructions on how to handle these specimens of tissue and blood [15].

28.1.5 Post-exposure Prophylaxis

Maintenance of universal precautions is important when evaluating patients with suspected anthrax. However, a mask is not required given that transmission of pulmonary anthrax requires the infection with anthrax spores, not the active bacteria [15]. In addition, there is an anthrax vaccine (Anthrax Vaccine Adsorbed [AVA]; Bioport Corp, Lansing, MI, USA) which consists of a non-infectious sterile culture filtrate of an attenuated form of the bacillus. The vaccine is given at 0, 2 and 4 weeks, then again at 6, 12, and 18 months. Protection against an aerosolized anthrax challenge has been shown in monkeys. Annual boosters are necessary to retain immunity [10]. To date, the vaccine is not recommended for the public, due to limited availability. However, when widely available, its proposed use would be for post-exposure prophylaxis in combination with antibiotic therapy, a combination shown to be optimal for post-exposure prophylaxis in primates [8,15].

28.1.6 Antimicrobial Therapy

The treatment of bioterrorist-acquired anthrax may require different antimicrobial treatment than naturally acquired disease. A strain of *B. anthracis* has been produced outside to the United States that is resistant to multiple agents (penicillin, doxycycline, macrolides and rifampin). For this reason, ciprofloxacin is the leading drug of choice for initial therapy [6] (Table 28.1).

Table 28.1 Treatment of anthrax, Postexposure prophylaxis or cutaneous anthrax

Therapy	Adults (including those pregnant and immunocompromised)	Children
Empiric	Ciprofloxacin, 500 mg orally every 12 h	Ciprofloxacin, 10-15 mg kg^{-1} every 12 h
	or	or
	Doxycycline, 100 mg orally every 12 h	Doxycycline, 100 mg orally every 12 h if ≥8-year-old and ≥45 kg; 2.2 mg kg^{-1} orally every 12 h if <8-year-old and/or <45 kg
Optimized (if susceptible)	Amoxicillin, 500 mg orally every 8 h	Amoxicillin, 500 mg orally every 8 h if ≥20 kg; 40 mg kg^{-1} orally every 8 h if <20 kg
	or	
	Doxycycline, 100 mg orally every 12 h	

(Adapted from Inglesby et al. 1999 & CDC Recommendations) Fluoroquinolones are not recommended for use in pregnancy or for children, due to adverse effects on cartilage development. However, due to the high likelihood of antibiotic-resistant engineered anthrax strains, their use in this population is recommended at least for initial therapy. In addition, tetracyclines (including doxycycline) are generally not recommended for use in pregnant women due to hepatotoxicity and adverse effects on developing fetal teeth and bones. However, the initial use of doxycycline is recommended in these populations, due to the potential life-threatening nature of this illness. Overall, the use of tetracyclines and fluoroquinolones in younger populations has adverse effects, and these risks must be balanced against the potential for life-threatening anthrax infection. Total duration of treatment for postexposure prophylaxis (empiric plus optimized therapy) must be 60 days.

Clinical inhalation anthrax or severe cutaneous anthrax or cutaneous anthrax with systemic symptoms

Therapy	Adults (including those pregnant and immunocompromised)	Children
Empiric	Ciprofloxacin, 400 mg IV every 12 h (ofloxacin, 400 mg IV every 12 h or levofloxacin, 500 mg IV every 24 h are acceptable alternatives)	Ciprofloxacin, 20–30 mg kg^{-1} IV per day, divided into two doses
	or	or
	Doxycycline, 100 mg IV every 12 h	Doxcycycline, 100 mg IV every 12 h if ≥ 8-year-old and ≥45 kg: 2.2 mg kg^{-1} IV every 12 h if <8-year-old and/or <45 kg
	and	and
	(one or two of the following antibiotics: clindamycin, penicillin, chloramphenicol, imipenem-cilastatin, clarithromycin, rifampin or vancomycin)	(one or two of the following antibiotics: clindamycin, penicillin, chloramphenicol, imipenem-cilastatin, clarithromycin, rifampin or vancomycin)
Optimized (if susceptible)	Penicillin G, 4 million U IV every 4 h	Ciprofloxacin, 20–30 mg kg^{-1} IV per day, divided into two doses
	or	or
	Doxycycline, 100 mg IV every 12 h	Penicillin G, 50,000 U kg^{-1} IV every 6 h if <12–year-old; 4 million U IV every 4 h if ≥12-year-old

(Adapted from Inglesby et al. 1999 & CDC Recommendations) As clinical status improves, conversion to oral therapy is recommended. Doxycycline may be used in children when neither ciprofloxacin nor penicillin are possible due to susceptibility testing or hypersensitivity problems. In children weighing ≥45 kg, the adult dose is recommended. In those weighing <45 kg, the dose is 2.2 mg kg^{-1} IV every 12 h. Total duration of treatment (empiric plus optimized therapy) must be 60 days.

However, empiric antibiotic coverage should be broad enough to cover common entities like *Streptococcus pneumoniae* as well as the anthrax. When anthrax infection is confirmed, intravenous ciprofloxacin with additional antibiotics is the standard of care. Given the propensity of anthrax to cause meningitis, the addition of intravenous penicillin to empiric antibiotic therapy should be considered. In addition, given that the symptoms of anthrax are from the toxin, some experts suggest using antibiotics that inhibit bacterial protein synthesis, such as clindamycin [7]. Although ciprofloxacin is the preferred first-line therapy in adults and children, there

are other choices that may be more suitable given a specific population (Table 28.1).

28.1.7 Hospital Infection Control and Decontamination

There is no evidence to suggest that person-to-person transmission of anthrax, even severe inhalation anthrax, occurs. Therefore, patients with confirmed anthrax infection may be hospitalized in a standard room with standard universal precautions. Contact precautions are required when handling patients with draining cutaneous lesions or their dressings. The Country's National Public Health Agency must be contacted urgently if any isolate of B. anthracis is suspected. The U.S. State Department's communicable disease epidemiological service should contact as well if the outbreak occurs within the United States. Contaminated areas must be treated with sporicidal cleansers approved for hospital use. Standard commercially available bleach in a 1:10 dilution is most appropriate, but may be corrosive to some surfaces. More information is available through the CDC guidelines, www.cdc.phppo.

28.2 Smallpox (Variola Major)

28.2.1 Virology and Pathogenesis

The smallpox or variola virus is a member of the family *Poxviridae*, within the genus orthopoxvirus which includes vaccinia virus, monkeypox virus and several other poxviruses [16]. The poxviruses are double-stranded DNA viruses that replicate within the cell's cytoplasm. They resemble bricks on electron micrographs, with a size of 300 by 200 by 240 nm [17]. The virus penetrates and seeds the respiratory mucosa, passing rapidly to the regional lymph nodes. A brief flu-like viremia ensues, followed by 4–14 days of latency during which time the virus is replicating within the reticuloendothelial system. At this point, the prodromal phase commences where the virus infects the oropharynx as well as the conjunctiva and skin, leading to the characteristic cutaneous findings [17]. At the same time, several visceral organs, including the spleen, liver, bone marrow, kidneys and lymph nodes, will also harbor large quantities of virus [17].

28.2.2 Epidemiology

As smallpox was eradicated worldwide in the late1970s, and vaccination practices ceased in the 1980s, most clinicians have never seen this disease in its active form. Without routine vaccination since the early 1980s, there are many susceptible individuals in the populace. Nearly all persons under 30 years old in the United States are not vaccinated, and those previously vaccinated, while exhibiting lesser symptoms, may still be able to transmit it to others [17]. With no natural reservoirs for the virus in existence, the virus only exists in the laboratory. The World Health Organization made great strides in reducing the number of laboratories keeping stock of the virus from 76 in 1978 to just 2 in 1984; the CDC in Atlanta and the Research Institute of Viral Preparations in Moscow. Today, there is great concern that the variola virus has found its way out of these laboratories and may make its way into the hands of terrorists [18]. Primary dissemination and spread of smallpox occurs via respiratory droplets, yet fomites like bedding or infected clothing may also spread the virus [19]. Patients exhibit their highest infectivity rate from the time the enanthem ensues through to the end of the first week of the rash.

28.2.3 Clinical Features

After infection and a latent period of incubation (roughly 1–2 weeks), the patient experiences 2–3 days of abrupt onset prodromal symptoms (severe headache, backache, and fever). As this subsides over 2–3 days, the enanthem involving the oropharyngeal mucous membranes erupts and precedes the cutaneous findings by about 1 day. Skin findings begin as small, erythematous macules, then papules of 2–3 mm, and then similarly sized vesicles over the next 3–4 days. Vesicles progress to pustules over the following 2–3 days, so that by roughly 1 week after onset of cutaneous findings, the characteristic vesiculopustules with umbilication and crusting of smallpox are clearly evident [17] (Fig. 28.2). The eruption begins on the face and extremities, and moves inward to cover the whole body. In general, smallpox is defined by its centrifugal spread and the synchronous morphology of the cutaneous findings.

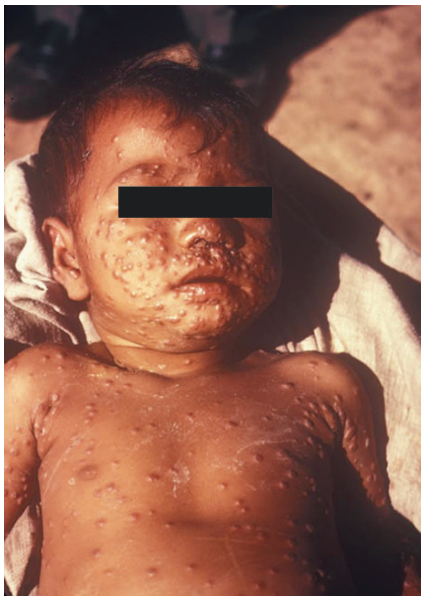

Fig. 28.2 Cutaneous smallpox, Courtesy of Public Health Image Library (PHIL), CDC/Don Eddins

28.2.4 Diagnosis

Several eruptive illnesses can be mistaken for smallpox. Florid varicella (chickenpox) is most frequently misdiagnosed, especially in adults with extensive cutaneous findings. The key differentiating features of varicella are a prodromal phase of 1–2 days, fever with the onset of rash, an eruption primarily over the trunk and non-synchronous vesiculopustules that crust within 24 h [17]. A morphologically very similar eruption comes from infection with human monkeypox. However, this disease shows significant lymphadenopathy and is difficult to spread person-to-person [17]. Other eruptions less commonly confused with smallpox include medication hypersensitivity reactions, the widespread morbilliform measles eruption, and widespread molluscum contagiosum in patients with AIDS [17]. The Centers for Disease Control and Prevention has an algorithm available for aiding in the diagnosis of smallpox, which is available in an interactive format online at http://www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm/index.asp. Confirmation of smallpox can be accomplished from a variety of testing. Skin lesion scrapings should be sent to the CDC (or a designated laboratory) after public health officials have been notified [20]. When the diagnosis is unclear, certain laboratory investigations may aid in clarifying the diagnosis. Orthropox viral cultures, PCR or electron microscopy as well as variola serologies are best suited for testing at defined governmental reference laboratories [21]. Further detailed information on specimen collection and diagnostic testing is available through the CDC website on Bioterrorism at http://www.bt.cdc.gov/bioterrorism.

28.2.5 Post-exposure Prophylaxis

After the diagnosis is established, measures must be taken to avoid spread of the disease. This should include isolation and treatment of the disease, but also notification of the appropriated governmental agencies. Isolation measures should include a negative-pressure isolation room with strict respiratory and contact isolation with universal precautions [17, 22]. Identification and vaccination of contacts within 3 days of exposure is critical to control spread. Substantial protection from smallpox infection is offered with this method; a primary rationale for not instituting widespread vaccination programs for healthcare personnel prior to an outbreak occurring [17]. Vaccination of the patient, if performed early in the incubation phase, can markedly diminish or prevent the clinical manifestations of smallpox [17]. At this time, due to a low risk of deliberate release of the variola virus, pre-exposure vaccination is not recommended by the CDC [23].

28.2.6 Antimicrobial Therapy

The general management strategy for smallpox includes supportive care, management of skin and oral lesions, treatment of any secondary bacterial infections, and possible antiviral medications, including cidofovir and or variola immunoglobulin. Cidofovir, approved for the treatment of cytomegalovirus, given at or just after exposure, has shown promise for the prevention of vaccinia [24]. Vaccination for smallpox can cause a wide variety of complications in those vaccinated as well as their close family contacts. Self-limited side-effects include headaches, fatigue, muscle ache, fever, chills, local skin reactions, non-specific rashes, multiforme erythema, lymphadenopathy, and pain at the inoculation site. More serious side effects include eczema vaccinatum,

post-vaccinial encephalopathy, and encephalomyelitis, peri-orbital cellulitis, conjunctival ulcers, iritis, fetal vaccinia and myocarditis [25]. Certain populations should not be vaccinated, including those with atopic dermatitis, pemphigus, patients with defective cell mediated immunity, HIV/AIDS, pregnant women, or persons on systemic immunosuppression [17].

28.2.7 Hospital Infection Control and Decontamination

Far different from anthrax, a suspected case of smallpox is a public health emergency [26]. If the case is in the U.S., the state public health officials must contact the Centers for Disease Control and Prevention in Atlanta, GA (01-770-488-7100). The CDC will then contact the WHO Department of Communicable Disease Surveillance and Response Unit in Geneva, Switzerland. If the suspected case occurs outside the U.S., the National Public Health officials should contact the WHO directly.

28.3 Tularemia

28.3.1 Bacteriology and Pathogenesis

F. tularensis is a Gram-negative coccobacillus, a member of the γ-subdivision of proteobacteria [27]. There are four subspecies of *F. tularensis*, with *F. tularensis* subspecies *tularensis* being the most virulent, with the highest mortality rates and most potential as a bio-weapon [28].

28.3.2 Epidemiology

Francisella tularensis is a highly infectious organism, able to cause disease in humans from infection by as few as ten colony-forming units [9]. In fact, it is far more infectious than anthrax, the favored agent of biological warfare programs, which requires between 8,000 and 50,000 inhaled spores to produce pulmonary disease [28]. The WHO predicts that 50 kg of dried *F. tularensis* released over a population of 5 million would result in 250,000 cases of disease [9]. Tularemia is considered a zoonotic infection, as rodents, hares and rabbits are the most important sources of human infection [29]. Others have suggested that the bacterium may be able to survive in infected ticks [29]. In addition, the bacterium may be able to live freely in the environment or within protozoans. In fact, the bacterium has been found in amoebal cysts, indicating a possible mechanism for long-term survival in the environment [30]. Moreover, the bacterium has been isolated from at least 250 species of wildlife, including the black-tailed prairie dog, indicating its broad host range and ability to survive in numerous ecosystems [31]. Transmission to humans likely occurs via vectors like ticks, biting flies and mosquitoes [28]. Also, infection in humans may occur after direct contact with infected carcasses [32].

28.3.3 Clinical Features

The incubation period after exposure to *F. tularensis* is roughly 3–5 days, followed by the abrupt onset of constitutional symptoms like high fever, malaise, rigors, sore throat and cephalgia [33, 34]. Additional symptoms are governed by the pathogen's route of entry. Infection through the skin, representing 90% of cases, is the predominant form, and termed ulceroglandular tularemia [35]. This form occurs by vector-born transmission or direct contact with infected animal flesh. The site of infection forms a solitary papule which transitions to a pustule, then ulcerates and is surrounded by inflammation [33] (Fig. 28.3). The ulcer heals within 1 week, but the draining lymph nodes become tender and swollen and may suppurate if antibiotic therapy is not instituted [36]. Oculoglandular (direct inoculation of the eye), oropharyngeal (ingestion of

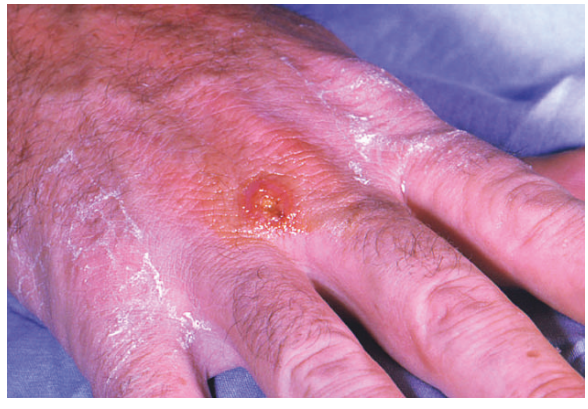

Fig. 28.3 Tularemia, Courtesy of Public Health Image Library (PHIL), CDC/Brachman

contaminated water) and respiratory tularemia (infection by inhalation) are much less common forms of naturally occurring disease. The most deadly form, typhoidal tularemia, presents with fevers, rigors, nausea, vomiting, abdominal pain and diarrhea. Death from this form can be rapid. Several exanthems have been described in tularemia, and range from macular, papular, pustular, petechial and mostly seen on the face and extremities. Erythema nodosum has been seen most often in pulmonary tularemia, while erythema multiforme and Sweet's syndrome have also been reported [37]. However, respiratory tularemia, caused by *F. tularensis spp. tularensis* represents the most dangerous of all forms of this disease, and is the likely candidate for use as an agent of bio-warfare [28]. The disease is contracted naturally by working with hay, straw or other farming activities where materials have been soiled by infected rodents [28]. Symptoms of this disease are high fever, rigors, malaise, cough, delirium and pulse-temperature dissociation [33]. The mortality rate from this form approaches 30% [38].

28.3.4 Diagnosis

Respiratory tularemia can often be confused with legionellosis, and does not have characteristic cutaneous findings. Patients may exhibit leukocytosis, transaminitis, hyponatremia, pyuria and myoglobinuria [33]. Rapid diagnostic testing is not widely available, yet physicians suspicious for respiratory tularemia should collect respiratory secretions, exudates, or biopsy specimens for Gram stain, direct fluorescent antibody testing or immunohistochemical stains. Up-to-date information on specimen collection and laboratory testing is available at http://www.bt.cdc.gov/agent/tularemia/

28.3.5 Post-exposure Prophylaxis

Post-exposure prophylaxis of close contacts of any form of tularemia is not recommended, since person-to-person transmission is not known to occur. However, if an attack is realized prior to displaying symptoms, all exposed persons should receive prophylactic antibiotic treatment with oral ciprofloxacin or doxycycline for 14 days. If the attack is discovered after individuals develop symptoms, then a fever watch should be instituted and those who go on to develop unexplained fever or flu-like illness should receive the oral treatment discussed above for the same time period [20].

If a mass exposure to *F. tularensis* occurs, oral administration of ciprofloxacin or alternatively doxycycline would be the preferred strategy for post-exposure prophylaxis [39].

28.3.6 Antimicrobial Therapy

Historically, the aminoglycoside streptomycin has been the drug of choice for treating tularemia. However, due to availability issues and problems with ototoxicity, streptomycin is rarely used today in most Western countries [28]. When serious forms of tularemia are encountered, the aminoglycoside gentamicin is the preferred agent. More recently, tetracyclines (specifically doxycycline) have been used to treat less serious infections when oral therapy is preferred. However, relapses are seen with this treatment, so doses at double the recommended standard are given for at least 2 weeks [28]. Recent in vitro and clinical data suggest that fluoroquinolones (especially ciprofloxacin) might be the best choice for oral treatment of tularemia [35]. In addition, ciprofloxacin may also be the best choice for pregnant women and children, despite the concerns for cartilage damage in utero and for children [40] (Table 28.2).

28.3.7 Hospital Infection Control and Decontamination

Isolation is not recommended for tularemia patients, as there is no evidence that person-to-person transmission exists. Therefore, standard precautions are recommended [20]. Contaminated clothing and bed linens should be disinfected per standard hospital protocol [20].

28.4 Plague

28.4.1 Bacteriology and Pathogenesis

Plague is a zoonotic illness, caused by the Gram-negative bacillus *Yersinia pestis*, a disease primarily in

Table 28.2 Treatment of patients with tularemia

In a contained casualty setting

Therapy	Adults	Pregnant women	Children
Preferred therapy	Streptomycin, 1 g IM every 12 h	Gentamicin, 5 mg kg^{-1} IM or IV every 24 h	Streptomycin, 15 mg kg^{-1} IM every 12 h (not to exceed 2 g per day)
	or	or	or
	Gentamicin, 5 mg kg^{-1} IM or IV every 24 h	Streptomycin, 2.5 mg kg^{-1} IM or IV every 8 h	Gentamicin, 2.5 mg kg^{-1} iM or IV every 8 h
Alternative therapy	Doxycycline, 100 mg IV every 12 h	Doxycycline, 100 mg IV every 12 h	Doxycycline: 100 mg IV every 12 h if ≥45 kg; 2.2 mg kg^{-1} IV every 12 h if <45 kg
	or	or	or
	Ciprofloxacin, 400 mg IV every 12 h	Ciprofloxacin, 400 mg IV every 12 h	Ciprofloxacin, 15 mg kg^{-1} IV every 12 h
	or		or
	Chloramphenicol, 15 mg kg^{-1} IV every 6 h		Chloramphenicol, 15 mg kg^{-1} every 6 h
In mass casualty setting and postexposure prophylaxis			
Therapy	Adults	Pregnant women	Children
Preferred therapy	Doxycycline, 100 mg orally every 12 h	Ciprofloxacin, 500 mg orally every 12 h	Doxycycline, 100 mg orally every 12 h if ≥45 kg; 2.2 mg kg^{-1} every 12 h if <45 kg
	or	or	or
	Ciprofloxacin, 500 mg orally every 12 h	Doxycycline, 100 mg orally every 12 h	Ciprofloxacin, 15 mg kg^{-1} orally every 12 h (not to exceed 1 g per day in children)

(Adapted from CDC guidelines) Treatment with streptomycin, gentamicin, or ciprofloxacin should continue for 10 days, while treatment with doxycycline or chloramphenicol should continue for 14–21 days. Transition from IV or IM administration to oral route is recommended as clinically indicated.

rodents with transmission to humans primarily through the infected flea vector [41]. However, human transmission may also occur via respiratory droplets from animals to humans and humans to humans [41]. The bacterium multiplies and blocks the passage of food in the flea's midgut, causing regurgitation of esophageal contents and release of the bacterium back onto the feeding surface, allowing a portal of entry [42].

28.4.2 Epidemiology

Yersinia pestis, first isolated by Alexandre Yersin in 1894 after its spread from main-land China to Hong Kong, was found to be transmitted by its vector, the flea, soon thereafter [43, 44]. Bubonic plague is the predominant form, and carries a mortality rate of 10–20% [45]. The rarest and most deadly form of the disease, primary pulmonary plague, has a mortality rate approaching 100% if not treated in the first 24 h of symptoms. The mortality rate drops to only roughly 50% even with early antimicrobial treatment [46].

28.4.3 Clinical Features

There are three clinical forms of the human plague; bubonic, primary septicemic, and primary pneumonic [47]. Bubonic plaque, noted by acute regional lymphadenopathy and bubo formation, is the most common form (80–90% of cases) [48]. Overlying the bubo, erythema, vesicles, pustules, eschars or ulceration may ensue. The pneumonic form represents the most likely manifestation of an aerosolized biologic attack [22]. Primary pneumonic plague has an incubation period of 1–3 days, followed by the abrupt onset of high fever, rigors, chills, cephalgia, progressive weakness and malaise (seen in all forms of plague). Additional symptoms specific for pulmonic plague are cough, dyspnea and haemoptysis [41]. The pulmonary symptoms of both the

plague and inhalation anthrax are quite similar, yet the inclusion of haemoptysis is more suggestive of pulmonic plague [45]. The likelihood of bubonic plague occurring as a terrorist act is low, given that the vector would have to include the use of fleas. More likely is the spread of pneumonic plague, which could be primary or secondary (resulting from bubonic or septicemic plague). Pneumonic plague has no specific cutaneous findings, but if septicemia ensues, vasculitis, DIC, or purpura and gangrene of the digits may appear (Fig. 28.4). A bioterrorist attack would likely involve aerosol spread. However, if insect vectors were used, recognition of bubonic disease would become paramount. Many of the bubonic cases would transition to secondary pneumonic and septicemic forms, possibly causing further confusion with inhalation anthrax.

28.4.4 Diagnosis

Several diagnostic tests are available to aid in the diagnosis of plague, using clinical specimens such as lymph node aspirates, blood, sputum smears and tracheal washings. Standard bacterial culture in addition to Gram, Wright–Giemsa, and immunofluorescence studies are helpful in suspected cases [41]. Specialized confirmatory testing like antigen detection and PCR analysis are available through specialized laboratories of the CDC and the military [45].

28.4.5 Post-exposure Prophylaxis

The use of oral antimicrobial therapy with ciprofloxacin or doxycycline is preferred in the mass-casualty scenario.

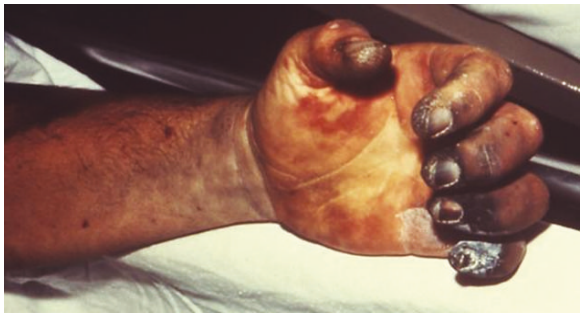

Fig. 28.4 Septicemic Plaque, Courtesy of Public Health Image Library (PHIL), CDC/Jack Poland

28.4.6 Antimicrobial Therapy

In confirmed cases of *Y. pestis* infection, streptomycin, gentamicin, chloramphenicol, doxycycline and ciprofloxacin are likely to be effective antimicrobial agents [45]. As with the other biologic agents discussed, the use of ciprofloxacin and doxycycline in children and pregnant women with pneumonic plague significantly outweighs the risk to bone, teeth and cartilage previously outlined [45,49]. When confirmed pulmonic plague occurs, intravenous aminoglycosides are preferred. Intravenous chloramphenicol is indicated for plague meningitis [47].

28.4.7 Hospital Infection Control and Decontamination

Respiratory precautions are indicated for all cases of suspected pulmonic plague until excluded, or after 48 h of therapy in confirmed cases [45]. Standard precautions are recommended for bubonic plague [41].

28.5 Viral Haemorrhagic Fevers

28.5.1 Bacteriology and Pathogenesis

All viral agents that cause viral haemorrhagic fevers (VHF) are lipid-enveloped RNA viruses whose host reservoir is either an animal or insect [50].

There are four distinct families of virus that cause VHF:

- Arenaviruses: lassa fever and South American haemorrhagic fever virus (SAHF)
- Bunyaviruses: hanta virus and Crimean–Congo haemorrhagic fever virus (CCHF)
- Flaviviruses: dengue haemorrhagic fever (DHF), tick-borne encephalitis, and yellow fever viruses
- Filoviruses: Ebola and Marburg viruses [41]

VHF agents spread haematogenously, seeding multiple organs, causing micro-vascular damage and increased vascular permeability [51]. The combined action of increased vascular permeability, release of pro-inflammatory

cytokines, cytotoxic factors, complement activation and systemic coagulopathy results in the severe manifestations of late stage, often fatal disease [51]. All viral agents cause clinical illness associated with high fever, myalgia, prostration, petechiae, haemorrhage and shock [52].

28.5.2 Epidemiology

These viruses are geographically confined to specific regions, where they create enzootic infection [51]. Disease in humans occurs after exposure to contaminated saliva, urine, and the feces of diseased animals, from insect bites that harbor the virus, and also from human-to-human transmission after exposure to contaminated tissue or body fluids [51]. With the exception of Marburg virus, there is no evidence that these agents have been weaponized, yet their dissemination as bio-weapons is a distinct future possibility [51].

28.5.3 Clinical Features

VHF usually presents with high fever, myalgias, headaches and prostration. Incubation periods are normally brief, but can vary from 2 to 19 days [51]. None of these entities carries distinct cutaneous manifestations, yet Marburg viral infection commonly elicits a maculopapular exanthem around day 5 of infection (Fig. 28.5). All entities can progress to petechiae, ecchymoses, and other signs of disseminated coagulation and eventually shock. End organ damage to the brain, kidneys, and liver is common, and varies according to the agent. Mortality rates are also quite variable, with dengue fever having rates between 1% and 50%, and Ebola/Marburg viruses showing death rates between 25% and 90%.

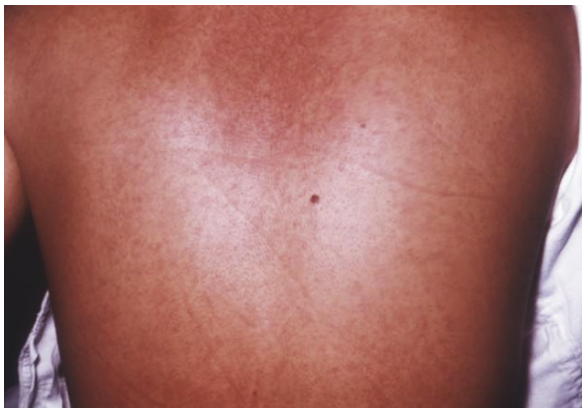

Fig. 28.5 Maculopapular exanthem of Marburg virus infection, Day 5, Courtesy of Public Health Image Library (PHIL), CDC/J. Lyle Conrad

28.5.4 Diagnosis

The diagnosis of viral haemorrhagic fevers is variable depending on the viral agent. Detection methods include viral antigen detection, PCR, immunofluorescence, ELISA, electron microscopy and culture [51]. Except for dengue fever, all agents require the use of specialized biosafety level-4 equipment for safe handling. Diagnostic testing is only available through the CDC or the US Army Medical Research Institute of Infectious Diseases (USAMRIID). All patients should be initiated on ribavirin pending viral identification.

28.5.5 Post-exposure Prophylaxis

Patients with fever and haemorrhagic manifestations should be reported to the public health authorities. These agents are highly contagious, and therefore require stringent universal precautions, barrier protection, and negative pressure isolation.

28.5.6 Antimicrobial Therapy

There are only limited treatment and vaccination options for persons exposed to or infected with these agents. Intensive care is required for all severely ill patients, with close monitoring of haemodynamics, as well as blood, kidney and liver function [51]. In addition to intensive supportive care, the antiviral ribavirin has been effective in some VHF cases. Also, convalescent plasma, which contains neutralizing antibodies, has improved survival in some instances of VHF [53,54].

28.5.7 Hospital Infection Control and Decontamination

All VHF agents, except dengue fever, pose tremendous hospital infection control problems. For the most up-to-date information on infection control and decontamination, see the CDC guidelines at http://www.bt.cdc.gov/agent/vhf/ or guidelines outlined by the World Health Organization at http://www.who.int/csr/disease/en/.

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29 Life-Threatening Complications of Dermatologic Therapies

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Core Messages

- Adverse drug reactions are either related to their pharmacologic activity or to idiosyncratic or immune-mediated reactions.
- Adverse drug reactions are sometimes life-threatening because of various organ injuries leading to organ (or multiple-organ) failure.
- Many drugs used in dermatologic diseases are involved in such severe manifestations.
- Adverse drug reactions and severe outcome of drug-induced adverse effects are partly preventable.
- Almost all drugs can induce life-threatening reactions, but these manifestations are unfrequent.
- There is a lack of information about the risks of new marketed products.

29.1 Adverse Effects of Drugs

Adverse drug reactions are a major cause of morbidity and mortality world-wide. A marked increase was found between 1998 and 2005 in deaths and serious injuries associated with drug therapy reported to the US Food and Drug Administration [1]. Despite some limitations or alternative explanations, this increase seems to be related to a real increase in the numbers of patients experiencing serious injuries from drug therapy.

During clinical trials, only a small number of patients are exposed to a new drug, over a limited period of time, compared to the number that might use it once a marketing authorisation has been granted. Thus, when a drug is first marketed, much may be known about its efficacy while relatively little may be known about its safety. Rare and possibly serious adverse reactions, occurring in only a small percentage of cases, may not be detected during clinical trials.

Pharmaco vigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects of drugs, especially by means of post-marketing surveillance. Spontaneous adverse drug reaction reporting or large-scale databases are useful to generate hypotheses and signals about potential risks of marketed drugs that require further investigation. Spontaneous reporting of suspected adverse drug reactions is particularly useful in identifying serious, rare and/or delayed reactions.

Establishing a diagnosis of drug-induced disease (i.e., imputability processes) may be difficult. Imputability relies upon the elimination of other causes and a compatible or a suggestive time-relationship between drug ingestion (onset and withdrawal) and the evolution of the adverse event. In addition, it is important to consider the nature of the reaction and the relationship to the dose administered.

Healthcare professionals must be aware of the benefit–risk ratio before prescribing. They should be particularly aware that some situations related to the patient may favour drug-induced reactions: children, elderly patients, pregnant women, and patients with liver or renal failure are susceptible to adverse reactions,

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and it is therefore important to monitor drug safety in these patient populations.

The risk of adverse effect may increase in situations related to the status of drugs:

- Newly marketed drugs or established products with a new indication or route of administration
- New combinations of established drugs or new targeted patient populations
- Drugs with a narrow therapeutic index
- Drugs known to interact

Drug reactions can be classified into immunologic and non-immunologic mechanisms.

- The majority of adverse drug reactions are caused by non-immunologic effects, which are either predictable (due to pharmacologic action, thus often dose-related), or unpredictable (idiosyncratic) such as pseudo-allergic reactions.
- Predominant mechanisms that lead to clinical symptoms of immune-mediated reactions (or allergy) are commonly described in the Gell and Coombs classification system. A revised nomenclature for allergy, including drug reactions, was proposed in 2004 [2]. Immune-mediated reactions are unpredictable and not clearly related to the dose.

This review will focus on the most severe and life-threatening adverse reactions to the common drugs or therapies used in dermatology. It is not meant to be exhaustive because of the number and the variety of agents prescribed by dermatologists, in inpatients as well as in outpatients.

29.2 Anaphylaxis

Anaphylaxis is a severe and potentially lethal immediate-type generalised hypersensitivity reaction affecting multiple organ systems. Severe anaphylaxis includes such serious symptoms as cardiovascular collapse, cardiac arrhythmia, severe bronchospasm, circulatory failure, cardiac and/or respiratory arrest, and finally lethal anaphylaxis.

Drugs are a frequent cause of anaphylaxis identified in epidemiological studies conducted in both hospital and emergency units [3]. Antibiotics were the more common cause of life-threatening drug anaphylaxis, as registered by the French Allergy Vigilance Network over 2003/2004, with amoxicillin involved in 40% of cases, cephalosporins in 15% and other antibiotics in 5% [3]. Injectable antibiotics (penicillin, cephalosporin, vancomycin, quinolones, macrolides) were responsible for 15% of anaphylaxis during anaesthesia among 502 patients referred to an allergo–anaesthesia centre between January 2001 and December 2002, taking the third position after curare and latex [4]. Local anaesthetics (articaine, lidocaine, mepivacaine) were involved in less than 1% of cases.

Death from an allergic reaction to penicillin occurs at an incidence of about 1 per 50,000 treatment courses of parenteral penicillin in the general population [5].

All routes of administration are potentially involved, even in topical skin application (antibiotics or antiseptics) [6] and prick-tests [7].

Urticaria may be a non-severe manifestation of anaphylaxis, but is more often a manifestation of pseudo-allergic reaction. In a prospective study including 350 patients who presented with immediate hypersensitivity (urticaria, angioedema, anaphylactic shock) suspected of being drug-induced, only 22 had definite allergy defined as positive tests for the suspected drug. Among these 22 patients, 20 had severe effects such as major angioedema, hypotension, bronchospasm or anaphylactic shock. The other 328 patients suffered from pseudo-allergic or not drug-related urticaria without severe manifestation, which made re-challenge of the suspected drug possible [8].

29.3 Life-Threatening Cutaneous Drug Reactions

A separate chapter in this book is devoted to severe cutaneous drug reactions such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and acute generalized exanthematous pustulosis (AGEP).

More than 100 drugs have been suspected to be a possible etiologic agent of SJS/TEN in case reports or retrospective studies. Among drugs used in dermatology, according to results of prospective case-control studies, anti-infective sulfonamides were the most strongly associated with SJS/TEN; a significant but lower risk was found with other antibiotic drugs (aminopenicillins, cephalosporins, quinolones, tetracyclines, macrolides) [9, 10].

A large variety of drugs possibly used in dermatologic therapies have been associated with DRESS, especially sulfonamides, dapsone, and minocycline [5, 11].

In the EuroSCAR case-control study, 97 cases of AGEP were included. A strong association was found with drugs commonly used by dermatologists: pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulfonamides and terbinafine [12].

29.4 Severe Drug-Induced Liver Injury

Drug-induced hepato-toxicity is a major cause of iatrogenic diseases. The liver is a particular target for drug toxicity because of its role in clearing and metabolizing xenobiotics. More than 1,000 compounds (including herbal medicines) are involved, and can reproduce the full spectrum of liver injuries. The pathogenesis of drug-induced liver injury usually involves the participation of a toxic drug or metabolite that either elicits an immune response or directly affects the biochemistry of the hepatocytes [13].

Three types are described:

- Acute hepatitis is frequently similar to viral hepatitis, presenting with markedly elevated serum aminotransferase levels and a minimal increase in the level of alkaline phosphatase. It is the most frequently observed pattern and the more serious presentation with substantial mortality rate related to fulminant liver failure; coagulopathy and encephalopathy are present in more severe cases. It may also lead more insidiously to cirrhosis.
- Cholestatic hepatitis is not usually life threatening; it presents with jaundice, pruritus, and marked increases in alkaline phosphatase levels, as well as mild increases in alanine aminotransferase (ALT) levels.
- Mixed injury patterns with intermediate to marked increases in ALT and alkaline phosphatase levels can resemble atypical hepatitis or granulomatus hepatitis.

Acute liver failure is the most severe complication of drug-induced hepato-toxicity, with a high spontaneous mortality rate, and represents the first cause of drug withdrawal from the market [14]. Drugs appear to be the first of all causes of acute liver failure. In Western countries, paracetamol intoxication represents the first cause of all liver failure, with a spontaneous mortality rate ranging from 32 to 50%. The frequency of acute liver failure due to non-paracetamol drugs given at normal doses is equivalent to that of viral hepatitis A and B. Herbal medicines are playing an important role in Asian and African countries [15], but also in western countries [16].

The course of acute liver injury to liver failure may be modulated by the following parameters: the continuation of causative drug administration despite the onset of liver injury, age (with a higher risk for older people), a pre-existing cirrhosis, fasting, denutrition, chronic alcohol abuse, and sometimes the amount of ingested drug such as in the case of paracetamol. It is usually recommended to stop the administration of a suspected drug when alanine aminotransferase levels increase to more than 3–5 times the upper limit of normal [14]. Once acute liver failure has occurred, there is no specific treatment (other than administration of N-acetylcysteine in paracetamol intoxication), and emergency liver transplantation represents the best chance of survival.

Dermatology-specific drugs suspected in acute hepatitis with liver failure [17–19]:

- Beta-lactam antibiotics: amoxicilline + /– clavulanate, flucloxacillin
- Cyclines: minocycline
- Other antibiotic agents: dapsone
- Antifungal agents: ketoconazole[1], terbinafine
- Immunosuppressive agents: methotrexate[2], azathioprine

Monitoring aminotransferase levels is recommended but standard liver function tests can be unreliable to assess the liver damage. Liver biopsies after a cumulative dose of 1 to 1.5 g have been recommended to determine hepatotoxicity [21], and some physicians perform baseline liver biopsies in those patients with a history of liver disease or other risk factors for hepatotoxicity including age, obesity, alcohol intake, and diabetes. Liver biopsies have however a significant morbidity and a mortality rate of up to 0.33% was reported in U.K. The benefit-risk ratio of this investigation is therefore questioned, and most practitioners world-wide do not do them anymore. Recently, it has been stated that

[1] Ketoconazole is a cause of severe hepatic injury, the incidence of symptomatic, potentially serious hepatitis being about 1 in 12 000–15 000 patients. Ketoconazole is therefore no longer used in first line treatment of fungal cutaneous or toenail infections.

[2] The major pattern of methotrexate hepatotoxicity in psoriatic patients is fibrosis/cirrhosis which is related to cumulative dose and may exceptionally lead to liver failure [20].

monitoring of serological markers of fibrosis such as the aminoterminal peptide of type III procollagen (PIIINP) can avoid follow-up biopsies in a significant fraction of patients on long-term low-dose methotrexate [22, 23]. More data are however required to make more definitive recommendations.

According to studies reviewed, the use of folate supplements in patients treated with methotrexate reduces the incidence of hepato-toxicity and gastrointestinal intolerance, without impairing the efficacy of methotrexate [24]. Most of these studies were, however, conducted in rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis, and few studies have addressed folate supplementation with the use of methotrexate for the treatment of psoriasis.

29.5 Serious Haematologic Drug-Induced Adverse Effects

29.5.1 Agranulocytosis

This condition is marked by a profound decrease in the number of granulocytes in circulating blood, resulting in a neutrophil count below $0.5 \times 10^9 l^{-1}$. In the majority of patients, the neutrophil count is below $0.1 \times 10^9 l^{-1}$. Drug-induced agranulocytosis is a life-threatening adverse event due to the frequency of severe sepsis, with severe deep infections, septicemia, and septic shock in about two-thirds of all patients. Poor prognostic factors are old age, septicemia or shock, metabolic disorders such as renal failure, and a neutrophil count below $0.1 \times 10^9 l^{-1}$ [25]. With appropriate management using pre-established procedures, with intravenous broad-spectrum antibiotic therapy, and haematopoietic growth factors, the mortality rate is currently around 5%.

Mechanisms that cause idiosyncratic drug-induced agranulocytosis are not completely understood, but neutropenia is supposed to be mediated by immuno-allergic or toxic mechanisms. When toxic mechanism is involved, anemia and/or thrombocytopenia may occur.

According to epidemiologic studies, the annual incidence of idiosyncratic drug-induced agranulocytosis is between 3.4 and 5.3 cases per million of population in Europe. In the USA, rates range from 2.4 to 15.4 per million per year. Apart from chemotherapy, many drugs can cause agranulocytosis [25, 26], but the frequency of this adverse effect is usually very low for each of them.

Dermatology specific drugs involved in agranulocytosis (usual suspects in italics)

- Antibacterial agents: *beta-lactam antibiotics*, *cephalosporins*, fluoroquinolones, *sulfonamides*, fusidic acid, clarithromycin, lincomycin, metronidazole, clindamycin, tetracycline, vancomycin, *dapsone*
- Anti-fungal agents: flucytosine, terbinafine
- Anti-viral agents: acyclovir
- Antihistamines: brompheniramine, chlorpheniramine
- Anti-malarial agents: hydroxychloroquine, chloroquine
- Immunosuppressant/immuno-modulator: imatinib, *rituximab*[3], prednisone
- Other: colchicines, acitretin

29.5.2 Thrombocytopenia

Drug-induced thrombocytopenia can sometimes be life-threatening. In case reports, thrombocytopenia was usually discovered after the occurrence of minor purpura, but major bleeding occurred in 9% of drug-induced thrombocytopenia, and fatal bleeding rate was found to be 0.8% [27]. A systematic updated review identified more than 150 drugs involved in thrombocytopenia.

Dermatology specific drugs involved in severe thombocytopenia (usual suspects in italics)

- Antibiotics: *vancomycin*, linezolid, cephalothin, piperacillin, methicillin, oxytetracycline, ampicillin
- Anti-tuberculous agents: *rifampin*, ethambutol, isoniazid
- Antifungal agents: *amphotericin B*, fluconazole, terbinafine
- Other: interferon-α, *rituximab*, *cyclosporine* [27–29]

Drug-induced platelet destruction is usually caused by drug-induced antibodies, several mechanisms being involved to explain immune thrombocytopenia [30].

It is, however, important not to forget that heparin is the most common drug-related cause of immune drug-induced thrombocytopenia. The major threat in cases of heparin-induced thrombocytopenia is thrombosis rather than bleeding [31].

[3] In the case of rituximab, delayed-onset agranulocytosis is reported. A plausible time relationship to drug administration was assumed if the last rituximab infusion was given within 6 months before onset of agranulocytosis.

Patients with drug-induced thrombocytopenia occasionally present with disseminated intravascular coagulation or renal failure and other findings indicative of the *haemolytic-uremic syndrome* or *thrombotic thrombocytopenic purpura*. These terms describe various syndromes of multiple etiologies, with the common features of thrombocytopenia and micro-angiopathic haemolytic anaemia. Other organ involvement, including renal failure, neurologic and gastrointestinal symptoms, is common. Without appropriate management, these syndromes are fatal in more than 90% of cases. Plasma exchange treatment induces remissions in more than 80% of patients. Many drugs have been rarely associated with the development of haemolytic–uremic syndrome or thrombotic thrombocytopenic purpura. Some of these drugs are used in dermatology, *cyclosporine* being a usual suspect, and very occasionally ampicillin, clarithromycin, oxytetracycline, penicillin, rifampicin, interferons or valacyclovir [32].

29.5.3 Other Serious Haematologic Adverse Effects

- Myelotoxicity: bone-marrow aplasia related to direct drug toxicity is rarely associated with low-dose methotrexate, azathioprine or colchicine. Various conditions leading to drug overdosage are reported, such as renal insufficiency or drug–drug interactions. Medication errors (prescription, dispensation and administration) have to be considered. In the case of azathioprine, as the association between thiopurine methyltransferase (TPMT) deficiency (affecting 0.3–0.6% of Caucasians) and myelosuppression is well-recognized, some authors recommend a pre-treatment assessment of red blood cell TPMT activity, to avoid myelosuppression by treating a deficient patient with a greatly decreased dose. Cost-effectiveness studies of TPMT activity screening are unfortunately lacking.
- Haemolysis: a variety of drugs can be associated with haemolysis. Among them, some antibiotics are inducers of immune or auto-immune haemolytic anaemia. Dapsone may induce severe haemolytic anaemia in people with glucose-6-phosphate dehydrogenase deficiency. A pre-treatment screening of G6PD deficiency may be recommended in patients originating from communities known to have a high G6PD deficiency prevalence (Africa, Southern Europe, the Middle East and Asia).
- Methemoglobinemia occurs in all patients receiving dapsone. Dyspnea, nausea, and tachycardia are considered to occur at methemoglobin levels of 30% or above, but as dapsone-induced methemoglobinemia is not chronic and haemolytic anaemia is usually present, the first symptoms are present for a 10% level; consciousness disorders occur as methemoglobin level approaches 55%, and levels of 70% are usually fatal [33].

29.6 Life-Threatening Renal Drug-Induced Adverse Effects

Drug-induced kidney injury is a major adverse effect in clinical practice. Renal injury associated with drugs may involve several components of the kidney: glomerulus, tubules, interstitium, and blood vessels. Moreover, therapeutic agents may induce an allergic reaction, leading to interstitial inflammation and tubular damage [34, 35].

Acute renal failure is often reversible upon discontinuation of the culprit medication, but haemodialysis is sometimes required and a fatal outcome is possible.

Dermatology-specific drugs involved in severe renal injury (usual suspects in italics)

- *Acyclovir* (production of insoluble crystals, intratubular precipitation of crystals leading to acute renal insufficiency)
- *Penicillin A* (tubulo-interstitial nephropathy)
- *Cyclosporine* (reductions in glomerular filtration occurring in the first 3–6 months of the treatment)
- *Cidofovir* (tubulo-interstitial nephropathy)
- *Intravenous immunoglobulin* (IvIg) (acute tubulo-interstitial nephropathy related to the occurrence of osmotic nephrosis in the proximal tubule. It has been reported mainly with sucrose containing IvIg but also with maltose and glucose containing IvIg)
- *Amphotericin B* (systemic use) (reduction of the glomerular filtration rate and tubular dysfunction)
- Interferon-α (interstitial, glomerular and vascular nephropathy)
- Methotrexate (intratubular precipitation of insoluble crystals after high-dose administration).
- Chinese herbal (interstitial or tubular nephropathy)
- Etanercept and infliximab (glomerular nephropathy)

Rhabdomyolysis is a common and potentially lethal clinical syndrome that results from acute muscle fibre

necrosis, with leakage of muscle constituents into blood. Myoglobinuria is the most significant consequence, leading to acute renal failure in 15–33% of patients. Rhabdomyolysis leads to death in about 10% of cases [36]. Drugs are sometimes involved in rhabdomyolysis, colchicine being one of the causative drugs [37]. Because renal impairment is the primary risk factor for development of colchicine-induced myotoxicity, dosage adjustment or alternative therapy may be required.

29.7 Life-Threatening Cardiologic and Vascular Adverse Effects

29.7.1 Long QT Syndrome and Torsade De Pointes

Drug-induced long QT syndrome is characterized by acquired QT interval prolongation and increased risk of torsade de pointes (TdP). Symptoms of TdP include palpitations, syncope, and seizure-like activity. Torsade de pointe is usually self-limited, but may degenerate into ventricular fibrillation and cause sudden cardiac death. Several risk factors predispose patients to drug-induced long QT syndrome and TdP [38]: female sex (the most common risk), structural heart disease (myocardial infarction, heart failure, valvular disease, or cardiomyopathy), hypokalemia, multiple QT-prolonging drugs or agents interfering with their metabolism, excessive dosing, prolonged baseline QTc (≥450 ms), family history of congenital long QT syndrome prior to drug-induced TdP. In addition, hepatic impairment, bradycardia, and atrioventricular block also increase the risk of TdP.

A variety of medications have been implicated in drug-induced long QT syndrome [39]. Among these drugs are:

- *Erythromycin* and *clarithromycin* have been implicated in sudden death due to TdP. These drugs are metabolized by and inhibit CYP3A4. They are especially dangerous for patients receiving another CYP3A4 inhibitor or a QT-prolonging medication metabolized by CYP3A4.
- Sporadic incidents of TdP have been reported with fluoroquinolones.
- Case reports describe TdP in patients receiving systemic *azole antifungals* (fluconazole, itraconazole, ketoconazole, and voriconazole), but these are unlikely to cause TdP without pre-existing risk factors.
- Anti-malarials, including *chloroquine*, have been associated with QT prolongation and TdP.
- Third-generation antihistamines, unlike the second-generation agents, have not been shown to induce long QT syndrome.
- Vorinostat is a histone deacetylase inhibitor approved by FDA for "the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease on or following two systemic therapies". During the clinical trials, some patients exposed to vori-nostat had QTc prolongation, but a definitive study of the effect of vorinostat on QTc has not been conducted [40].

29.7.2 Drug-Induced Heart Failure

Several classes of drugs may induce heart failure in patients without concurrent cardiovascular disease, or may precipitate the occurrence of heart failure in patients with pre-existing left ventricular impairment [41]. If cardiac toxicity is a constant concern when using anti-mitotic drugs or some immuno-modulator drugs, it is also advisable to exercise caution in the use of many other drugs when treating patients with cardiac insufficiency, even if the clinical situation is well-controlled. Interferon, glucocorticoids (systemic and topical super-potent steroids) [42, 43] and anti-TNF-α [44] appear among these drugs.

29.7.3 Thrombosis

Thalidomide: thalidomide has been found to be effective in many malignant and inflammatory conditions, including various inflammatory dermatological diseases [45]. It was observed that this drug might be associated with an increase in the risk of venous thromboembolic events (including pulmonary embolism). In a review of literature, the risk of venous thromboembolism in patients receiving thalidomide for multiple myeloma was found to be significantly increased, by 2.6 [46]. The use of dexamethasone in combination with thalidomide was associated with an increase of this risk by eight times. In a series of 25 patients treated

by thalidomide for different inflammatory dermatological diseases, deep vein thrombosis occurred in 20% of cases [47]. Patients receiving thalidomide should thus be carefully monitored for any signs of deep venous thrombosis and pulmonary embolism.

– *Intravenous immunoglobulin therapy* (IvIg) may be associated with arterial and venous thrombosis, including deep venous thrombosis or pulmonary embolism, myocardial infarction and stroke, especially in patients with autoimmune disorders. These adverse events have occurred during IvIg infusion or within 1–8 days following IvIg infusion [48].

29.8 Life-Threatening Psychiatric Manifestations

– *Interferon-α*: psychiatric side effects of interferon-α (IFN) including manic symptoms, bipolar disorder and depression have been reported as common adverse events [49]. The reported rates of depressive symptoms associated with IFN range from 3% to 57% of the patients, the variation being partly due to differences in dosage, disease and length of treatment. Suicidal ideations are possible and usually remit after discontinuation of IFN treatment. Suicidal attempts have been rarely reported. In one single double-blind study conducted in 40 patients with malignant melanoma eligible for high-dose IFN therapy, pre-treatment with paroxetine significantly reduced the rate of major depression induced by IFN [50].
– *Isotretinoin*: A number of case reports and case series linking isotretinoin to depression or suicide have been published. Between 1982 and 2000, the FDA received reports of 394 cases of depression, and 37 suicides occurring in patients exposed to isotretinoin [51]. In a systematic review of studies reporting primary data on depression and suicidal behaviour in patients treated with isotretinoin for acne vulgaris, rates of depression among isotretinoin users was found to range from 1 to 11%, with similar rates in oral antibiotic control groups [52]. Some studies demonstrated a trend toward fewer or less severe depressive symptoms after isotretinoin therapy. Moreover, the available data on suicidal behaviour during isotretinoin treatment are insufficient to establish a meaningful causative association. Nevertheless, because acne in itself has been associated with depression, suicidal ideation and suicide, it is wise to carefully monitor patients undergoing treatment with isotretinoin for the emergence of depressive and suicidal ideation.

29.9 Severe Neurologic Adverse Effects

– *Acyclovir*, and its prodrug valacyclovir, may have neurological toxicity due to high concentrations in the spinal fluid related to high plasma concentrations. This neurotoxicity can deteriorate into coma [53]. Renal dysfunction is a known risk factor for acyclovir neurotoxicity; thus, dosage reduction and increased monitoring should be carried out when renal dysfunction is present.
– *Cyclosporine* may produce a clinical spectrum that varies from tremor and acute confusional state to seizures, or more rarely to coma. On CTscan or magnetic resonance imaging, the most characteristic feature is posterior leukoencephalopathy. This neurotoxicity is predominantly described in patients after organ transplantation. It occurs usually when toxic levels are reached, and the manifestations are reversible in most instances after discontinuation or adjustment to a lower target level. It is important to identify drugs that may increase levels of cyclosporine such as cephalosporins, diltiazem, verapamil, and high-dose methylprednisolone [54].

29.10 Life-Threatening Pulmonary Toxicity

Drug-induced interstitial lung disease can produce acute widespread pulmonary infiltrates, with life-threatening respiratory failure. Some drugs used in dermatologic diseases are involved in such cases, the most frequently being various antibiotics (especially *minocycline*) and *methotrexate* [55]. Pulmonary toxicity of methotrexate has been well-described, and may take a variety of forms [56]. It occurs in 0.5–14% of patients receiving low-dose methotrexate, and includes parenchymal inflammation, pneumonia, airway hyperreactivity and air-trapping [57, 58]. In most patients, symptoms present sub-acutely with progression over several weeks. Dyspnea, dry cough, fever, and bibasilar

crackles are the major symptoms. Peripheral eosinophilia has been cited in one third of cases. Chest radiography commonly shows bilateral interstitial or mixed, interstitial and alveolar infiltrates with a predilection for the bases. Pulmonary function studies show a restrictive ventilatory defect and/or impaired gas exchange. Bronchoalveolar lavage may be helpful in supporting the diagnosis and in ruling out an infectious etiology. Once pulmonary toxicity of methotrexate is suspected, the drug should be withdrawn. Corticosteroids may accelerate resolution, and are recommended in severe cases. The prognosis is usually favourable, but occasionally the outcome may be fatal.

29.11 Life-Threatening Infectious Diseases

Infectious diseases are a major cause of mortality in patients receiving immunosuppressive agents for connective tissue diseases. Systemic corticosteroids, as well as topical super-potent steroids, can induce serious infections [43, 59]. These infections are bacterial infections such as pneumonia or bacteraemia, viral and opportunistic, mainly fungal infections. *Pneumocystis carinii* pneumonia exhibits significant mortality in patients with Wegener's granulomatosis, polymyositis/dermatomyositis, and systemic lupus erythematosus [60]. There is currently no adequate data on the specific effect patterns of *corticosteroid* and *immunosuppressant* treatment on infection risk, and no data regarding the effect of prophylactic practices on morbidity and mortality. Nevertheless, a strategy aiming at minimizing the infectious risk of corticosteroid-treated patients based on the analysis of the literature has been proposed [59].

Life-threatening infectious diseases such as fulminant pneumonia with acute respiratory distress, severe tuberculosis and *Pneumocystis carinii* pneumonia have been reported in patients treated with *anti-TNF-α* therapy [61].

29.12 Teratogenic Risk

The major teratogenic drugs, i.e., isotretinoin, acitretin and thalidomide, are used in dermatology. The risk of major malformation is 20–25% with systemic retinoids, and about 30% with thalidomide. This high risk imposes strict conditions of prescription in women of childbearing age, including monitoring of β-hCG (before, during and 1 month after treatment) and prescription of effective contraception.

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Part V

Diagnostic Charts for the Skin Signs in the Acutely Ill Patient

Mechanisms of Pupura, Livedo, Necrosis

30

Jean-Claude Roujeau

Core Messages

- Purpura, livedo, necrosis, all result from vascular lesions
- The causes are multiple.
- The appearance of skin lesions depends on the type of vessels involved.

Purpura, livedo, skin necrosis, purpura fulminans… There are a lot of overlap and confusion between these terms. One reason is that the causes are often the same; another is a lack of clear clinical and pathological definitions. I propose a probably too simplistic but at least easy way to deal with these signs, based on the organization of blood circulation in the skin.

Purpura is hemorrhage within the skin, resulting sometimes from abnormal platelet functions and more often from lesions of capillary walls. Purpura can consist of small spots (petechiae) or in larger ecchymoses. Intra-cutaneous hemorrhage per se does not induce necrosis. The denomination of "purpura fulminans" is ambiguous, since most lesions consist actually of superficial necrosis.

Skin necrosis has several possible mechanisms.

It is most often the ultimate consequence of profound ischemia. It depends then on vessel occlusion, either of large vessels (deep necrosis) or of all, or nearly all, terminal capillaries irrigating the skin area involved (superficial necrosis). In such cases, both deep and superficial necroses should be considered as the visible expression of skin infarction. Infarction being hemorrhagic, areas of necrosis will look like purpura, but actually differ from petechiae by a larger size and from ecchymoses by the development of blisters or eschars. Vascular necrosis is usually associated with other manifestations of vessel involvement, purpura or livedo.

Skin necrosis can also result from direct toxicity on skin cells and proteins, including the vessels. Such cell destruction can be initiated by "external" (trauma, burns, etc….) or "internal" aggression (bacterial toxins, proteolytic enzymes released by neutrophils, eosinophils or macrophages…).

Livedo can be considered an equivalent for skin of angina pectoris for the heart: pre-necrotic ischemia. Ischemia will affect preferentially the periphery of the blood distribution system, hence its reticulate pattern. The cause of livedo can be vasoconstriction or obstruction of deep vessels.

Based on the schematic presentation of skin vasculature in the figure, one may expect the following correlation between the type of vessels involved and clinical expression (Fig. 30.1).

Involvement of terminal capillaries of the dermis can induce *purpura* when a few capillaries are inflamed (vasculitis), and *superficial necrosis* when all are obstructed in a delimited area (purpura fulminans, DIC, anticoagulant induced necrosis, monoclonal cryoglobulinemia). Capillary lesions, whatever their extent, are not expected to induce livedo or deep necrosis.

Involvement of medium-size arteries in the hypodermis can be compensated for in part by collateral

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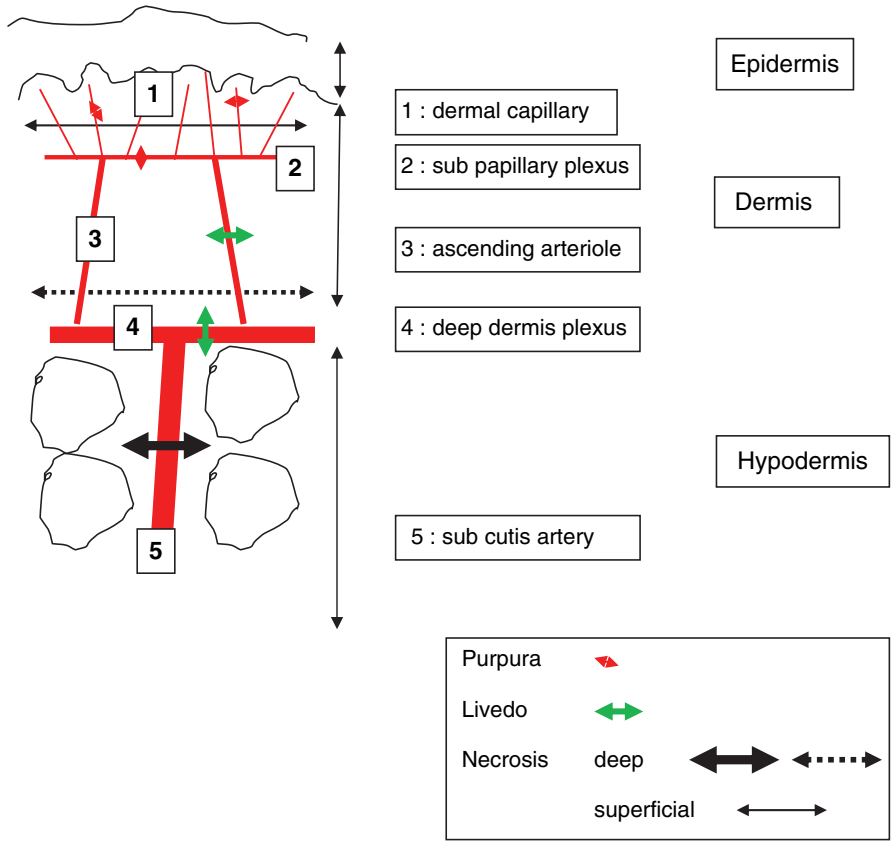

Fig. 30.1 Schematic presentation of skin vessels, and tentative correlation between site of lesions and presentation of signs such as purpura, livedo, and necrosis

circulation if a few vessels are involved. That will induce *livedo*. If too many arteries are involved, *deep necrosis* will occur. Purpura is not an expected feature, it can occur only in the causative process which also alters superficial capillaries at other sites. Livedo, with or without necrosis, is observed in *cutaneous* peri-arteritis nodosa, cholesterol crystals embolism, clot embolism, calciphylaxis, anti-phospholipid syndrome, intra-arterial injections (Nicolau), and shock.

Occlusion of deeper large arteries will result in deep necrosis. Livedo may be present at the periphery of necrosis, but not at a distance.

Necrosis of inflammatory origin is often hemorrhagic but not associated with livedo or distant purpura (pyoderma gangrenosum, ecthyma gangenosum…).

Skin Necrosis

31

Zuleika L. Bonilla-Martinez and Robert S. Kirsner

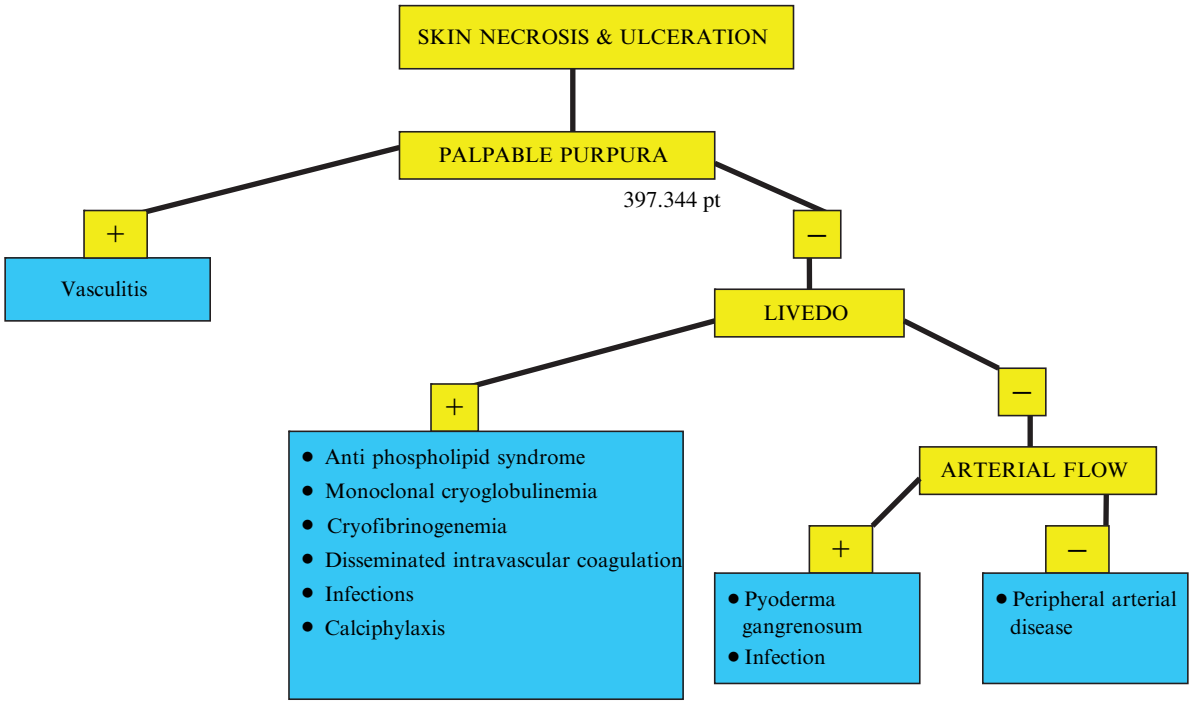

Fig. 31.1 Skin necrosis and ulceration

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Core Messages

- Skin necrosis is a clinical manifestation of tissue death, most commonly due to alteration of cutaneous blood flow.
- Tissue death may occur from blockage, destruction or physiologic constriction of vessels supplying the skin, in either large vessels (peripheral arterial disease) or small vessels (thrombi or emboli), causing ischemia.
- Vessel destruction may be direct as in vasculitis or indirect as in pyoderma gangrenosum.
- Cutaneous signs such as purpura and livedo can suggest both presence and type of blood-vessel damage.
- Vascular studies, biopsy and laboratory tests are important in rendering a diagnosis.

31.1 Introduction

Ischemia is the prominent mechanism in all cases of skin necrosis. Ischemia is defined as insufficient blood supply resulting in painful ulceration. When large vessels of the lower extremity are involved, classic symptoms range from intermittent claudication (pain when walking), and rest pain. Additionally, decreased or absent pedal pulses, cold skin, red and/or shiny skin, ulceration, wasting of calf muscles, and gangrene of the feet and toes may be present. Doppler ankle brachial index (ABI) measurements are useful as a tool to assess leg circulation. An ABI between 1.3 and 0.9 is normal, with worsening disease farther from 1.0 [1]. Arterial and venous Doppler studies also aid in excluding different conditions associated with ischemia.

A variety of conditions may lead to skin necrosis. The associated diagram will help differentiate among them (see Fig. 31.1). Some of these conditions are discussed in other chapters and are therefore only mentioned in this chapter. Burns and malignancies are beyond the scope of this chapter.

I. Congenital

A. Protein S and C deficiencies

- Proteins S and C are vitamin K-dependent proteins mainly produced in the liver. Although these inherited protein deficiencies are rare, their presence predisposes patients to venous thromboembolic effects. Patients with protein S deficiency may suffer their first thrombotic event at an early age, such as by age 25 [2]. Half of the patients who are heterozygote for protein C deficiency may suffer a thrombotic event by age 50 [3]. When functional, protein C is a cofactor to protein S, and both work together to have an anticoagulant effect by inhibiting the propagation of the coagulation cascade and subsequent thrombin formation. Protein S also directly inhibits the factor X clotting factor-activating and pro-thrombin-activating complexes.
- It is important to obtain a detailed patient history of any previous thrombotic events, and abnormal coagulation studies, as well as family history of thrombosis.
- Laboratory tests to confirm these conditions or distinguish them from other causes of thrombosis include: protein S antigen, functional protein test (clotting assays), protein C level, anti-thrombin level, factor V Leiden gene, and prothrombin G20210A gene. Also, assess the haemodynamic status by obtaining the following tests: prothrombin time (PT), partial prothrombin time (aPTT), fibrinogen level, and D-dimer.
- Conditions to be excluded: Factor V Leiden, prothrombin G20210A mutation, anti-thrombic deficiency, DIC, mesenteric venous thrombosis, warfarin use, cancer-related thrombosis, and homocystinemia.

II. Infections

A. *Vibrio vulnificus* infection

- *V. vulnificus*, a Gram-negative bacillus, has a high affinity for warm weather and contaminated sea water. Although rare, risk factors for this infection are patients with liver disease (especially iron overload) and immuno-compromised states which when present increase the likelihood of mortality as well.
- Acquired by either direct inoculation or parentally cutaneous involvement, conditions range from erythema to bullae (especially hemorrhagic) to ulcer formation that can rapidly develop into cellulitis and necrotizing fasciitis [4].
- The mechanism of infection is exposure to contaminated sea water, either through an open wound or ingestion of contaminated sea food (mainly raw oysters and shellfish). If ingested, the bacillus binds to the intestinal mucosa and rapidly spreads through

the blood [4]. Virulence factors associated with *V. vulnificus* infection include proteases, elastases and collagenases [5] as well as bradykinin, haemolysin, DNase, lecithinase, gelatinase and cytolysin [6–8].

- Helpful laboratory tests include: a complete blood count, a comprehensive metabolic panel, stool exam for ova and parasites, stool and blood cultures, Gram stain and culture of the bulla or ulcer, radiographic examination of the extremities with ulcer involvement,
- Conditions to be excluded: other bacterial and other Vibrio species infections, i.e., cholera, disseminated intravascular coagulation (DIC), and gas gangrene.

B. Ecthyma gangrenosum (EG)

- Although most commonly associated with systemic infection with *Pseudomonas aeruginosa* in immunocompromised patients, this rare cutaneous infection can also be caused by other Gram-negative bacteria (*Klebsiella pneumonia*, *Aeromonas hydrophila*, *Escherichia coli*), Gram-positive bacteria (*Staphylococcus aureus* and Streptococcus pyogenes), fungi (*Candida albicans*, *Mucormycosis*) and Herpes simplex virus among others.
- The characteristic cutaneous lesions start as erythematosus or hemorrhagic papules and vesicles that can rapidly evolve into a painless indurated ulcer with central necrosis with periulcer erythema.
- The bacteria invade the dermis and subcutaneous tissues through the blood supply, mainly veins, and multiply in the wall of small vessels [9].

The edema and necrosis further decrease blood supply to the involved tissues resulting in ischemic necrosis and necrotizing vasculitis.

- Helpful tests: Gram stain, skin biopsy for culture and histopathology, blood cultures, radiograph of the involved extremity.
- Conditions to be excluded: other causes of septicemia, necrotizing fasciitis and vasculitis, cryoglobulinemia

C. Necrotizing fasciitis (see Chap. 6)
D. Diabetic foot ulcers (see Chap. 6)

III. Inflammatory

A. Vasculitis
B. Vasculopathy

(1) Thrombotic

(a) Purpura fulminans or intra-vascular coagulation

- Systemic haematologic disorder characterized by both bleeding and coagulation of the microvasculature damage causing organ dysfunction.
- Involvement of the dermis and the subcutaneous tissue characterized by fibrin deposition in the small veins and post capillary venules, with hemorrhage and necrosis in the dermis and subcutaneous tissue [10].
- Usually affects adipose tissue; therefore, lesions are usually seen on the breasts, buttocks, thighs, and abdomen. Pain in the affected area is the initial symptom, followed by bullae, ulceration and skin necrosis. A clinical picture consistent with DIC, thrombocytopenia ($<100 \times 10^9 l^{-1}$, prolonged PT and aPTT, and presence of FDP/D-dimer is suggestive. The following laboratory tests are adjunctive when diagnosing: D-dimer test (greatest specificity), Prothrombin fragment 1 and 2 (abnormal in 90% of patients), anti-thrombin III, fibrin and fibrinogen degradation products (FDP is elevated in 90%), thrombin time (prolonged), prothrombin time and partial thromboplastin time (less reliable tests for diagnosis but elevated in 50–75% of patients), and platelet count (decreased). Patients with protein C or S deficiencies are at greatest risk.
- Conditions to be excluded: thrombotic thrombocytopenic purpura, haemolytic uremic syndrome, haemolysis, severe liver failure, idiopathic purpura fulminans, primary fibrinolysis, and vitamin K deficiency.

(b) Calciphylaxis

- Vasculopathy (vascular thrombi) characterized by excessive calcification in the skin and vessels, often a fatal complication of secondary hyperparathyroidism due to end-stage renal failure in the obese, women and diabetics.
- Calcium deposits in subcutaneous tissue and arterial calcifications obliterating small blood vessels and calcium concentrated in the media of vessel walls have been described on histopathology [11, 12].
- Skin lesions range from painful ulcers to multiple violaceous plaques, mainly on areas with thick adipose tissue such as the abdomen, breasts and thighs. The violaceous plaques may have features of livedo

reticularis [13] which constitute a vascular pattern. With time, these lesions usually progress to gangrenous plaques that ulcerate, leading to amputation [14]. Calf pain is often the first symptom. Painful myopathy secondary to ischemia and necrosis causes debilitating symptoms.

- Laboratory findings include high levels of parathyroid hormone (PTH), calcium, and phosphate. Radiological studies show calcium in the skin and soft tissue supporting the diagnosis.
- Conditions to be excluded: vasculitis, lupus, scleroderma, CREST syndrome, protein C and S deficiencies, cryoglobulinemia, DIC, cholesterol emboli, Henoch–Schonlein Purpura, homocysteinemia among others.

(c) Cryoglobulinemia type I

- Cryoglobulinemia type I, or primary cryoglobulinemia is a rare condition caused by increased concentrations of monoclonal immunoglobulins (Ig) [15]. IgM is the most common Ig involved, followed by IgG and IgA.
- Complement activation is induced by inflammation caused by the high concentration of immunoglobulin deposition, resulting in hyper-viscosity, or by direct destruction of blood vessels.
- Histologically, small, dilated vessels in the dermis with eosinophilic, diastase resistance PAS positive material and extra-vasation of erythrocytes are usually seen [16]. A mild perivascular lymphocytic infiltrate can also be seen. [17] Interestingly, similar histopathologic changes have been reported in skin biopsies of patients with a clinical picture of tick bites [18].
- Cutaneous involvement ranges from purpura to erythematous papules to ulcer formation [17].
- Ischemic necrosis usually follows ulcer formation.
- Although ulcers, typically located in the lower extremities, are common in all types of cryoglobulinemia, it has been reported that head, and oral or nasal mucosa lesions suggest type I cryoglobulinemia [17]. Other common cutaneous lesions include Raynaud's phenomena with ulceration and scarring of digits, hemorrhagic crusts, and post-inflammatory hyper-pigmentation.
- Laboratory workup should include: serum cryoglobulins (precipitation occurs within 24 h at a concentration of 5 mg ml^{-1} or higher, compared to other types of cryoglobulins which required up to a week to precipitate), complete blood cell count (leukocytosis is present in leukemia), urinalysis and (for concomitant renal disease) rheumatoid factor, chest radiograph, CT scan (to rule out malignancy), and angiography
- Conditions to be excluded: chronic lymphocytic leukemia (CLL), lymphoproliferative diseases (i.e., multiple myeloma), non-Hodgkin's lymphoma, and anti-phospholipid antibody syndrome (APS).

(d) Cryofibrinogenemia

- Cryofibrinogenemia, which may be primary or secondary to an underlying thrombotic, autoimmune disease or malignancy, is a rare disorder characterized by presence of a cold cryoprecipitate composed of fibrinogen, fibrin and fibronectin [19, 20].
- Alpha 1-antitrypsin and alpha 2-macroglobulin are protease inhibitors associated with the pathogenesis of cryofribinogenemia [20]. They directly inhibit plasmin and therefore fibrinolysis, which results in cryofibrinogen accumulation. The accumulated cryofibrinogen lead to occlusion of small and medium arteries by thrombi formation. Although underlying thrombosis is the dominant feature, vascular occlusion by cryofibrinogen deposition may also occur through hyper-viscosity, reflex vasospasm and vascular stasis [19, 20]. Zouboulis et al. [21] have also reported immunoglobulin and complement deposits associated with the pathogenesis.
- Histologically, small, dilated vessels in the dermis with eosinophilic globular PAS positive material and peri-vascular mononuclear infiltrate are seen. In contrast to mixed cryoglobulinemia, inflammatory or non-inflammatory purpura without vasculitis is seen [17, 22]. Necrosis of epidermis and dermis may also be seen.
- The skin is the most commonly affected organ, mainly in the lower extremities, tip of nose and ears. Cutaneous involvement ranges from purpura, livedo reticularis, painful ulcerations and Raynaud's phenomena to gangrene and skin necrosis upon cold exposure [17, 22, 23].
- Laboratory workup should include: serum cryofibrinogen (precipitation occurs between 24 and 72 h at cold temperatures 4°C, and redissolve upon warming at 378°C), serum cryoglobulins, serum 1-antitrypsin and 2-macroglobulin, skin biopsy, complete blood cell count, chest radiograph, angiography, and CT scan. Note: Cryofibrinogen precipitates in plasma

but not in serum, differentiating it from cryoglobulin which precipitates in both serum and plasma.
- Conditions to be excluded: cryoglobulinemia, purpura fulminans, protein C deficiency, thrombotic thrombocytopenic purpura, peripheral vascular disease, disseminated intravascular coagulation, vasculitis, hyper-coagulable states, cholesterol emboli, antiphospholipid antibody syndrome, and lymphoma.

(e) Antiphospholipid antibody syndrome (APS)

- Hyper-coagulable disorder characterized by recurrent venous or arterial thrombosis, thrombocytopenia and/or miscarriages, along with increased levels of anti-phospholipid antibodies [24, 25]. In contrast to primary APS, secondary APS is associated with autoimmune diseases, most commonly with systemic lupus anticoagulant (SLE) and rheumatoid arthritis. A higher prevalence has been observed in elderly patients with chronic diseases compared to healthy individuals [26].
- Cutaneous manifestations are very common in APS. Livedo reticularis and digital necrosis have been reported to be the most common dermatological manifestations [27]. Splinter hemorrhages, ulcer formation and superficial venous thrombosis are also common [28]. Although up to 50% of the patients present with cutaneous lesions [28], they are not part of the diagnostic criteria for APS [29, 30]. A definitive diagnosis is made following the revised Sapporo criteria.
- Conditions to be excluded: DIC, thrombotic thrombocytopenic purpura (TTP), hyper-coagulable states such as malignancy, Factor V Leiden mutation, protein C or S deficiencies, and hyperhomocysteinemia.

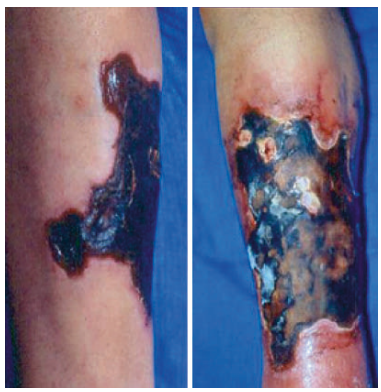

Fig. 31.2 Ischemic ulcer

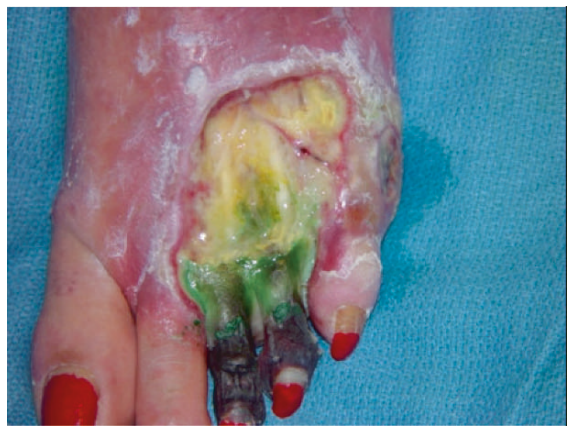

Fig. 31.3 Calciphylaxis

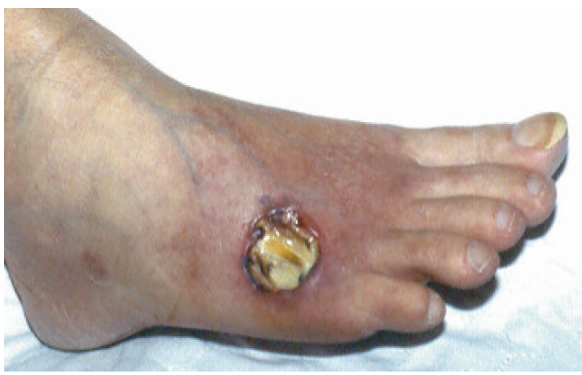

Fig. 31.4 Ulcerative pyoderma gangrenosum

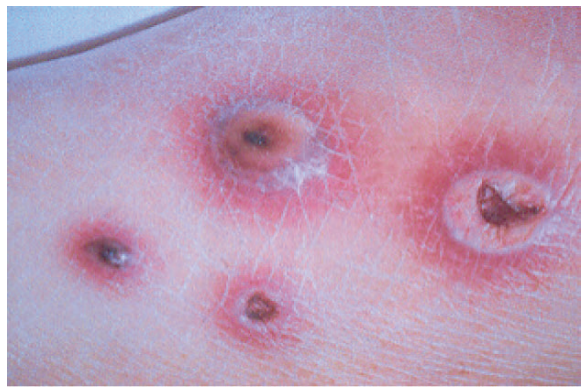

Fig. 31.5 Pustular pyoderma gangrenosum

(f) Purpura fulminans (see Chap. 5)
(g) TTP

(2) Embolic

(h) Cholesterol emboli (see Chap. 6—Livedo)

C. Pyoderma gangrenosum (PG)

- Rare inflammatory disease characterized by chronic cutaneous ulcerations usually affecting lower extremities.
- Five clinical types of PG (ulcerative, pustular, bullae, vegetative, and periostomal) exist, and are characterized by painful papules, nodules, pustules or superficial bulla resulting in enlarging ulcers (Figs. 31.4–31.5).
- Increased levels of IL-8 are part of pathogenesis. Histopathology shows edema and massive neutrophilic inflammation with undermining of the ulcer edges but the main utility of the biopsy is to exclude other diseases (e.g., atypical infections, vasculitis, vasculopathy and cancer) [31].
- PG is a diagnosis of exclusion. Excluding other causes is critical through biopsy for histology and tissue culture. The first symptom is usually pain out of proportion. The first sign is sudden red small bumps (nodules) appearing on the skin that progress into painful, irregularly shaped and violaceous ulcers with central necrosis and edematous borders. A history of Crohn's disease, ulcerative colitis, rheumatoid arthritis, and venous diseases are associated with PG.
- Conditions to be excluded: Sweet's syndrome, cutaneous vasculitis, hematologic malignancy, venous disease, and infections.

IV. Burns

A. Chemical
B. Thermal
C. Frostbites (see Chap. 4)

V. Malignancy

A. Solid tumors

(1) Squamous cell carcinoma
(2) Basal cell carcinoma

B. Lymphoreticular

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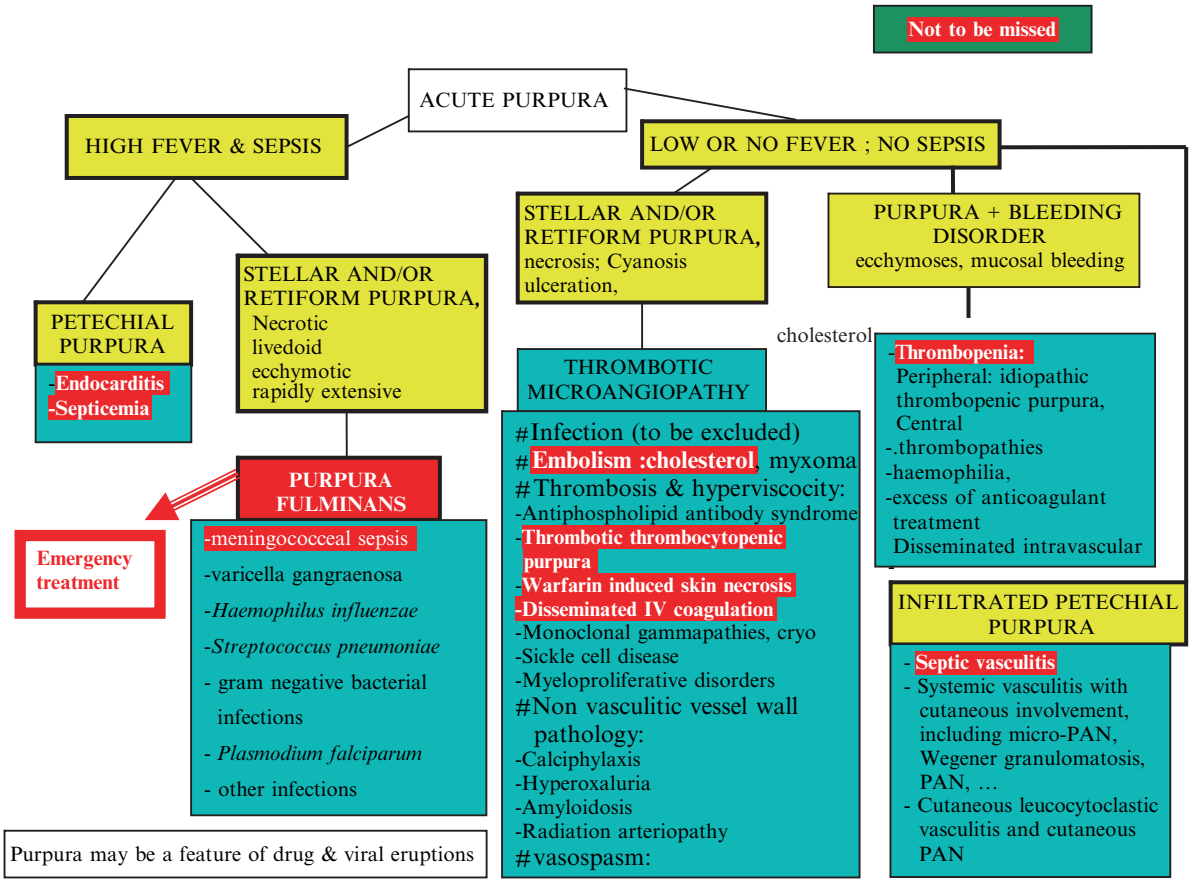
The Patient with Purpura in the ICU or in the Emergency Room

32

Dan Lipsker



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Core Messages

- A serious life-threatening infection, especially meningococcemia or endocarditis, should always be considered in acutely ill patients with purpura.
- A haematological work-up including platelet count, fibrinogen, plasma D-dimer levels, thrombin time and fibrin degradation products should be performed in patients presenting with purpura in the emergency room.
- Stellate and retiform (net-like arrangement) purpura must always raise concern, because they are indicative of an acute thrombotic purpura, of which purpura fulminans is one possible cause.

The goal in the acutely ill patient with purpura is not to miss a serious but curable infection or a haematological disorder.

A cutaneous haemorrhage is called purpura. It is a red spot that does not blanch with pressure. Depending on origin of purpura, the same process that provokes cutaneous bleeding might be responsible of bleeding in other organs.

Purpura can result from different mechanisms and four disease categories, with overlapping mechanisms, should be considered in patients with acute onset purpura:

- Serious infectious diseases, especially meningococcemia and endocarditis
- Haematological disorders, either involving primary haemostasis, as for example thrombopenia ($<20{,}000\,mm^{-3}$), or involving coagulation
- Thrombosis involving microcirculation, as for example in the catastrophic anti-phospholipid antibody syndrome
- Vasculitis, an inflammatory disease involving vessel walls

Some clinical findings are suggestive of a mechanism:

- A bleeding diathesis with widespread purpura and ecchymoses and/or mucosal bleeding suggests an haematological disorder involving primary haemostasis.
- Stellate purpura and/or retiform purpura (a purpuric livedo), with associated findings like cyanosis, blue toes, ulceration, necrosis are suggestive of acute thrombotic microangiopathy; if rapidly extensive and associated with signs of sepsis, it is a purpura fulminans.
- Fever, hypotension, heart murmur, confusion should always raise suspicion of a serious infection.
- Infiltrated, palpable purpura, located mainly on the lower limbs, is indicative of vasculitis.

Disseminated intravascular coagulation exemplifies the overlapping nature of the disease categories, as it can complicate serious infections or haematological disorders and it can be the main mechanism involved in thrombotic micro-angiopathy. Bacterial sepsis can result in both thrombotic micro-angiopathy and palpable purpura of (septic) vasculitis.

When signs of infection are present, haemocultures and CSF cultures should be performed and antibiotic treatment must be immediately started. A complete blood count and an exploration of haemostasis should be performed in all purpuric patients. Coagulation and haemostasis work-up should at least include: platelet count, fibrinogen, plasma D-dimer levels, thrombin time and fibrin degradation products.

Some clues:

Purpura in a patient with signs of infection, especially when the purpura is stellar, size >3 mm, livedoid, necrotic or rapidly extensive, should always be considered as purpura fulminans, and the patient should be referred immediately to an intensive care unit or a reanimation unit, after administration of ceftriaxone ($50\,mg\,kg^{-1}$ in children or 2 g in adults). At a very early stage, elementary lesions are small (less than 1 or 2 mm) irregular macules, some of which are centred by a petechia. The irregularity of the macule is the key to diagnosis. However, small purpuric (petechial, <2 mm) eruptions are frequent in febrile children, especially during entero- and adenoviral infections. Thus, the constellation "fever, petechial eruption and meningeal irritation" is not uncommon in the child infected with neurotropic echovirus. When petechiae are located exclusively in the upper body part, the face, the neck or the upper trunk, they are usually the result of elevated pressure in vena cava superior territory related to coughing or vomiting, and they do not reflect a disorder of haemostasis. Multiple petechiae and palpable purpura involving only the extremities and sometimes the buttocks is the hallmark of the papulopurpuric gloves and socks syndrome which is a paraviral eruption, the commonest causes of which are parvovirus B19 infection in adults and Epstein–Barr virus infection

in children. When only a small number of petechiae are acrally located, especially when associated with pustules on an erythematous and/or purpuric base, septicaemia (*Neisseria gonorrhoeae*) and endocarditis should be considered.

Petechiae involving skin and mucosa (conjunctivae, oral mucosa) are indeed also a common finding in patients with infective endocarditis, and this diagnosis should be suspected in each patient with fever and a heart murmur.

In patients with a recent travel history to the tropics, malaria must always be excluded. Other infectious diseases that need to be considered in these patients are haemorrhagic fevers, especially dengue, and rickettsial infection, mainly African tick-bite fever. Some rickettsial infections, like Rocky Mountain spotted fever are endemic in North America, and others like "fièvre boutonneuse" in Europe.

32.1 Acute Onset Purpura, ill Patient

I. *Signs suggestive of infection*: *fever, precessive flu-like illness, heart murmur, hypotension, headaches, photophobia, etc. Work-up including blood and urine cultures for bacteria and fungus, lumbar puncture for CSF culture, and, depending on context, transoesophageal echocardiography… → ICU. Immediate antibiotic treatment*.

   a. Stellar, necrotic, livedoid and ecchymotic rapidly extensive purpura: purpura fulminans

      (1) Invasive meningococceal sepsis
      (2) Post-varicella (varicella gangraenosa)
      (3) Other: *Haemophilus influenzae*, *Streptococcus pneumoniae*, Gram-negative bacterial infections, *Plasmodium falciparum*, other infections
      (4) Idiopathic

   b. Petechial purpura
      (1) Infective endocarditis
      (2) Other infections

II. *Signs suggestive of bleeding diathesis: ecchymoses, mucosal bleeding, known haematological disorder*.

   a. Peripheral thrombopenia, including idiopathic thrombopenic purpura, and thrombopathies
   b. Central thrombopenia (numerous causes)
   c. Other: haemophilia, excess of anticoagulant treatment, disseminated intravascular coagu-lation…

III. *Signs suggestive of thrombotic microangiopathy: cyanosis, ulceration, stellar and/or retiform purpura, necrosis… Again, infection should be excluded*.

   a. Exclude infection
   b. Embolism

      (1) Cholesterol embolus
      (2) Atrial myxoma
      (3) Other: cancer-associated

   c. Thrombosis and hyper-viscocity
      (1) Antiphospholipid antibody syndrome
      (2) Thrombotic thrombocytopenic purpura
      (3) Warfarin (coumadin)-induced skin necrosis
      (4) Disseminated intravascular coagulation
      (5) Monoclonal gammapathies, cryoglobulins, cryofibrigenemia
      (6) Sickle cell disease
      (7) Myeloproliferative disorders
      (8) Homozygous protein C or protein S deficiency (neonates)

   d. Non-vasculitic vessel wall pathology

      (1) Calciphylaxis
      (2) Hyperoxaluria
      (3) Amyloidosis
      (4) Radiation arteriopathy

   e. Vasospasm
      (1) Ergot derivatives
      (2) Methysergide
      (3) Cocaine

   f. Other

IV. *Infiltrated purpura: vasculitis. Cutaneous biopsy, ANCA. Refer to specialist*.

   a. Always exclude septic vasculitis
   b. Systemic vasculitis with cutaneous involvement, including micro-PAN, Wegener granulomatosis, PAN, …
   c. Cutaneous leucocytoclastic vasculitis and cutaneous PAN

32.2 Stable Patient, Progressive Purpura

Eliminate haematological disorder and refer to specialists.
Numerous causes, among which:

– Pigmented and purpuric dermatosis
– Mycosis fungoides
– Scurvy

- Solar/senile purpura
- Traumatic purpura*
- Purpuric arthropod assault*
- Purpuric drug eruptions*
- Purpuric viral exanthemas*
- Venous insufficiency/stasis dermatitis
- Amyloidosis
- Histiocytosis
- Cutaneous involvement in myelodysplasic disorders, haemorrhagic metastasis of melanoma…
- Gardner–Diamond syndrome
- Ehlers–Danlos syndrome (haemorrhagic variant)
- Purpuric variants of numerous dermatosis: pityriasis lichenoides, pyoderma gangrenosum, granuloma annulare…

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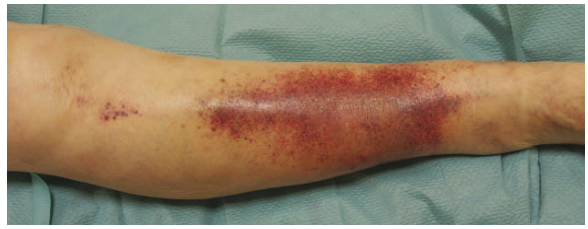


Fig. 32.3 Corresponds to situation A.II: purpura in a thrombopenic patient

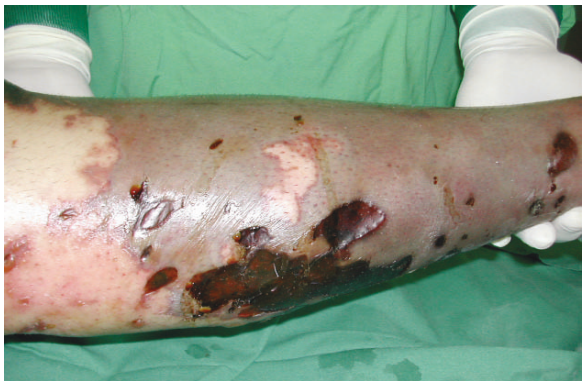


Fig. 32.1 Corresponds to situation A.I.a: idiopathic purpura fulminans in a 17-year-old girl

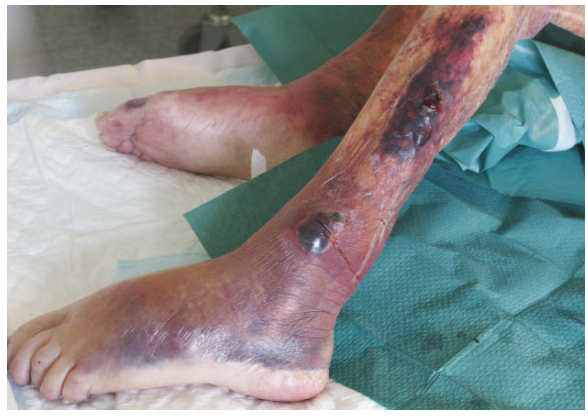


Fig. 32.4 Corresponds to situation A.II.c: bleeding with extensive purpura related to excessive anticoagulant therapy

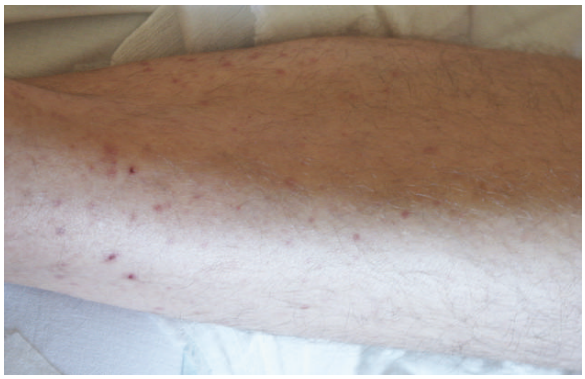


Fig. 32.2 Corresponds to situation A.I.b.i: petechiae in a patient with subacute endocarditis related to *Streptococcus oralis*

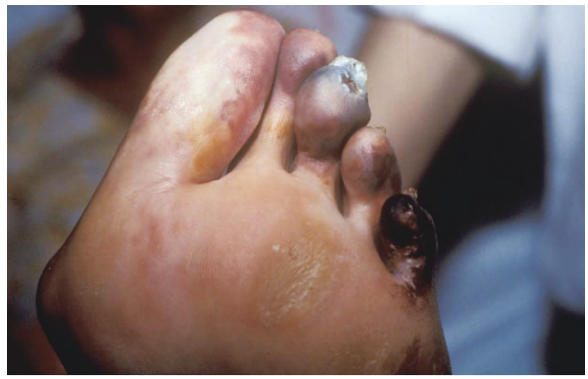


Fig. 32.5 Corresponds to A.III.b.i: acral cyanonis with necrotic purpura in a patient with cholesterol embolus

* acute onset purpura in a patient who does not appear ill

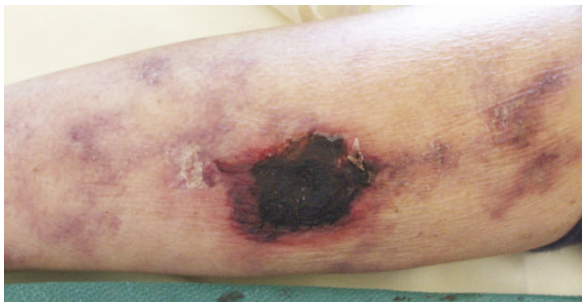


Fig. 32.6 Corresponds to A.III.d.i: necrotic retiform purpura in a patient with caciphylaxis

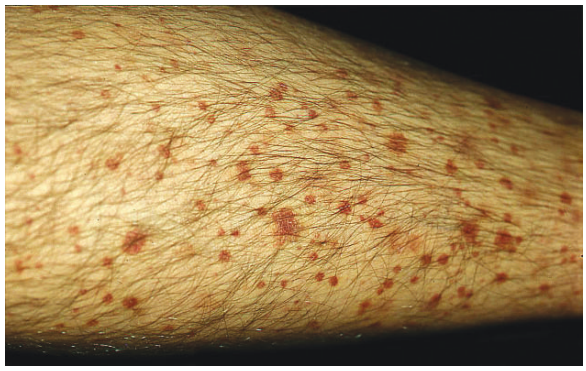


Fig. 32.7 Corresponds to A.IV: palpable purpura involving the lower limbs in patient with leucocytoclastic vasculitis

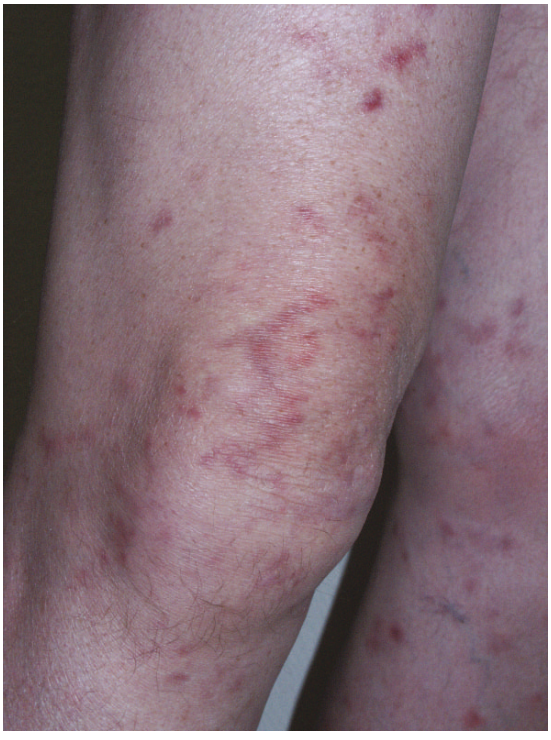


Fig. 32.8 Corresponds to A.IV.b: infiltrated livedo with purpuric nodules in a patient with panarteritis nodosa

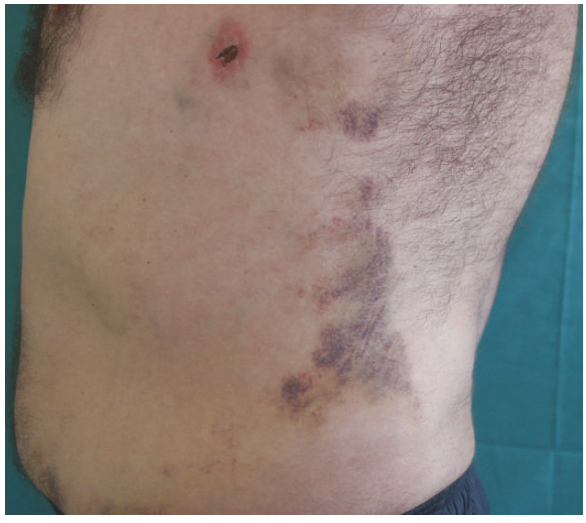
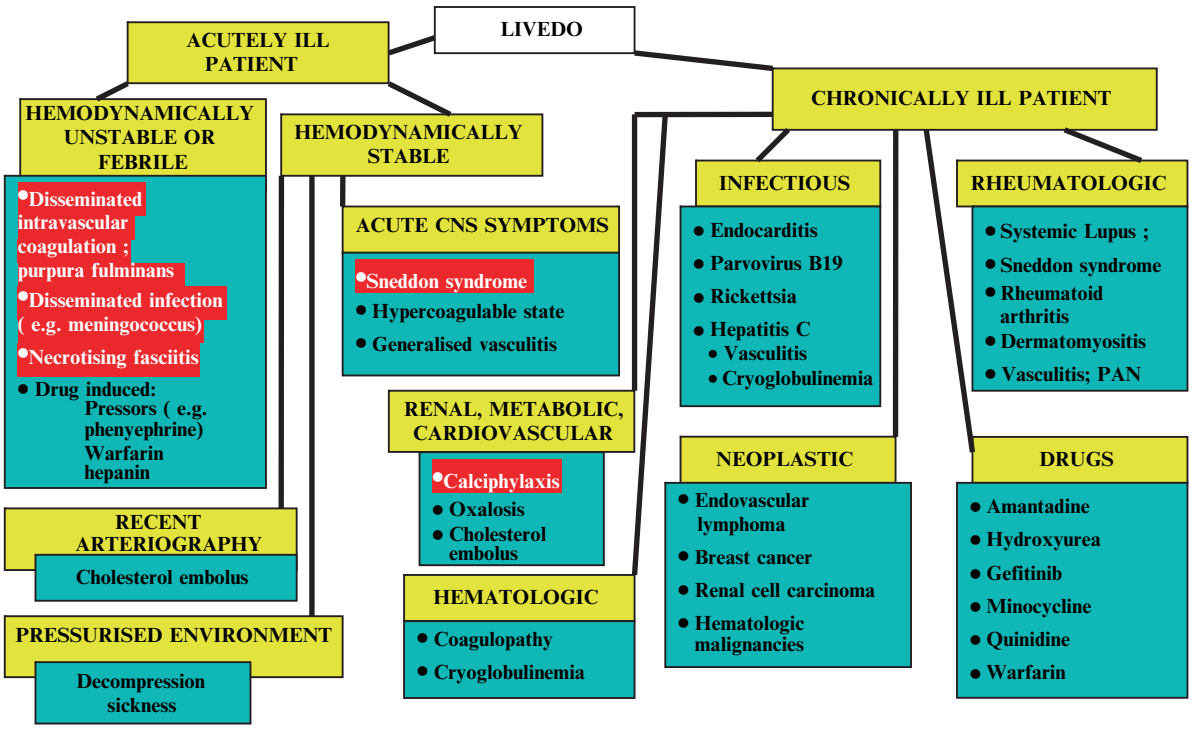


Fig. 32.9 Corresponds to B. …traumatic purpura: ecchymoses in patient who fell from a chair

Livedo

33

Julia S. Lehman, Arlo J. Miller, Megha M. Tollefson, and Lawrence E. Gibson



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Core Messages

- Livedo is a cutaneous sign characterised by violaceous patches and plaques in a reticulated configuration.
- Many acute, potentially life-threatening conditions may lead to livedo.
- In evaluation of the acutely ill patient with livedo, one must consider disseminated infection, disseminated intravascular coagulation, and medication effect.
- Many chronic conditions may contribute to livedo. A thorough history and physical examination are required to identify the etiology of livedo in the chronically ill patient who is haemodynamically stable.
- In well-appearing patients in whom other causes of livedo have been excluded, one may consider physiologic, idiopathic, or primary livedo in the diagnosis.
- Erythema ab igne, a condition that may mimic livedo, is diagnosed after obtaining a history of prolonged heat exposure at the involved area.

33.1 Diagnosis of Livedo

In distinguishing potentially life-threatening causes of livedo, the first question to be asked is, "Is the patient acutely ill?" If the answer is "yes", then several clinical clues can direct the provider to the underlying etiology of livedo (Fig. 33.1):

- *Fever and haemodynamic instability:* Consider serious infection, including sepsis from any cause, meningococcus, and pneumococcal sepsis [1, 2]. Disruption of coagulation parameters may implicate disseminated intravascular coagulation or purpura fulminans. Rapidly progressive livedo-like lesions with exquisite pain out of proportion to physical findings may herald the presence of necrotizing fasciitis.
- *Acute central nervous system symptoms:* Sneddon's syndrome is characterised by multiple cerebral vascular accidents and livedo, and has been associated with the lupus anticoagulant [3]. Other hyper-coagulability states or vasculitis could lead to concomitant CNS and skin ischemia [4–7].
- *Recent exposure to pressurised environment:* Several cases of livedo in association with decompression sickness have been reported [1, 8]. Index of suspicion for this rare but potentially serious condition should be high in patients with the appropriate history, as symptoms may develop several days following exposure.
- *Recent arteriography:* Instrumentation of the peripheral vasculature in patients with atherosclerotic disease can dislodge plaque material, leading to ischemia of the superficial blood vessels and the appearance of livedo [1].
- *Medications:* Pressors (e.g., phenylephrine), warfarin, heparin, thrombolytics, gefitinib, and hydroxyurea may contribute to livedo [9–14].
- Once the acute, potentially life-threatening conditions are excluded, one should then consider the patient's underlying *chronic illnesses* as a potential source of livedo [15] (Fig. 33.2). Some entities associated with chronic disease, such as calciphylaxis in the patient with end-stage kidney disease [1, 12, 16], also may be life- or limb-threatening.

In the well-appearing patient, the most likely diagnoses are primary, idiopathic, or physiologic livedo, or erythema ab igne [1] (Fig. 33.3).

The clinical appearance of livedo from various etiologies may be similar (Fig. 33.4), so a careful and complete patient assessment is required.

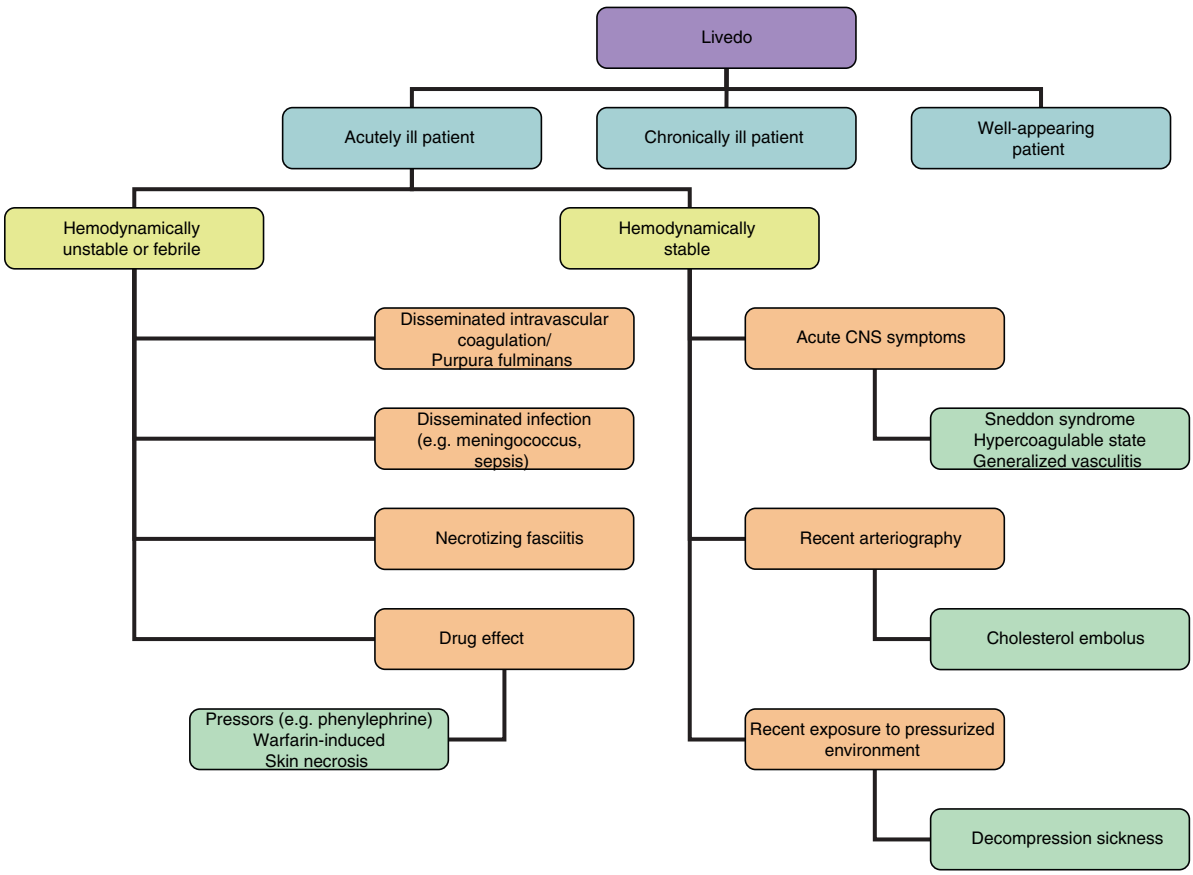

Fig. 33.1 Diagnostic approach to patients with livedo who are acutely ill

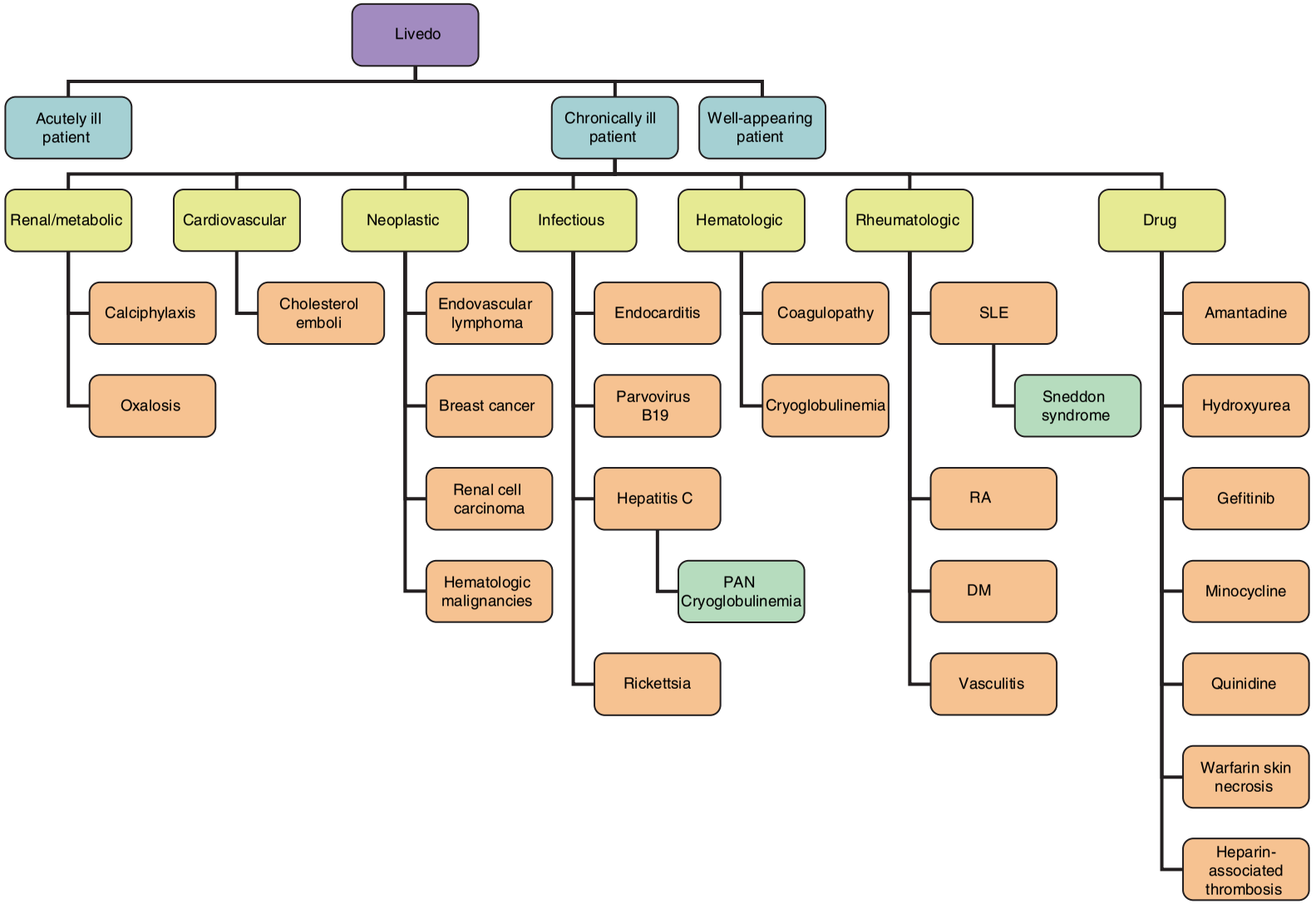

Fig. 33.2 Diagnostic approach to the patient with livedo who may have an underlying chronic illness, SLE = systemic lupus erythematosus; RA = rheumatoid arthnitis; DM = dermatomyositiz; PAN = polyartenitiz nodosa

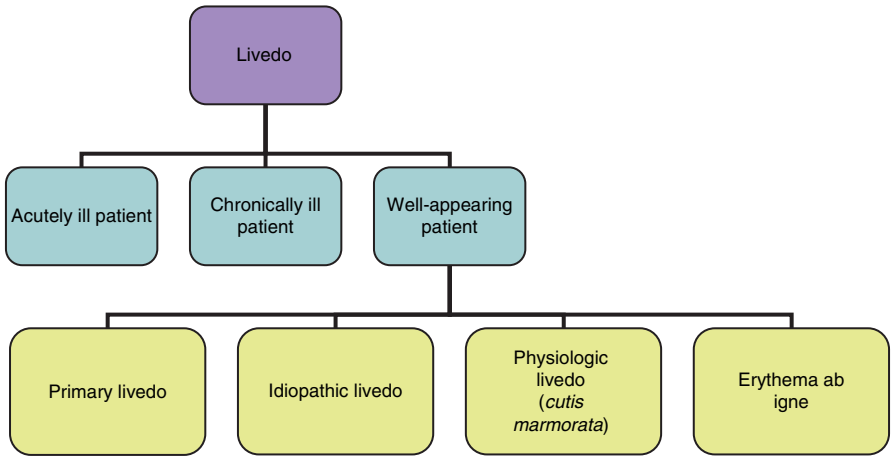

Fig. 33.3 Diagnosis to consider in well-appearing patients with livedo, since other causes are excluded

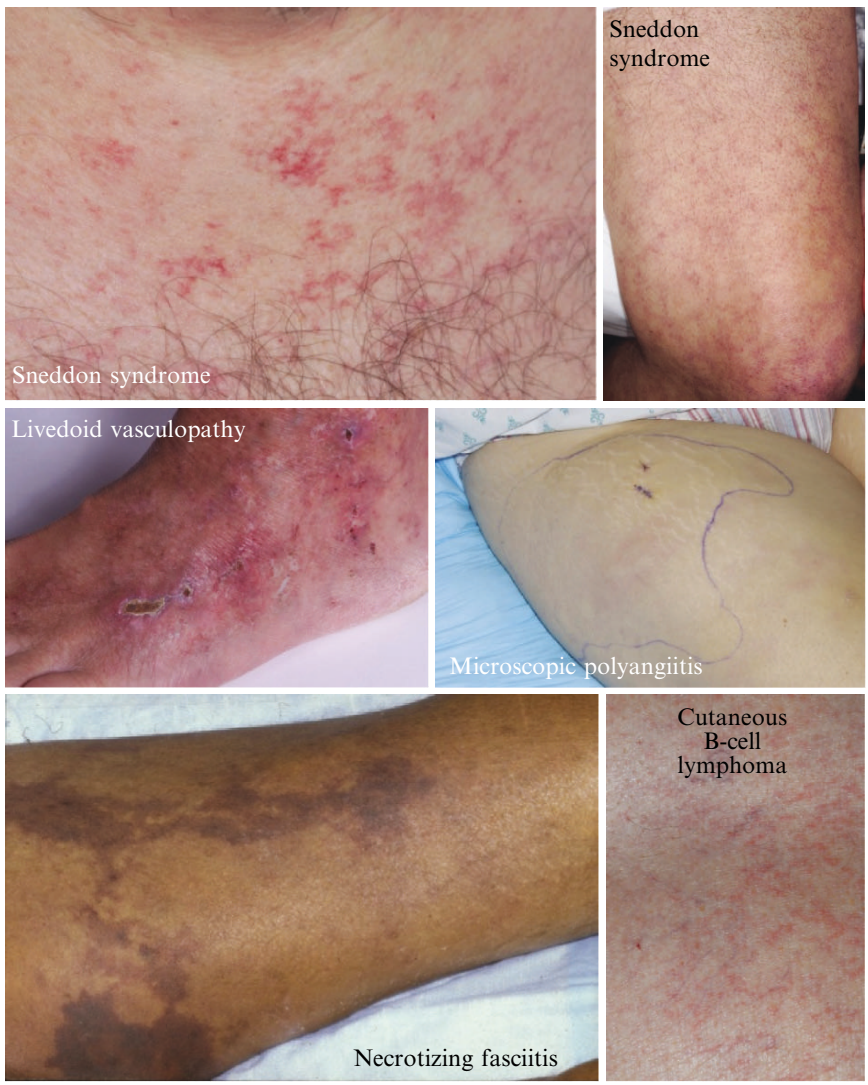

Fig. 33.4 Livedo reticularis. Note that livedo is a non-specific sign that may accompany many underlying conditions. PAN = polyasteritis nodosa

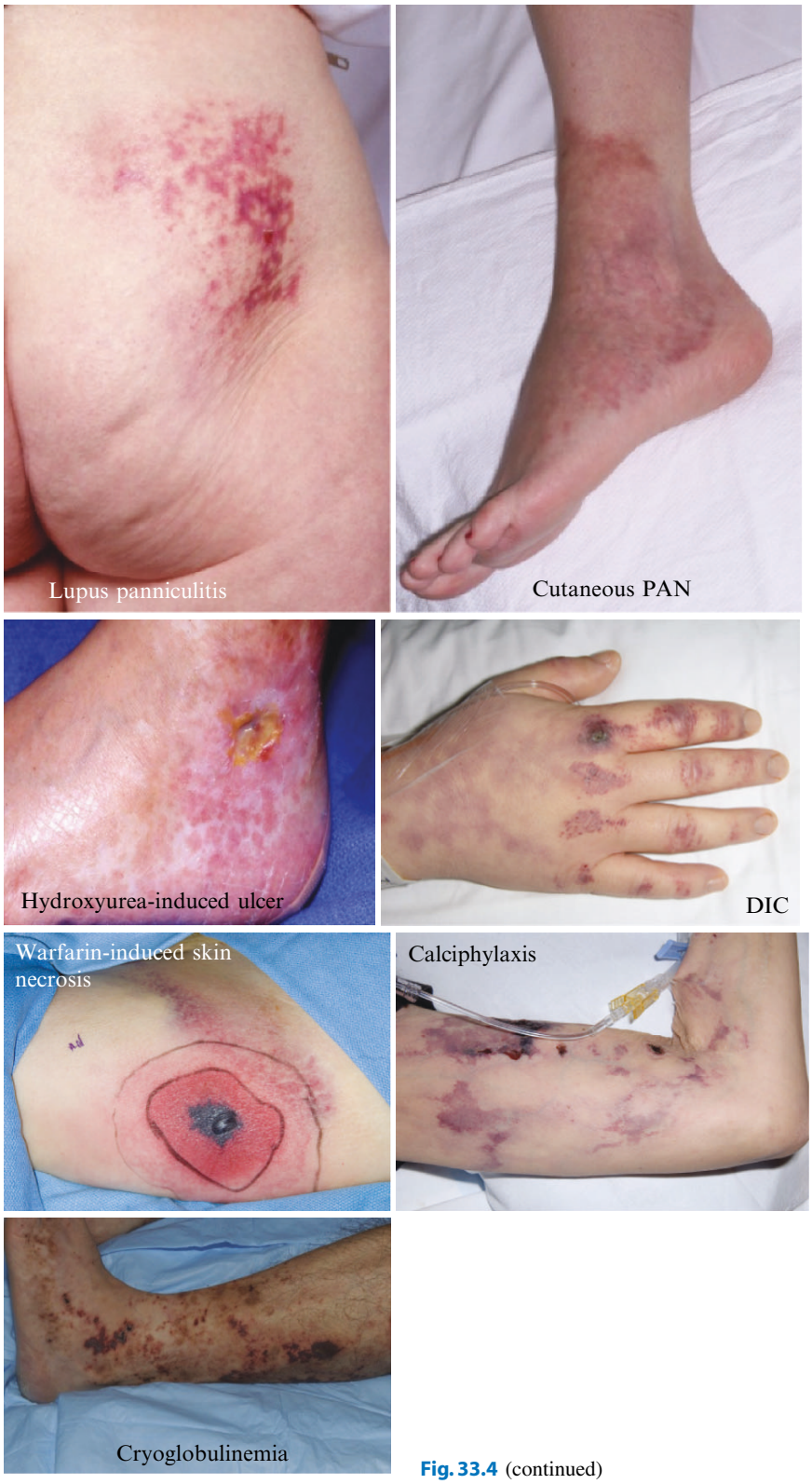

Fig. 33.4 (continued)

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Diagnosis of Blisters and Vesicles

34

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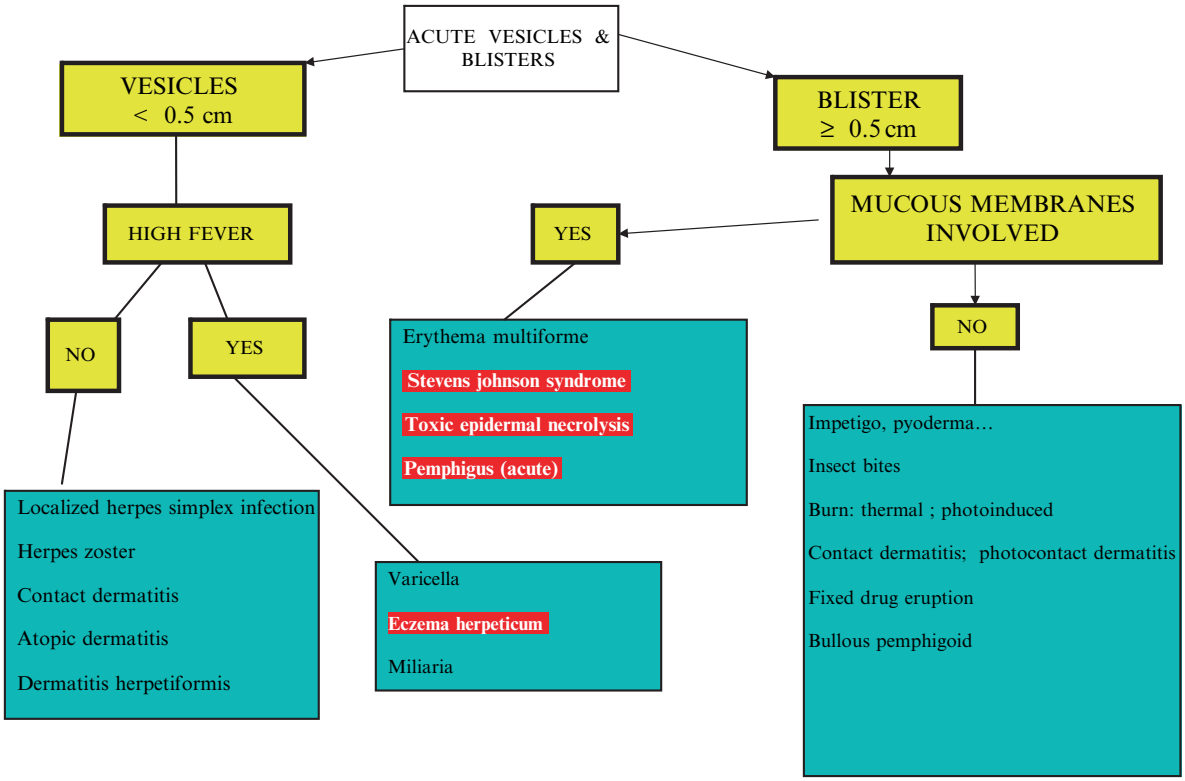

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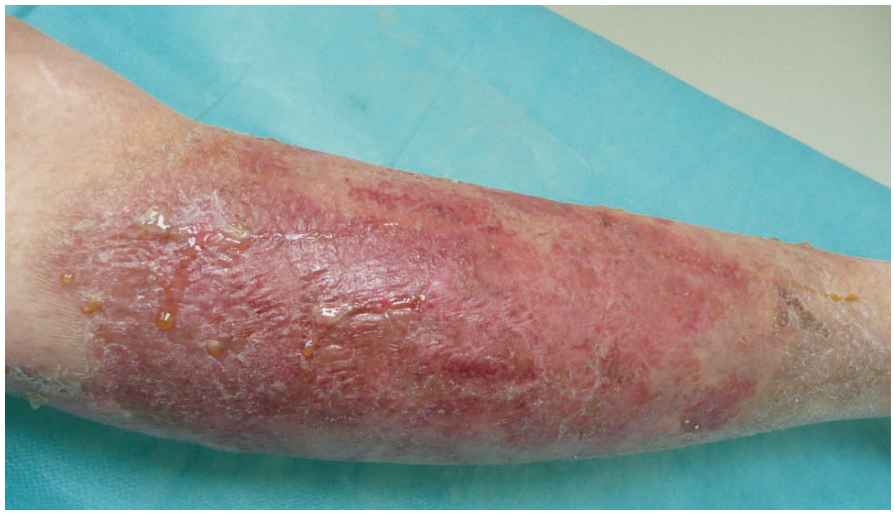

Fig. 34.1 Contact dermatitis characterized by confluent vesicles

Vesicles and/or bullous lesions can be associated with potentially life-threatening dermatosis including severe cutaneous adverse drug reactions, infections, etc. Blisters and vesicles are features of numerous skin diseases [1]. Their clinical features as well as accompanying signs help to ascertain the final diagnosis. Exam of the total body surface area including the five mucous membranes is mandatory.

- High *Fever* is frequent in infectious diseases: smallpox, eczema herpeticum…However, high fever and/or "pseudo influenza syndrome" is usually present in other dermatoses such as epidermal necrolysis, multiforme erythema…
- *Vesicles*, a feature of contact (Fig. 34.1) and atopic dermatitis, are also present in viral infections (herpes virus…). Umbilicated and diffuse vesicles are seen in varicella. Viral vesicles are frequently well-circumscribed and recurrent (herpes simplex) or metameric (herpes zoster) (Fig. 34.2).

Miliaria crystallina is characterized by subcorneal or intracorneal vesicles that are centered by the acrosyringium. It resolves without any treatment, and can be prevented by avoidance of overheating and overswaddling. It is mainly observed on the back and the neck and may be mistaken for infectious or other febrile vesicles [2].

- *Mucous membrane involvement* is an important clue:

Mucous membrane erosions are frequently observed in auto-immune bullous diseases, mainly pemphigus. The presence of acantholytic cells on Tzanck cytodiagnostic makes it possible to rapidly confirm the diagnosis. Mucous membrane lesions may also be observed associated with other auto-immune bullous diseases (Fig. 34.3).

Involvement of at least two mucous membranes associated with atypical targets such as cutaneous lesions are features of toxic epidermal necrolysis (TEN) (Fig. 34.4). The association with typical target lesions on acral location is more suggestive of erythema multiforme [3].

- *Pruritus* is suggestive of eczematous reaction, but also of auto-immune bullous dermatosis including dermatitis herpetiformis and bullous pemphigoid.
- *Pain* is a feature of herpes zoster, but is also observed in other conditions such as toxic epidermal necrolysis and erythema multiforme.
- *Recent intake of a "new" drug* (new for this particular patient) within the last 4 weeks is indicative of drug reaction, e.g., toxic epidermal necrolysis. The appearance of isolated bullous cutaneous lesions within 48 h after drug intake is a hallmark of fixed drug eruption. Local viral sampling, cutaneous biopsy with immunofluorescent stainig are the basic investigations to be performed.

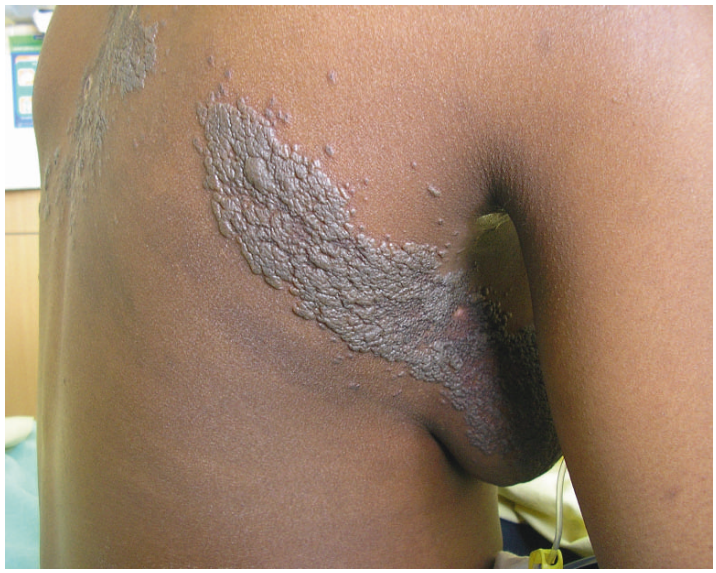

Fig. 34.2 Intercostal herpes zoster

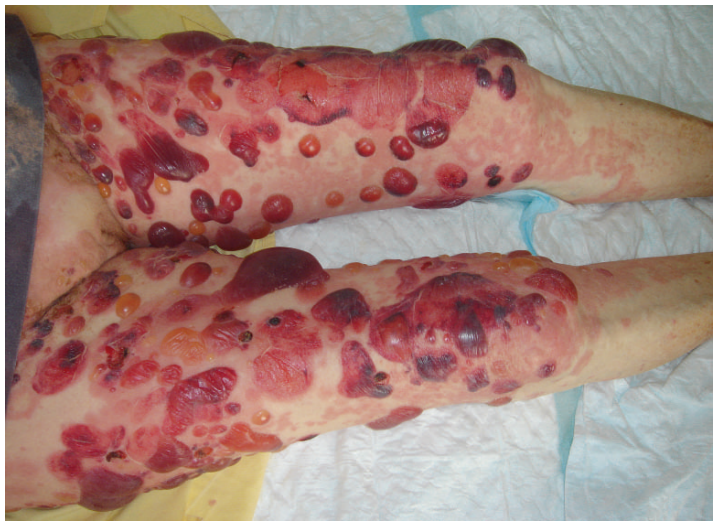

Fig. 34.3 Bullous pemphigoid

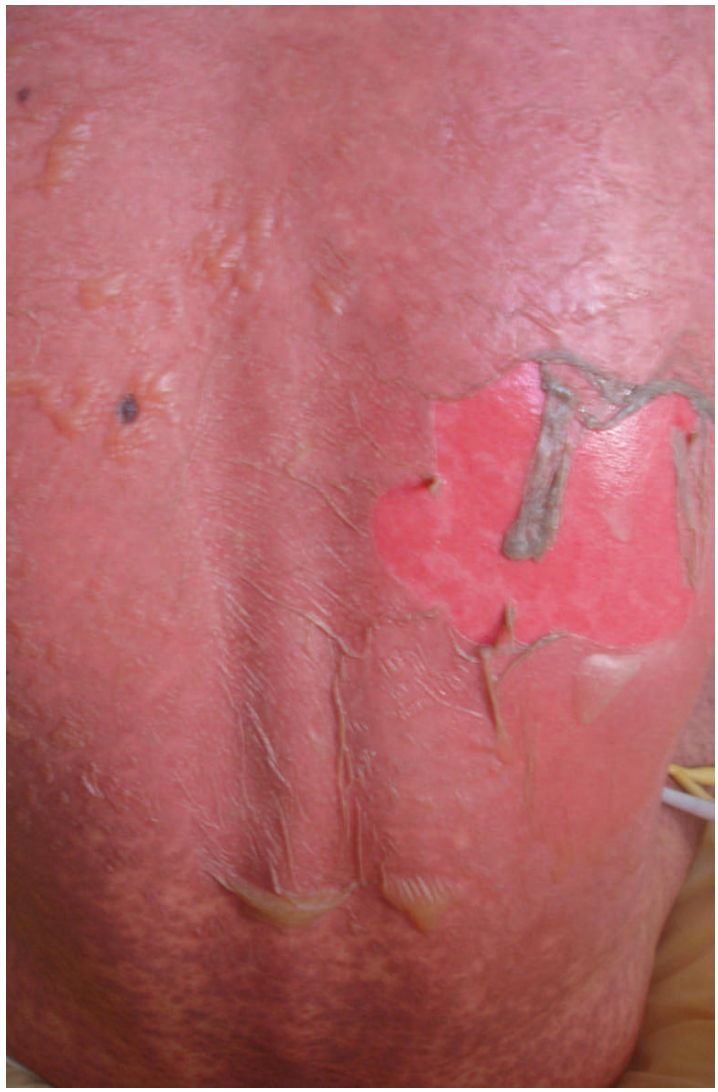

Fig. 34.4 Toxic epidermal necrolysis characterized by full-thickness epidermal necrosis leading to skin detachment on the trunk

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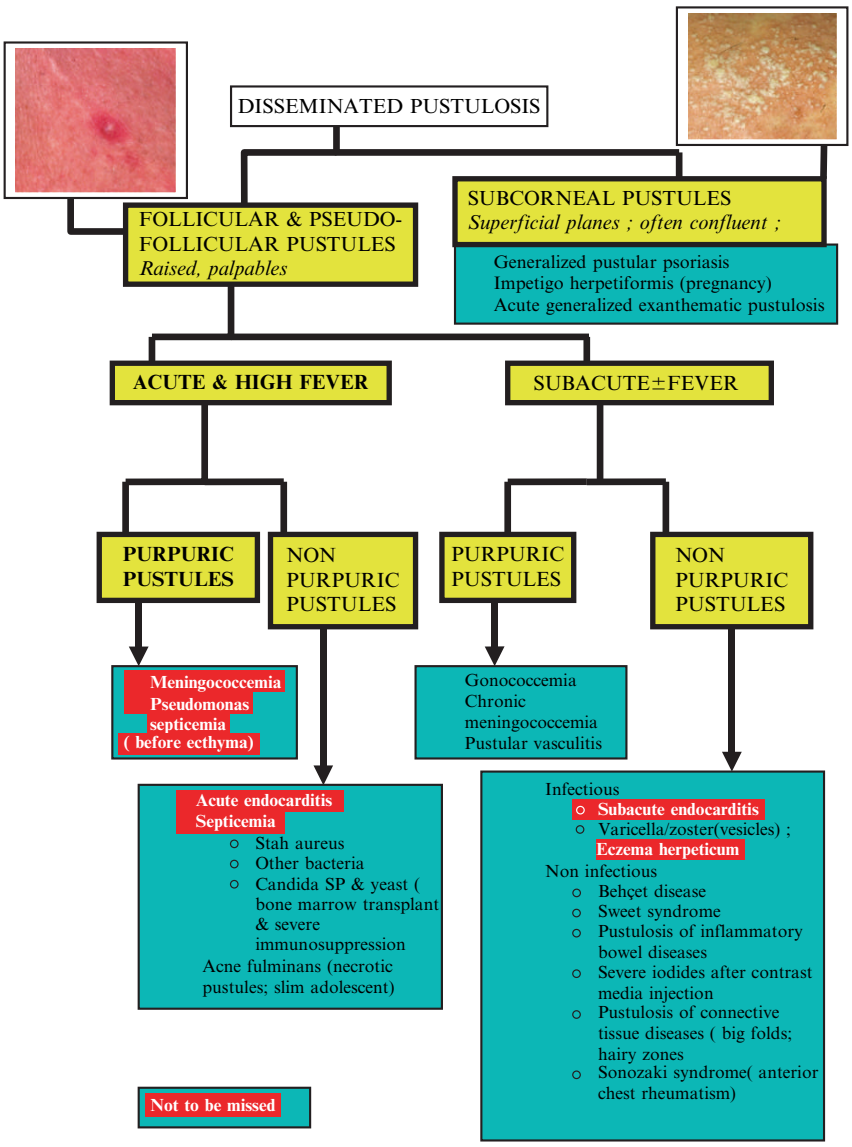
Diagnosis of Disseminated Pustulosis

35

Jean Revuz



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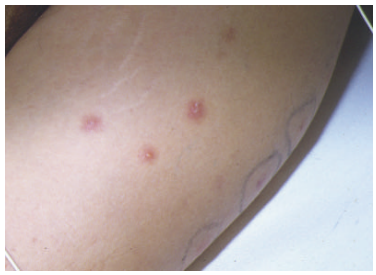
The main questions are: "Is it infectious?" and "Is there a life saving procedure to be implemented within hours?" Several clues exist to solve these questions:

- *Fever* is important but may not always be a sign of sepsis: acne fulminans, systemic vasculitis, pustular psoriasis.
- *Systemic signs*; a severe impairment of vital signs will narrow the diagnostic hypothesis, and at first focus on acute severe systemic infections.
- *Clinical features of the pustules*: subcorneal, superficial (milky, confluent) pustules are non-infectious as a rule; purpuric pustules raise the alarm for potentially rapidly lethal infection (meningococcemia); raised palpable pustules, whether follicular or not, open a wide range of possible diagnosis.
- *Topography*: "disseminated" means that pustules are not confined to a particular area, e.g., palms and soles, but may be situated in every part of the body, even if they are few. Yet some diseases may have a preferential topography, e.g., big folds for acute generalized exanthematic pustulosis (AGEP).
- The local bacteriological sampling may be helpful when performed on closed lesions during septicemias when blood cultures are negative; on open lesions, such sampling may be valid if the bacteria does not belong to the cutaneous flora.

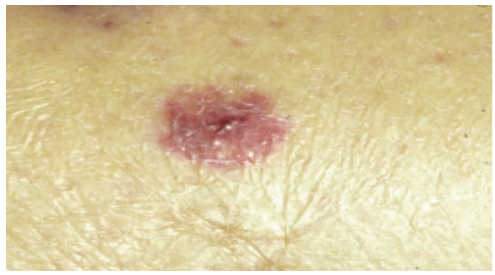
Two stages in the recognition of the pustules:

  - Blisters or vesicles: the liquid sooner or later becomes filled with polymorphonuclears (even in the absence of superinfection) and thus looks like a pustule. This happens early for herpetic vesicles.
  - Short-lived, labile pustules. The subcorneal, superficial non-follicular pustules may be extremely short-lived, especially in the case of AGEP, and the diagnosis must sometimes rely on "remnants", i.e., superficial desquamation mimicking exfoliative dermatitis.

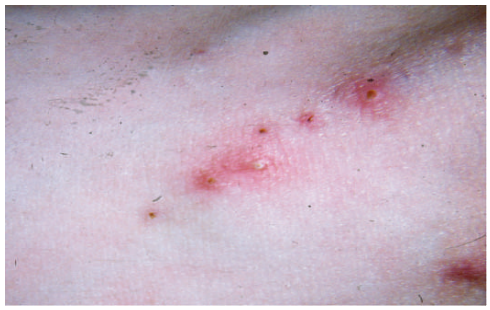
The diagnostic algorithm in the figure doesn't cover children or regional forms of pustulosis (Fig. 35.1).



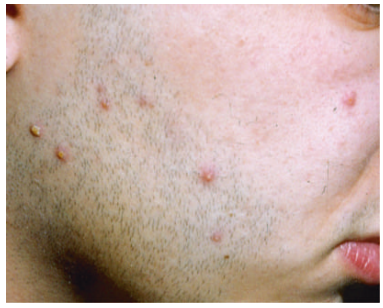
Staph aureus septicemia



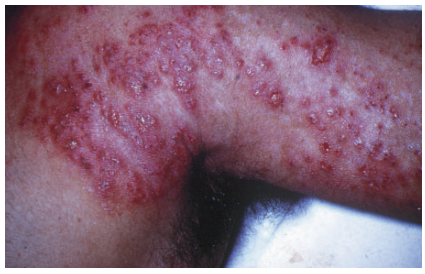
meningococcemia



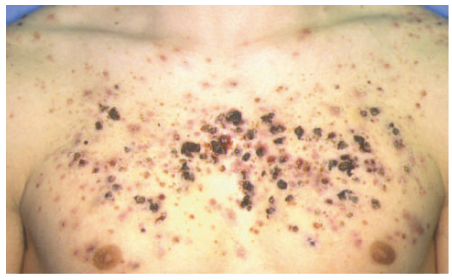
Behçet disease



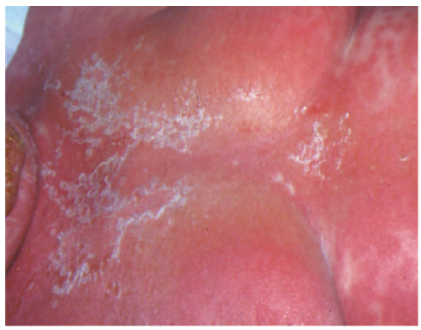
Candida septicemia



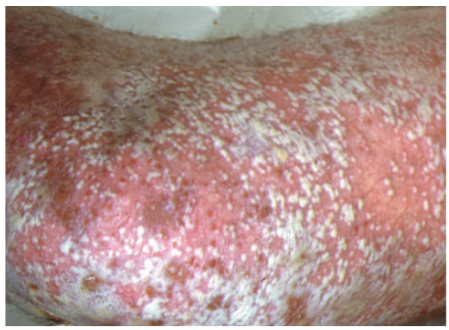
Kaposi - Juliusberg



Acne fulminans



AGEP



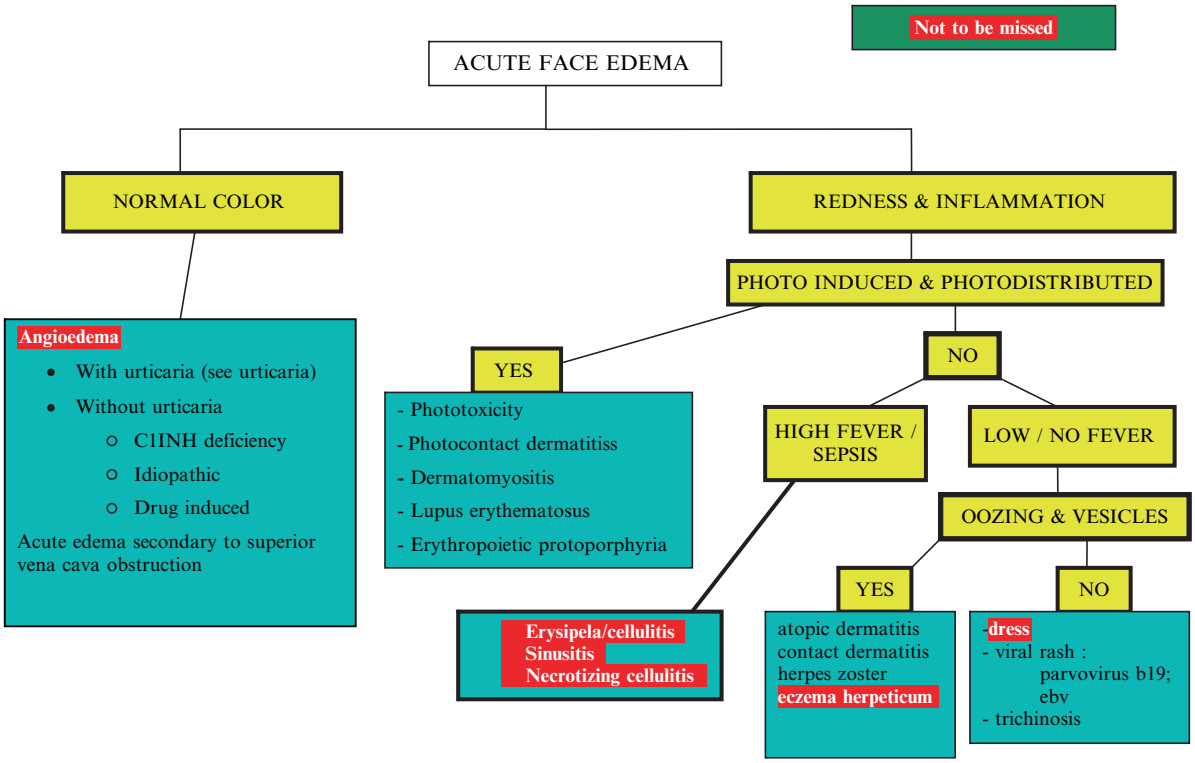
Pustular psoriasis

Fig. 35.1

Diagnosis of Face Oedema

36

Marion Gabillot-Carré



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Face oedema can be life-threatening in the case of oropharynx mucosal involvement.

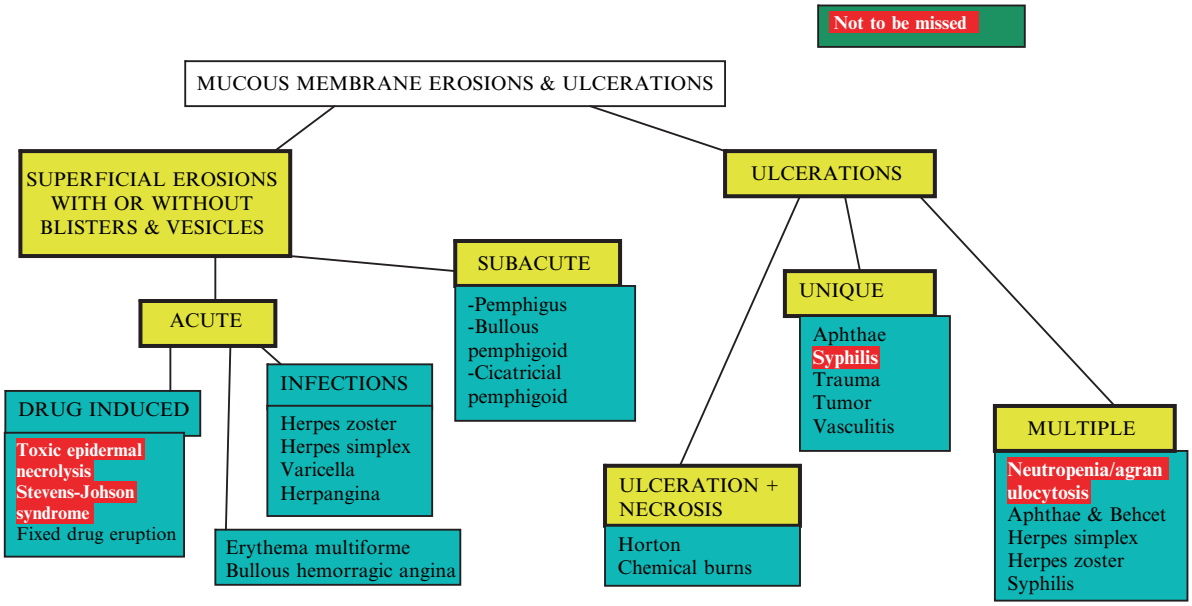
Various aetiologies are responsible for face oedema, but usually their clinical features are a help for diagnosis:

- *Coloration of oedema* (white or red) and *the rapidity of installation* are the main clues. Rapid installation of a white, non-pitting and well-defined face oedema is characteristic of angio-oedema or allergic reaction. In the case of red coloration, other signs accompanying oedema such as vesicles, oozing, localisation of the eruption, and systemic signs should be evaluated.
- *The rapidity of apparition of oedema* is a major sign: A rapid installation with progressive swelling involving oropharynx mucosal (angio-oedema) is an emergency, with a high risk of asphyxia. In this case, note the lack of pruritus. Systemic signs with hypotension, tachycardia, bronchospasm may be associated in case of anaphylactic shock. Recent new medication, food, insect bites are the major causes of angio-oedema. In the case of angio-oedema without body urticarian eruption and a positive *family history,* a C1-esterase inhibitor deficiency should be explored.
- *Vesicles* are a feature of contact dermatitis but also of viral infection (herpes-zoster). Viral vesicles are usually grouped in a circumscribed area (herpes simplex) sometimes unilateral and metameric (herpes-zoster). Vesicles of contact dermatitis are more diffusely distributed and rapidly ruptured, with subsequent oozing.
- *Fever* is a sign of bacterial infections such as cellulitis or erysipelas, with sudden and warm swelling and sharp borders. Viral infections (parvovirus B19 with swollen cheeks, or varicella herpes zoster with disseminated vesicles) are usually accompanied with fever. On the other hand, fever with marked systemic signs associated with a body eruption, enlarged lymph nodes, and eosinophilia 2–5 weeks after introduction of a new medication is suggestive of DRESS.
- *Pruritus* is a major sign, accompanying contact dermatitis, atopic dermatitis and light-induced dermatoses.
- *Pain* is a sign in case of infectious disease (bacterial infection such as erysipelas and cellulitis; viral infection such as herpes zoster or Kaposi-Juliusberg varicelliform eruption).
- *Recent medication* and the time of drug ingestion is an important clue for the diagnosis: angio-oedema occurs a few minutes to 2 h after drug intake.
- DRESS occurs weeks after introduction of the responsible drug.
- Drugs such as angiotensin conversion enzyme (ACE) inhibitors or non-steroidal anti-inflammatory drugs (NSAID) are frequent causes of chronic face oedema, with a different mechanism.
- *Topics* on the face can be responsible for eyelid oedema or face oedema, usually accompanied by vesicles and oozing (contact dermatitis).
- *Light-induced face oedema* is characterized by its topography: absence of involvement of the anterior sub-mandibular area. Sunburn, topical and systemic photosensitization including phyto-photodermatosis are of acute onset; aggravation of a chronic disease such as a systemic lupus erythematosus or dermatomyositis may be mistaken for such acute photodermatoses.

Diagnosis of Oral Lesions

37

Loïc Vaillant and Laurent Machet



Blisters and vesicles are very transient in the oral cavity, and rapidly result in painful superficial erosions. Identification of the cause may be helped by the presence of cutaneous blisters and vesicles and of other mucosal lesions. The main cause of acute bullous diseases is erythema multiforme (Fig. 37.1), sometimes isolated with no cutaneous lesion. Mucous erosions from Stevens–Johnson syndrome, toxic epidermal necrolysis and fixed eruption are very similar.

Bullous hemorrhagic angina (*angina bullosa haemorroragica*) is a benign common condition of the elderly, usually situated on the palate, presenting as a blister with blood content which ruptures after a few hours leaving ulceration.

Ulcerations are deeper than erosions, but the confusion is frequent between "aphthae" and post-bullous erosions. Typical aphthae are round ulcerations 2–3 mm in diameter with a yellowish centre and a red rim. Ulceration may be necrotic in Horton's disease or after chemical burn.

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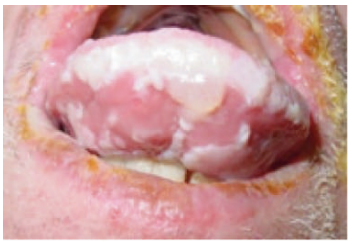
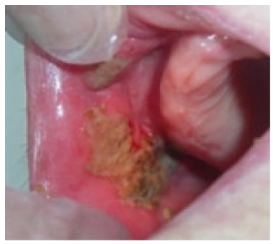
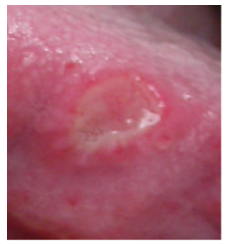
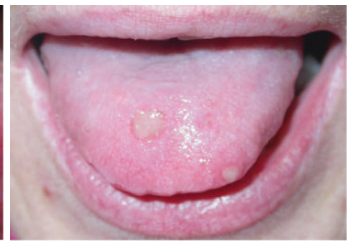


BLISTER

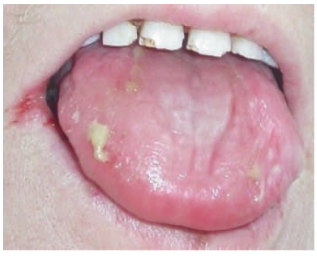


SUPERFICIAL EROSION

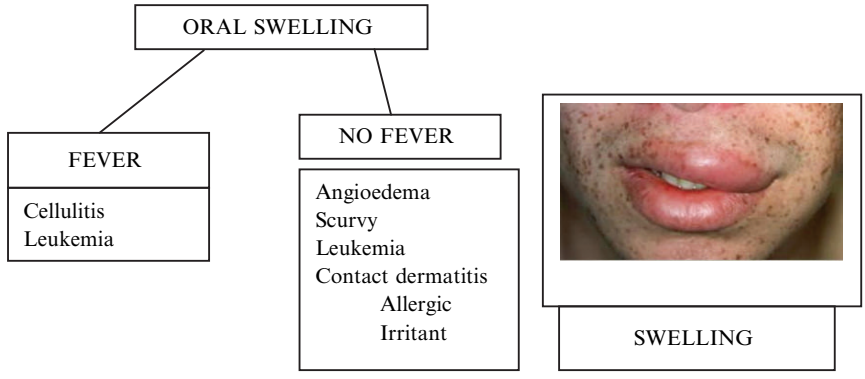




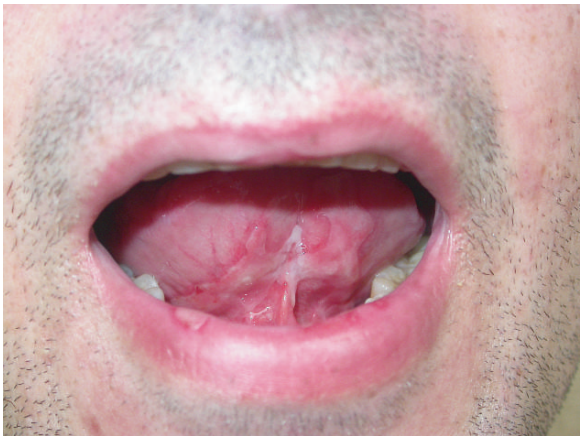
ULCERATION: APHTHAE



PSEUDOMEMEBRANE



SWELLING



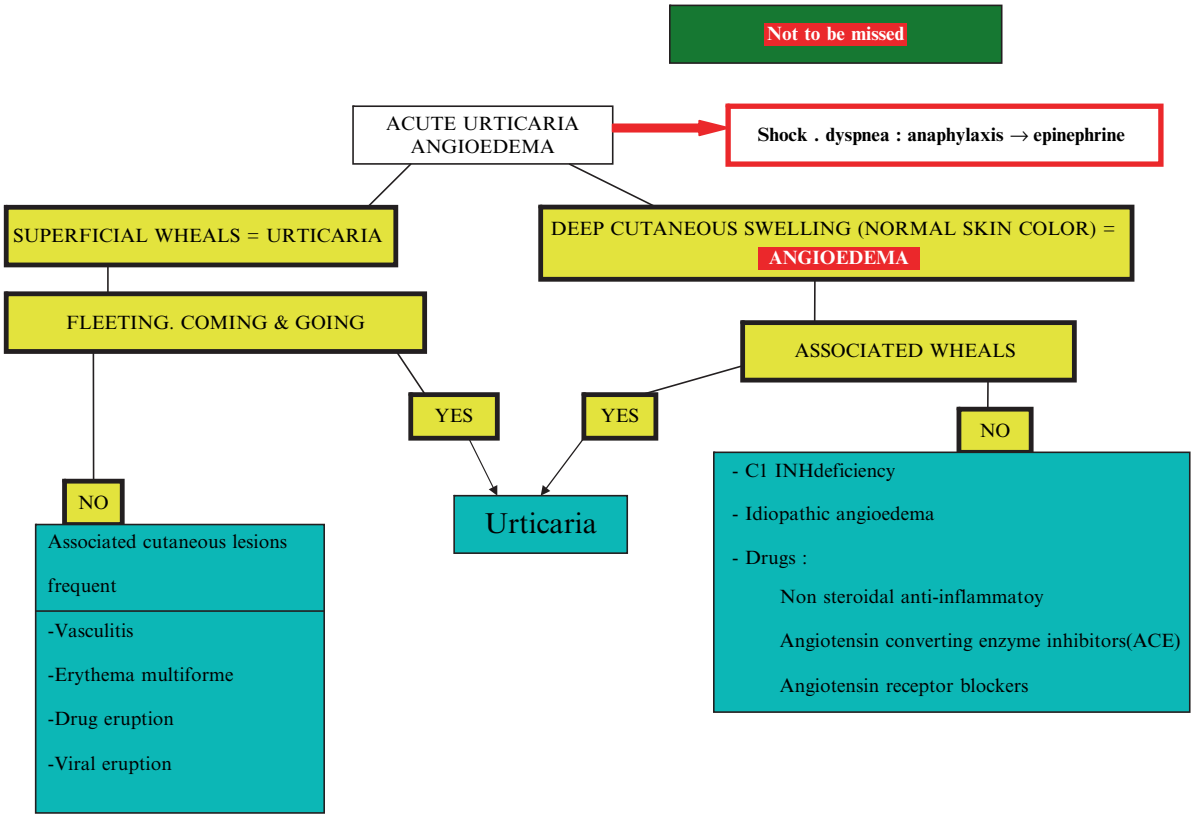
Pseudo membrane of the oral cavity may be acute: thrush seen after wide spectrum oral antibiotics or in immunosuppressed patients. Hairy leucoplakia secondary to EBV infection is chronic and mainly observed in HIV infected patients.

Fig. 37.1

Acute Urticaria and Anaphylaxis

38

Catherine Pecquet



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Urticaria is characterized by the rapid appearance of wheals with three typical features:

- A central swelling of variable size, surrounded by a reflex erythema.
- Associated itching or sometimes burning.
- A fleeting nature with a duration of usually 1–24 h; the lesions resolve without any trace.

The size of the wheals varies, ranging from a few millimetres to many centimetres. They appear on any part of the body, and may be associated with angioedema.

Some clues for the diagnosis of urticaria:

- If the wheals are not transient, or are associated with blisters, pigmentation or purpura, vasculitis, erythema multiforme, erythema annulare centrifugum, bullous pemphigoid, or maculopapular drug eruption, viral eruption must be considered.
- If the epidermis is injured (vesicles, desquamation, etc.), allergic or irritative contact dermatitis, infectious diseases, etc. may be involved.

Angioedema (Quincke's oedema) is defined by a sudden, pronounced swelling of the lower dermis and sub-cutis, sometimes painful rather than itching, with a frequent involvement of mucous membrane the resolution of which can take 72 h.

If epidermal injury (vesicles, desquamation, etc.) or fever is present, or if the oedema is bilateral and symmetrical, it is not an angioedema.

A familial history of angioedema, some previous episodes, associated abdominal pain are in favour of C1 Inh deficiency;

Some drugs may be responsible for angioedema: non-steroidal anti-inflammatory drugs (NSAID), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor (AR) blockers.

Generalised urticaria and angioedema are the most common manifestations of *anaphylaxis,* and are often the initial signs of this acute life-threatening reaction with respiratory compromise and cardiovascular collapse.

A classification of urticaria is proposed on the basis of the duration:

- In acute urticaria, the duration of appearance of wheals is less than 6 weeks. Anaphylaxis can occur in this form. Most often, there is only one episode. No diagnostic tests are necessary. Questioning for a triggering factor in the few hours before the onset (drugs, foods, insect bites, infection, etc.) is important in order to identify and treat or avoid it. Secondary, allergic evaluation is useful.
- In chronic urticaria, the duration of appearance of wheals is more than 6 weeks, daily or almost daily in continuous chronic urticaria, or with symptom free-intervals in chronic recurrent urticaria. No allergic reactions are responsible for such urticaria, but some drugs, physical stimuli (pressure with dermographic urticaria or delayed urticaria, cold, cholinergic, etc.) and infections can raise the lesions. The risk of anaphylaxis is very low. No tests are needed during the events. Secondary, dermatologic evaluation is useful (Figs. 38.1–38.2).

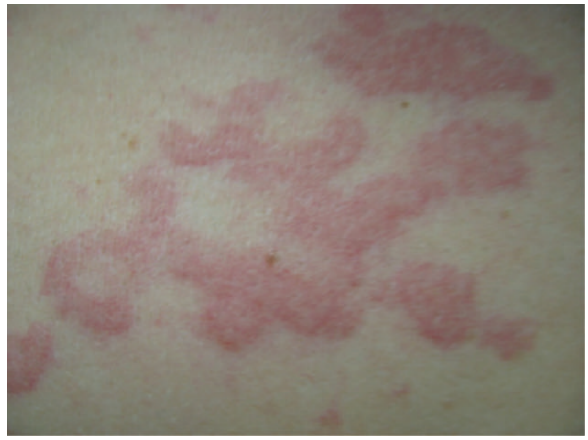


Fig. 38.1 Urticaria

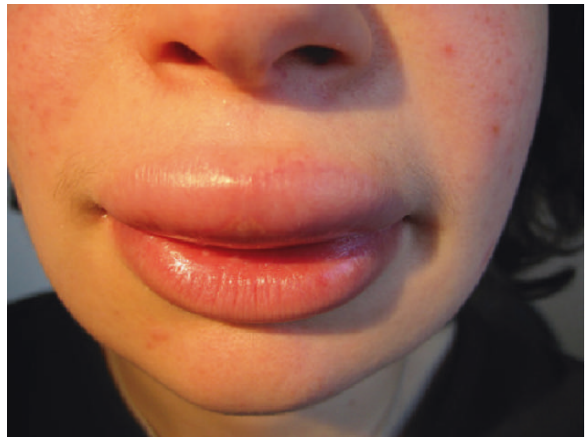


Fig. 38.2 Angioedema

Anaphylactic shock
Severity grades:

(1) Disseminated skin and mucous membranes signs: erythema, urticaria ± angioedema
(2) Moderate systemic involvement: hypotension, high pulse rate, bronchial hypersecretion
(3) Severe systemic involvement: collapsus, high or low pulse rate with arrhythmia, bronchial spasm ± skin and mucous signs
(4) Cardiac and/or respiratory arres

Treatment:

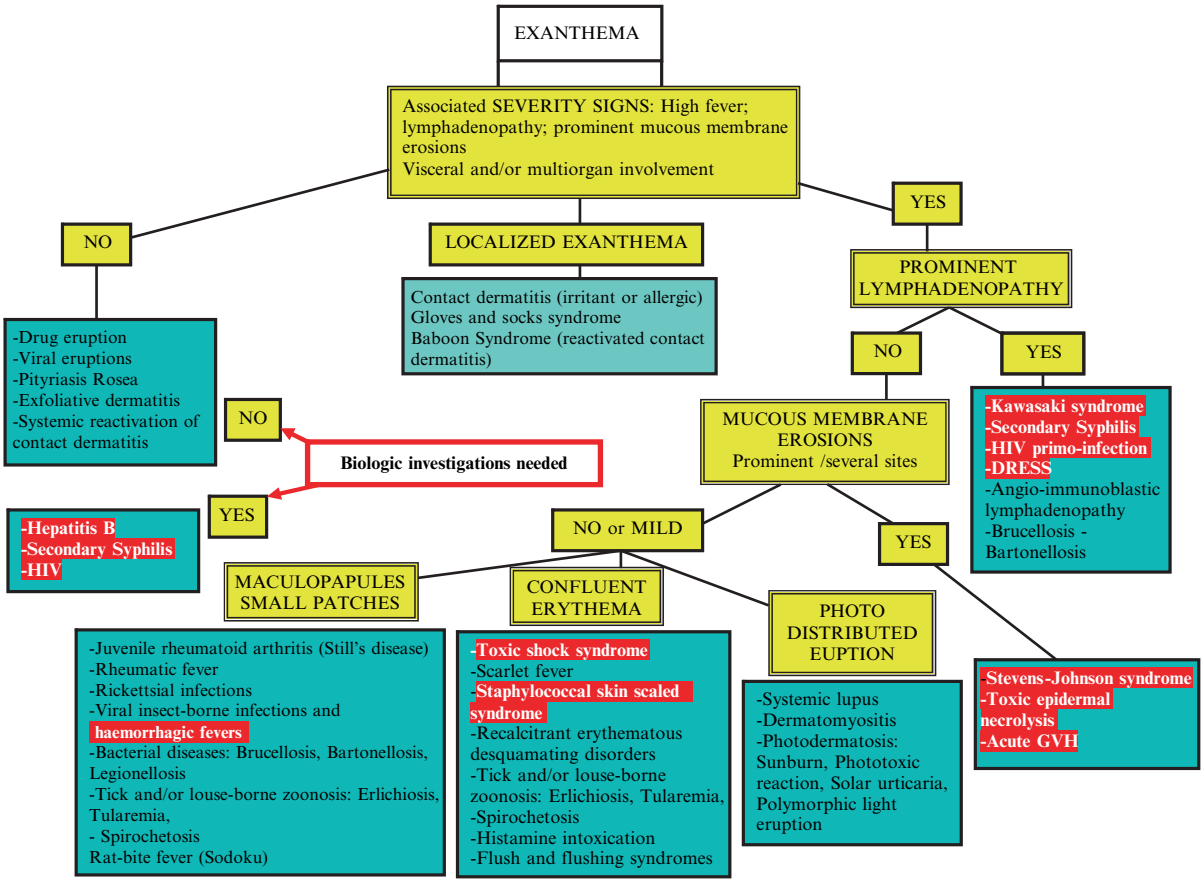
- Stop any suspected drug
- Oxygen
- Permeability of upper respiratory way
- Emergency phone call
- Venous line

In Grade 1: no epinephrine
Grade 2: epinephrine 10–20 μg intravenously or 100–200 μg intramuscularly
Grade 3: epinephrine 100–200 μg intravenously or 500 μg intramuscularly
Grade 4: cardiac massage, epinephrine 1 mg every minute, 5 mg at the third injection.
Bronchospasm: salbutamol inhalation

Exanthematic Rash

39

Bruno Sassolas



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39.1 Acute Exanthema

39.1.1 Exanthema with Vesicles, Blisters, Pustules Excluded; No Prominent Early Desquamation

This clinical situation is frequent in the daily practice of emergency doctors. Three questions must be answered early for better care of patients, as they point toward life-threatening diseases like *toxic epidermal necrolysis, DRESS or toxic shock syndrome*:

Are there severity signs? Are there several mucous membranes involved? Is there lymph-node enlargement at different sites?

Aetiology is dominated by viral infections (precise identification seldom needed, except in the context of travelling patients from tropical or subtropical areas) and drug eruptions (1, 2). Efficient questioning of the patient is essential. However, other possible causes are worth identifying. Of interest is to note that one aetiology may be concerned with different diagnostic steps.

The clinical approach will take into account several criteria given by a thorough clinical investigation: (a) *Age* of patient, with higher rate of benign viral rashes or drug eruptions in childhood or elderly respectively, (b) *Context* — environmental, professional and epidemiologic informations, associated diseases, recent travel with exposure to new specific infectious agents, drug or toxic exposure and more importantly (c) *associated clinical signs*: **constitutional symptoms**, even non-specific, such as fever, chills, headache, general malaise, accelerated heart rate, and hypotension, **lymph node enlargement** on different sites, **other visceral involvement** (liver, spleen, kidney, gastro-intestinal with diarrhoea, vomiting, lung), myalgia, or arthralgia, and finally **mucous membrane involvement**.

Exanthema will be further analysed on:

– *Extension* that may be diffuse or more limited, mainly on the upper trunk (rose spots on the trunk in typhoid fever) even only localized.
– Some *localizations* have some specificity:

• Prominent involvement of palms or soles, in syphilis, parvovirus B19, Rocky Mountain spotted fever or Mediterranean fever
• Involvement on photo-exposed areas (face and neck with respect of underneath the chin, dorsum of hands, and lower legs)

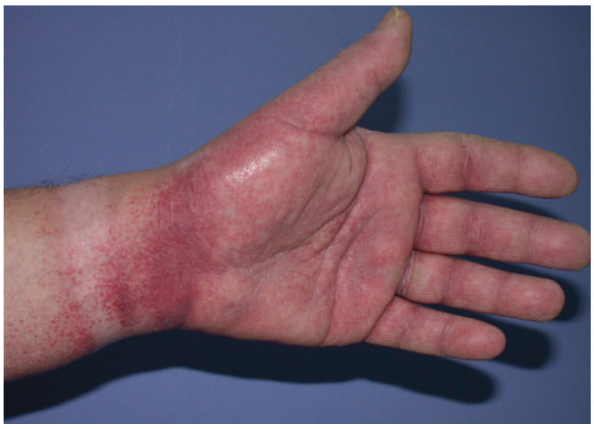
– *Pattern of exanthema* may be macular (small spots) or patchy (pityriasis rosea) versus coalescent and confluent in toxin-mediated exanthema. Some specific figurate features with wreath on limbs are easy to recognize in parvovirus infection (epidemic megalerythema). Palpable exanthema (morbilliform, scarlatiniform) are to be differentiated from non-palpable exanthema. Panel of colours ranges from pale (early phase of syphilis, or subitum exanthema) to dark red in toxic epidermal necrolysis.

Remember that Erythema on Dark-Complexioned Skin Demonstrates as Darker than Normal Skin.

– *Associated cutaneous lesions* concomitant or delayed with oedema of the face (DRESS), purpuric lesion (rickettsial or meningococcal infections), even pustules or vesicles or bullous (see related chapters).
– *Pattern of evolution*: short duration in flush and flushing syndrome (including flushing erythema in many viral and bacterial infections), relapses in Still's disease, desquamation in Kawasaki syndrome or streptococcal infection, progressive enlargement in Lyme disease.

Further investigations are needed, which include skin biopsy that is mandatory to confirm some specific diseases as Stevens–Johnson, toxic epidermal necrolysis or specific photo-dermatosis. In many diseases discussed here, skin pathology, often non-specific, is helpful to discard other specific diseases such as in DRESS.

Blood sampling, with cell blood count, liver or renal function test, is useful when any severity sign or symptoms are present. Some specific tests (syphilis, hepatitis and/or HIV serology) should be investigated if any risk factor is expressed by the patient. Other specific serology is occasionally requested for severe eruption or in specific epidemiologic context (Rubella and contact with pregnant women) (Figs. 39.1–39.10).



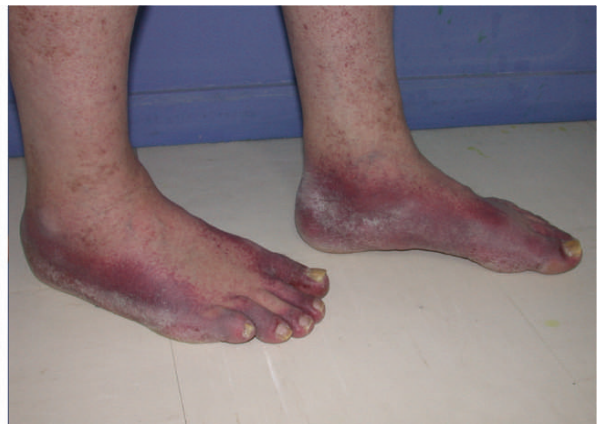


Fig. 39.1 Gloves and socks syndrome. Parvovirus infection

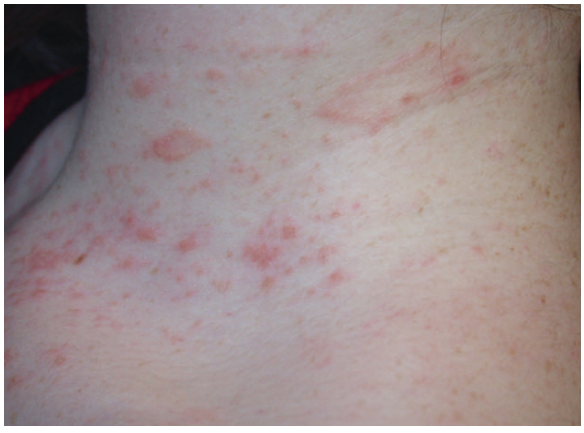


Fig. 39.2 Pityriasis rosea

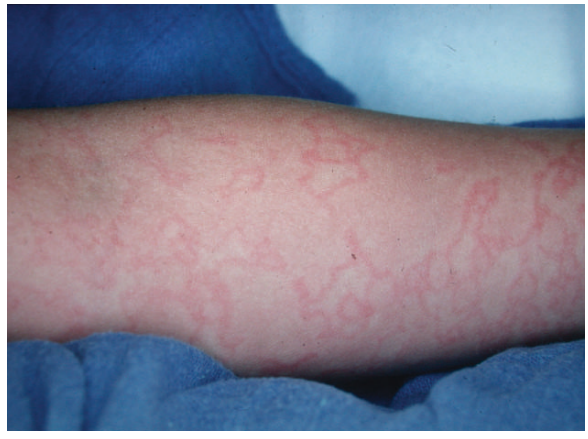


Fig. 39.4 Parvovirus infection (epidemic megalerythema)

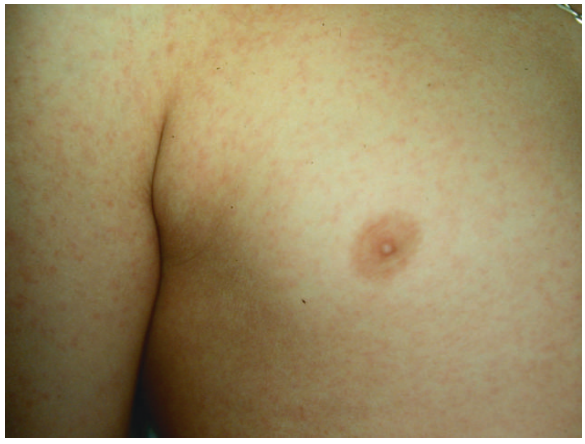


Fig. 39.3 Rubella

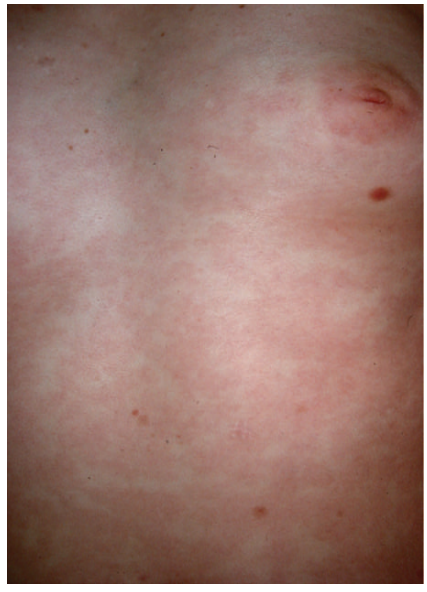


Fig. 39.5 Early secondary syphilis

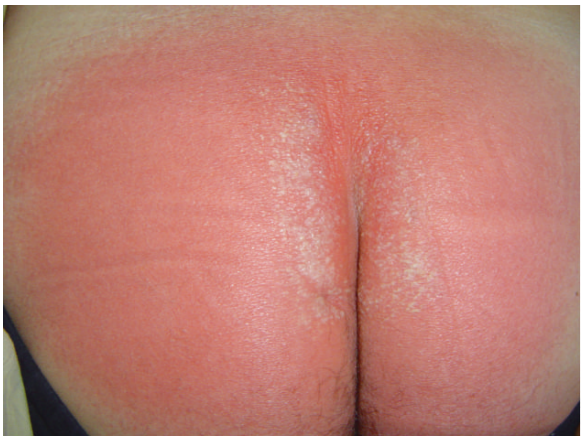


Fig. 39.6 Baboon syndrome: widespread exanthema with buttock involvement

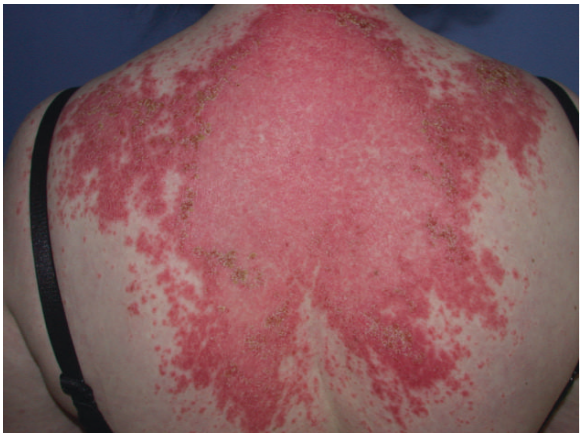


Fig. 39.7 Systemic lupus

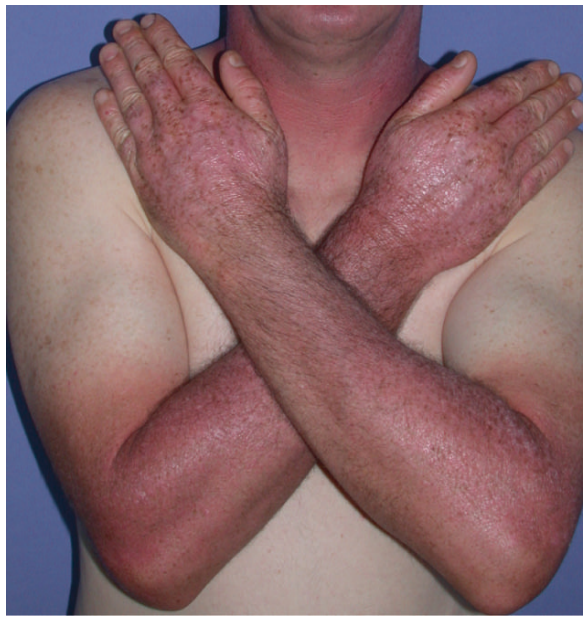


Fig. 39.8 Phototoxic reaction

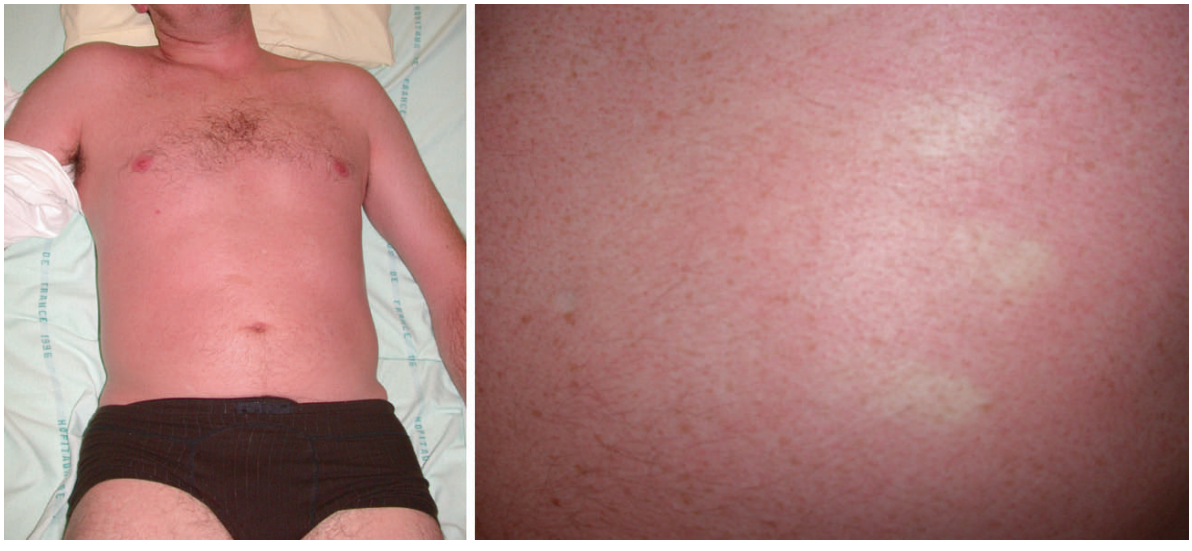


Fig. 39.9 Beta haemolytic group A streptococcal toxin-mediated exanthema

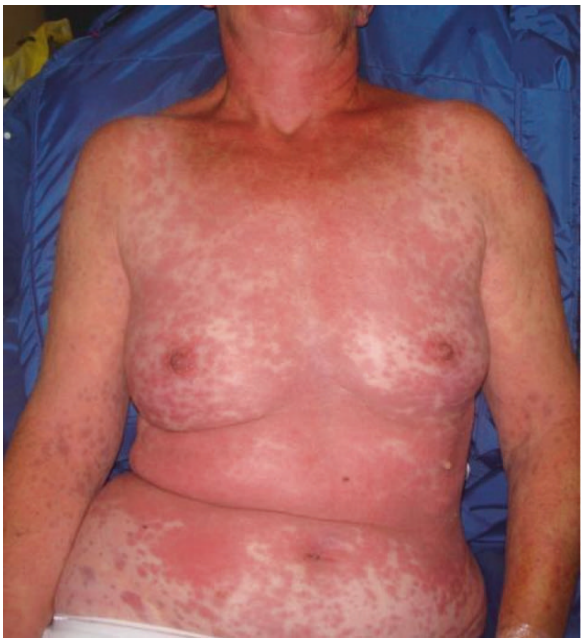


Fig. 39.10 Widespread and benign drug eruption

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