Tulio Pinho Navarro · Alan Dardik
Daniela Junqueira · Ligia Cisneros *Editors*

Vascular Diseases for the Non-Specialist

An Evidence-Based Guide

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Foreword

With the surfeit of vascular surgical textbooks, one might wonder why another book is necessary. The editors have taken a different route from most vascular texts and organized a compendium of chapters designed for the nonvascular individual, which would include medical students and allied professionals such as physician assistants, nurse practitioners, and even scientists in the biological world. I would argue with this focus by the editors in that this text also has exceptional value for the trainee and practitioner of vascular medicine and surgery. This is not a text for how to do particular procedures but rather how to think about the enormous variety of pathologies encountered by those dealing with vascular disease. The chapters are well written and have been edited to provide a smooth transition as one progresses through the various systems. The basic sciences are not neglected. In fact, commentaries dealing with biology, pathology, and pharmacology are matched by sections dealing with statistics, epidemiology, and gathering of information. This is truly an unusual text assembled under the guidance of two experienced vascular surgeons. This book is readable, practical, and will not be relegated to obsolescence. This text is an excellent source of practical information for the novice as well as the expert healthcare provider.

Herbert Dardik
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Preface

Over the last several decades, improved healthcare systems coupled with improvements in public health works such as sanitation have led to major epidemiological shifts and alterations of prevalent trends in nosology. One of these changes is the general improvement in health allowing people to live longer and better. The price for this, however, is the aging population that is burdened with nontransmissible chronic disease. Atherosclerosis is now the leading cause of death worldwide, responsible for one-third of deaths; as such, vascular diseases are now widely prevalent and are currently a major public health issue. Vascular diseases such as aneurysms, peripheral arterial disease, the diabetic foot, venous thromboembolism, cerebrovascular disease, aortic dissection, and acute limb ischemia are now much more common, especially in emergency rooms.

However, many healthcare practitioners have little or no knowledge about the modern diagnosis and therapy that are appropriate for these common vascular diseases. Interestingly, each of these vascular diseases has its own risk factors, demographics, natural history, and treatment; even peripheral artery and coronary artery disease are quite distinct. Simply using a non-evidence-based approach could increase morbidity and costs of treatment, and even lead to mortality.

The idea of this book was born after we realized that most of our undergraduate students and nonvascular expert healthcare professional colleagues did not have an objective evidence-based guide for their education and daily practice. Most of the vascular textbooks available to them are typically intended for experts and not for general practitioners.

The aim of this book is to provide nonspecialist healthcare practitioners with current, focused, objective, and evidence-based information on the most common vascular diseases encountered in daily clinical practice. For each disease, the concept, epidemiology, natural history, diagnosis, and treatment are described, followed by essential advice on what the nonspecialist can do for the patient and when to refer the patient to a specialist.

Belo Horizonte, Minas Gerais, Brazil — Tulio Pinho Navarro
New Haven, CT — Alan Dardik

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A publication of this magnitude is accomplished only by the combined efforts of many people. We would like to acknowledge the persistence and dedication of all involved in this project, especially the chapter's authors who contributed their expertise and the reviewers that took part in the process of improvement of quality, coherence, and content of the chapters.

A very special thanks to Raquel Ferreira Nogueira, who ignited the idea to provide a book for nonexperts; once as an undergraduate student, she only had access to textbooks intended for experts. She also gathered our group of undergraduate students as contributors and started all the process that ended in this book.

Another special thanks to Patric Oliveira Gonçalves for the invaluable support, helping the authors in their quests. His work in this project was *sine qua non* for finishing the book in time, organizing all chapters and files with unique competence.

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We thank the editorial staff of Springer, especially Gabriel Pires, from Springer Brazil, who gently and patiently helped us during all the process of this book.

We hereby acknowledge our families for encouraging and supporting our mission and for the patience and understanding that editing a book is not a simple task.

The editors

Contents

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How to Make Decisions in Healthcare?

1

Daniela R. Junqueira

Abstract

Scientific valid evidence may be acquired from a number of studies capable of supporting or denying a theory about a healthcare treatment, a diagnostic intervention, or about the frequency of occurrence of a health event. However, the translation of scientific knowledge into decisions in healthcare requires methodological expertise and comprehension of the potentials and limitations of each type of evidence. In this chapter, we invite the readers to think more scientifically in their daily practice. We didactically discuss relevant aspects related to the clinical question and study design, and we use this discussion to guide the reader to an improved comprehension of how to use systematic reviews in the context of evidence-based healthcare. Finally, we present some tools and resources to help professionals to search for qualified and preapraised evidence to inform their clinical decisions.

Nowadays, claims about scientific knowledge are not only on the pages of scientific journals, but in newspapers and magazines of wide circulation, in bulletins produced by universities and research institutes, at web sites of the pharmaceutical industries, in collaborative written encyclopaedias, and even in blogs developed by non-scientists. This modern scenario, which is encourage by the online world, probably reflects the nature of the scientific evolution itself: a continuing evolving search for knowledge, and a continuing evolving knowledge. However, the translation of scientific knowledge into decisions in healthcare requires that professionals are

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capable of understanding the potentials and limitations of each channel and each type of research. The current amount of information available through these different channels may, for example, amplify research claims that are not based on qualified and rigorous scientific principles. Even when we consider information sources that hold good scientific reputation, the journalistic format may distort the information or part of the scientific rigour. Therefore, the understanding of the fundamental concepts related to how the scientific knowledge in healthcare is developed, and communicated to the public, is essential.

Scientific valid evidence must be acquired from a number of studies capable of supporting or denying a theory about a healthcare treatment, a diagnostic intervention, or about the frequency of occurrence of a health event. Not all evidence is similar, and it may be necessary a critical appraisal and skills in research methods and analysis to assess the quality of the evidence, its accuracy, and practical application [1]. In this scenario, the terminology evidence-based healthcare, or medicine-based healthcare, has become popular. Evidence means the combination of elements used to support the confirmation or denial of a particular theory or scientific hypothesis. Evidence-based healthcare means simply a practice where decisions are guided or informed by these scientific elements. It is about using the evidence effectively to make decision in healthcare instead of relying on the former paradigm [2]:

- Unsystematic observations from the clinical experience
- Clinical practice supported only by the study and understanding of basic mechanisms of disease and physiopathology mechanisms
- Combination of traditional medical training and common sense as sufficient elements to evaluate new test and treatments
- Expertise and clinical experience as sufficient elements to generate valid guidelines for clinical practice

To be translated into practical decisions in healthcare, the evidence has to be relevant and meaningful. A meaningful evidence is based on well-conducted studies with appropriate design to answer the clinical question under investigation. Data analysis and the format of the results presentation are also important factors that may influence the conclusions arising from a particular clinical study. Finally, the conduction and publication of studies by entities deemed to be qualified or respectful does not guarantee research quality *per see*. For instance, many cases of data fabrication and research fraud were conducted in universities with an outstanding reputation, by applauded researchers, and published in high impact journals [3–5]. Studies about drugs and medical devices funded by the manufacturing companies usually lead to more favourable results and conclusions than studies funded by other sources [6, 7], and even animal studies have results exaggerated when sponsored by the industry [8]. This situation is true even when there is a conflict of interest disclosure in the accompanying papers.

Clinical Question and Study Design

Any question addressing a clinical problem has four essential elements: patients (P), intervention (I), comparison (C), and outcomes of interest (O) [9]. This structure is commonly referred as PICO question. For example, one could be interested in the effects of cilostazol (Intervention) in comparison with placebo or other antiplatelet agents (Comparison) in the initial claudication distance (Outcome) of patients with stable intermittent claudication (Patient) [10]. More recently, an additional element has been introduced to the PICO question: the study design (S) [11]. The PICOS question structure is informative because it highlights the fact that not all evidence is appropriate to answer a specific clinical question. In this example, the scientific question was related to the efficacy of a therapy and we would be interested in a randomised clinical trial (an experimental study) where two groups of participants with a disease receiving different treatments according to a randomised allocation are compared. Clinical trials may be regarded as fair, unbiased evaluations, when conducted according to high standard methods [12].

Despite the hype about the substance of clinical trials, they are not the optimal study design to answer all types of clinical questions. This is basically linked to the research method itself: different clinical questions require different types of studies (Table 1.1) [13–16], and the design of the clinical trials is suitable for answering questions about efficacy. Another important question related to the above case study would be the diagnostic accuracy of the ankle-brachial index for the diagnosis of peripheral arterial disease in people with intermittent claudication [17]. This is a fundamental problem, and it is estimated that 85 % of the research is wasted and not useful to answer practical clinical problems because of flaws in research such as wrong question and inappropriate study design [18, 19].

Table 1.1 Study design according to clinical question

Question	Type of question	Study design
What are the benefits of this intervention and its relative safety?	Treatment benefits and common and predicable harms	Experimental studies: randomised controlled trials or *n*-of one trials
What are the harms induced by this intervention?	Treatment harms	Experimental studies: *n*-of 1 trials
		Observational studies: cohort studies, case-control studies, case-series
Is this diagnostic test accurate?	Diagnosis	Cross-sectional or case-control study designs
What will happen if we do not add a therapy?	Prognosis	Cohort studies with incident cases
What is the frequency of a condition or health-related problem in the population? How many people are affected?	Prevalence	Cross-sectional, surveys

Evidence-Based Healthcare and Systematic Reviews

As stated above, the scientific knowledge is always evolving. Our comprehension about the effects of the healthcare interventions, being it a treatment or diagnostic test, is continuing evolving too. However, this oath is frequently ignored and a static piece of information, such as that provided by a product manufacturer or by one published paper, is continuously used to guide decisions.

As a case example, the development of a drug intervention starts with the chemical design and then follows a series of preclinical tests consisted of laboratory and animal experiments. If the drug under investigation succeeds in the preclinical tests, further researches are conducted in human under controlled situations. In this process, the laboratory tests performed in the pre-clinical phase are useful to test the intervention in disease models—animals. The potential efficacy and relativeness safety of the new treatment need to be evaluated in real patients, in a clinical phase constituted of a series of studies named clinical trials. Together, the pre-clinical and clinical data provide relevant answers related to a medical intervention might include a drug, a medical device, or a screening method. Nevertheless, our knowledge about these healthcare interventions is limited at the time they are granted marketing approval. For instance, at the time a drug is approved to be used in real-life situations, only several hundreds to about 3000 volunteers who have the disease to be treated are expected to have been tested [20, 21]. In Europe, from 2000 to 2010, the median total number of patients studied before a drug approval was 1708 [22].

The above numbers demonstrate that the accumulated data related to any intervention is very limited at the time marketing approval is granted. Moreover, to be approved in the United States, there must be adequate data from just two clinical trials [21]. After marketing approval is granted, additional studies and reanalysis of the available published and non-published results may depict more details about the efficacy and harms of the intervention. In addition, the clinical phase of tests continues with observational studies intended to accumulate data on harmful effects. This is essential since clinical trials can only detect frequently and predict harm outcomes, and a complete investigation of all types of harmful effects induced by a healthcare intervention requires the assessment of mainly non-randomised studies [23]. It may now be clear why "no study, whatever the type, should be interpreted in isolation" [24], and why the evidence gathered by all the studies related to a given intervention should be taken collectively to inform healthcare decisions [25]. The research method more capable of accomplishing such a critical overview of the evidence is the so-called systematic review.

A systematic review may be understood as a research undertaken with previous completed studies. Therefore, a systematic review uses an explicit method to collate the primary studies that answer a specific research question [26]. A qualified systematic review may also include a quality assessment of the studies collated, i.e., a judgment of the risk of bias of each included study. A systematic review may or may not include a meta-analysis, which is a statistical method to combine the results of independent studies [27]. Consider the treatment of intermittent claudication

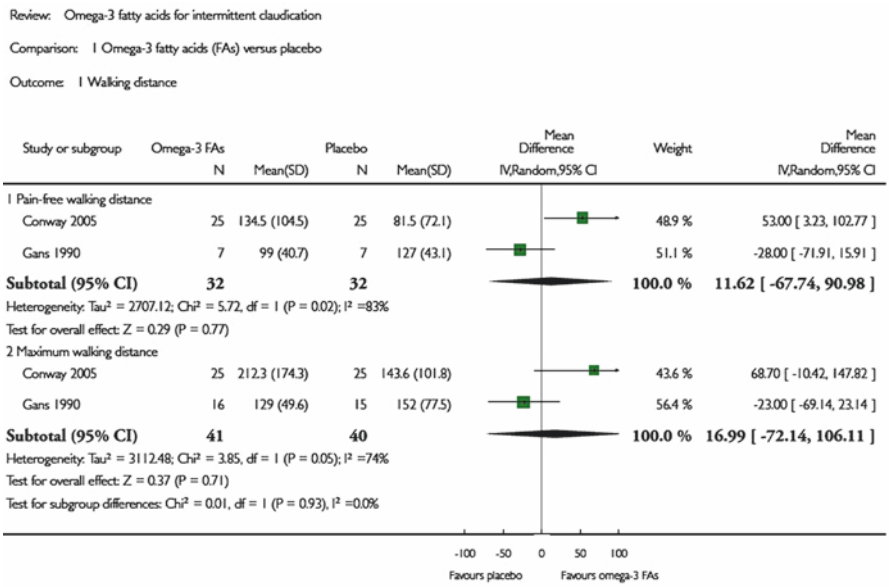

Fig. 1.1 Statistical illustration of two trials demonstrating opposite effects on the pain-free walking distance of omega-3 fatty acid in the treatment of intermittent claudication [28]. The figure presents a graphic name to forest plot. In a forest plot, the point estimate of the result of the individual studies are shown as *squares centred*, and the confidence interval is represented by a *line crossing through the square*. The combined estimate from the meta-analysis and its confidence interval is represented by a *diamond* at the bottom of the graphic [31]. The parallel line crossing the graphic where the mean difference is equal to zero accounts for a result that is equal in the intervention and comparison group. **Reprinted with permission from:** *"Campbell A, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. Cochrane Database Syst Rev. 2013;7:CD003833".*

discussed above. Omega-3 fatty acid [28] has been studied to improve the pain-free walking distance and the maximum walking distance achieved by patients after treatment. Since this is a treatment question, if we search for clinical trials investigating the problem we could find one study published in 2005, which appears to demonstrate that omega-3 is effective to improve the pain-free walking distance and probably an option to also improve the maximum walking distance of individuals with intermittent claudication [29]. However, another trial failed to support the hypothesis that omega-3 was effective to improve either the pain-free walking distance or the maximum walking distance [30]. The combined effect of these trials shows that there is no evidence that omega-3 consistently improves clinical outcomes of patients with intermittent claudication (Fig. 1.1) [28]. If we have not appraised the combined effect of both of these trials in a systematic review, we would be taking decisions informed by biased evidence.

Harms, Not Just Efficacy

Every healthcare intervention will carry a risk—great or small—of inducing harm effects causing injury or disability to patients. Usually, optimistic misconceptions about harms induced by healthcare interventions result in researchers and clinicians inadvertently not taking data on harm in consideration when reporting a study or making decisions in healthcare. Since research reports frequently fail to detail data on harmful effects, the intervention may be erroneously declared safe [32–37]. However, "absence of evidence of harm should not be construed as evidence of absence of harm" [37], and at most we will have data on a relativeness safety of an intervention in these situations. Another issue complicating the evaluation of harms is the several terms used to describe all the harmful events that can be associated to healthcare intervention [23, 38] (Table 1.2). Furthermore, some of the harm effects may be recognised by the healthcare professionals as mild and non-relevant events. Even mild or moderate harmful effects could be of major significance for a treated patient, resulting in poor treatment adherence and in the use of additional medications to treat the harm effect. Drug-induced acute or chronic diarrhoea, which is one of the harms induced by omega-3 and cilostazol [10, 28], can be severe and poorly tolerated [39]. A headache, another harm effect reported by patients treated with cilostazol [10], imposes a recognisable burden on sufferers, including substantial personal suffering, impaired quality of life, and financial cost [40, 41].

The inconsistent report of the frequency of events related to harm effects is another challenge when assessing data on harmful effects. A biased report may

Table 1.2 Terminology of harmful effects

Terminology	Meaning
Adverse event	An unfavourable outcome that occurs during or after the use of a drug or another intervention but is not necessarily caused by it
Adverse effect	An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility
Adverse drug reaction	An adverse effect specific to a drug
Side effect	
This is an old term and should no longer be used because it underestimates the importance of harms associated to healthcare interventions	Any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment
Harms	The totality of all possible adverse consequences of an intervention

Adapted from: "*Loke YK PD, Herxheimer A. . Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from http://www.cochrane-handbook.org.*" **and** *"Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol. 2010;63(5):502–12".*

Table 1.3 Classification of harmful effects according to the frequency of occurrence [42]

Frequency	Classification
>10 %	Very common
>1 % and <10 %	Common
>0.1 % and <1 %	Uncommon
>0.01 and <0.1 %	Rare

Adapted From: "*WHO. Glossary of terms used in Pharmacovigilance 2011 20 March 2015. Available from: http://www.who-umc.org/DynPage.aspx?id=22684*".

often describe a harm effect as rare when it is, in reality, a common effect. The Uppsala Monitoring Centre (UMC), the international drug monitoring programme of the World Health Organization (WHO), suggests a standard classification for the frequency of harmful effects induced by healthcare interventions (Table 1.3) [42].

Finally, it is important to distinguish between harms induced a healthcare intervention and harms caused by professional err. Errors can be prevented by training and by implementing systems that identify and block the error. These systems can be implemented at a institution level, or can consist of simple actions such as avoiding writing a prescription containing abbreviations, symbols, and dose designations that are frequently misinterpreted, to more complex structures and procedures. Harms induced by the intervention itself may not be related to the professional training or experience level, and can only be prevented if we are able to better understand the intervention potential to do more good than harm, or the opposite.

How to Make Decisions in Healthcare

The amount of methodological skills and critical considerations required to evaluate research in healthcare may frustrate any healthcare professional trying to make sense of the evidence at the point of care. Usually, these professionals are already challenged by work overload and cumulative administrative tasks. In this scenario, a few minutes is the time available to answer frequent questions about patient care [43]. The answers are usually built on a "collectively reinforced, internalised, tacit guidelines" [44], meaning that knowledge may be constructed by leaders' opinions and interactions with colleagues, and not based on qualified evidence from research.

To support the availability and the access to qualified evidence, which is relevant to inform decisions in healthcare, there are currently a number of organisations supporting the development of systematic reviews (Table 1.4). In addition, systems of preapraised evidence are being structured with the goal of synthesising the evidence gathered in systematic reviews (Table 1.5). These systems of preapraised evidence are expected to support healthcare professionals to consistently make decisions informed by reliable and accurate evidence. Nevertheless, this goal may only be achieved together with the comprehensiveness of the fundamentals of the scientific knowledge in healthcare, its evolving nature, and the potential flaws that threaten

Table 1.4 Where to find qualified systematic reviews and evidence-based recommendations

Organization	Activity	URL
Cochrane Library	The periodical where the systematic reviews developed under the Cochrane methods are published	http://www.cochranelibrary.com
The Agency for Healthcare Research (AHQR)	The agency, through the Evidence-Based Centre, supports the development of reports using the systematic review methodology	http://www.ahrq.gov/research/findings/evidence-based-reports/index.html
National Institute for Health and Care Excellence (NICE)	NICE offers practical guidance to support effective decisions in healthcare	https://www.nice.org.uk/Guidance
Canadian Agency for Drugs and Technologies in Health (CADTH)	CADTH describes itself as an "independent, not-for-profit organization providing unbiased, reliable information about health technologies"	https://www.cadth.ca/
The Joanna Briggs Institute Library	Repository for publications and information for policy makers, health professionals, health scientists, and others with a practical or academic interest in evidence-based healthcare	http://joannabriggslibrary.org/
Rx for a change	Searchable database containing current research evidence about intervention strategies used to alter behaviours of health technology prescribing, practice, and use	https://www.cadth.ca/rx-change
Health evidence	Searches, compiles, and offer free access to quality-rated systematic reviews evaluating the effectiveness of public health interventions	http://www.healthevidence.org/

Table 1.5 Where to find preapraised evidence

Organization	Activity	URL
BMJ Best Practice	Articles designed to provide a systemic overview of the evidence about therapies available for a given condition	http://bestpractice.bmj.com/
UpToDate®	Overviews of the evidence in all the subareas of internal medicine	http://www.uptodate.com/
Dynamed Plus	Summaries and detailed recommendations based on evidence	http://www.dynamed.com/

the process of conducting and appraising evidence in healthcare. In the absence of systematic reviews, this comprehension becomes even more important. Some systems of preapraised evidence and organizations, such as BMJ Best Practice, Drugs and Technologies in Health (CADTH), attempt to search and appraise individual studies in the absence of systematic reviews, and this may be an invaluable resource in the decision-making process. In order situations, professionals are encouraged to seek the assistance of an epidemiologist or a methodologist with expertise in systematic reviews and evidence-based medicine.

References

1. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? Br Med J. 2008;336(7651):995–8.
2. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. J Am Med Assoc. 1992;268(17):2420–5.
3. Fang FC, Steen RG, Casadevall A. Misconduct accounts for the majority of retracted scientific publications. Proc Natl Acad Sci U S A. 2012;109(42):17028–33.
4. Dyer O. University of Toronto researcher resigns over "systematic" data fraud. Br Med J. 2015;351:h6097.
5. McCarthy M. Former Duke University oncologist is guilty of research misconduct, US officials find. Br Med J. 2015;351:h6058.
6. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. Br Med J. 2003;326(7400):1167–70.
7. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2012;12:MR000033.
8. Abdel-Sattar M, Krauth D, Anglemyer A, Bero L. The relationship between risk of bias criteria, research outcomes, and study sponsorship in a cohort of preclinical thiazolidinedione animal studies: a meta-analysis. Evid Based Preclin Med. 2014;1(1):11–20.
9. Oxman AD, Guyatt GH. Guidelines for reading literature reviews. Can Med Assoc J. 1988;138(8):697–703.
10. Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014;10:CD003748.
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
12. Evans I, Thornton H, Chalmers I, Glasziou P. Testing treatments: better research for better healthcare. 2nd ed. London: Pinter & Martin; 2011.
13. Joanna Briggs Institute Reviewers' Manual. The systematic review of studies of diagnostic test accuracy [Internet]. Australia: The Joanna Briggs Institute; 2015 [cited 11-04-2026]. http://www.joannabriggs.org/
14. OCEBM Levels of Evidence Working Group. "The Oxford 2011 levels of evidence" [Internet]. Oxford Centre for Evidence-Based Medicine; 2011 [cited 11-04-2016]. http://www.cebm.net/index.aspx?o=5653
15. Strom BL, Kimmel SE, editors. Textbook of pharmacoepidemiology. Hoboken: Wiley; 2006.
16. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. Methods in observational epidemiology. 2nd ed. New York: Oxford University Press; 1996. 432 p.
17. Crawford F, Chappell FM, Welch K, Andras A, Brittenden J. Ankle brachial index for the diagnosis of symptomatic peripheral arterial disease. Cochrane Database of Systematic Reviews. 2013;(8).
18. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86–9.

19. Naci H, Ioannidis JP. How good is “evidence” from clinical studies of drug effects and why might such evidence fail in the prediction of the clinical utility of drugs? Annu Rev Pharmacol Toxicol. 2015;55:169–89.
20. Information for consumers. The FDA’s drug review process: ensuring drugs are safe and effective [Internet]. United States: U.S. Food and Drug Administration; 2014 [cited 05-04-2016]. http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm
21. The drug development process. Step 3: clinical research [Internet]. United States: U.S. Food and Drug Administration; 2015 [cited 05-04-2016]. http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm
22. Duijnhoven RG, Straus SM, Raine JM, de Boer A, Hoes AW, De Bruin ML. Number of patients studied prior to approval of new medicines: a database analysis. PLoS Med. 2013;10(3):e1001407.
23. Loke YK, Price D, Herxheimer A. Adverse effects (Chapter 14). In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. http://www.cochrane-handbook.org
24. Glasziou P, Vandenbroucke JP, Chalmers I. Assessing the quality of research. Br Med J. 2004;328(7430):39–41.
25. Dickersin K. Systematic reviews in epidemiology: why are we so far behind? Int J Epidemiol. 2002;31(1):6–12.
26. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
27. Glass GV. Primary, secondary, and meta-analysis of research. Educ Res. 1976;5(10):3–8.
28. Campbell A, Price J, Hiatt WR. Omega-3 fatty acids for intermittent claudication. Cochrane Database Syst Rev. 2013;7:CD003833.
29. Conway K, Dillon M, Evans J, Howells-Jones R, Price P, Harding KG, et al. A double-blinded, randomised study to determine the effect of omega-3-marine triglycerides on intermittent claudication. Yearbook 2005, The Vascular Society of Great Britain & Ireland; 2005:Abstract 86.
30. Gans RO, Bilo HJ, Weersink EG, Rauwerda JA, Fonk T, Popp-Snijders C, et al. Fish oil supplementation in patients with stable claudication. Am J Surg. 1990;160(5):490–5.
31. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. Br Med J. 2001; 322(7300):1479–80.
32. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. Br Med J. 2014;349:g6501.
33. Loke YK, Derry S. Reporting of adverse drug reactions in randomised controlled trials—a systematic survey. BMC Clin Pharmacol. 2001;1:3.
34. Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. Br Med J. 2014;348:f7668.
35. Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med. 2009;169(19):1737–9.
36. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. J Am Med Assoc. 2001;285(4):437–43.
37. Loke YK, Mattishent K. If nothing happens, is everything all right? Distinguishing genuine reassurance from a false sense of security. Can Med Assoc J. 2015;187(1):15–6.
38. Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective healthcare program. J Clin Epidemiol. 2010;63(5):502–12.
39. Chassany O, Michaux A, Bergmann JF. Drug-induced diarrhoea. Drug Saf. 2000;22(1):53–72.
40. Robinson S. NICE alerts GPs to drug-induced headaches. GP. 2012;26:12.
41. WHO. Atlas of headache disorders and resources in the world. In: Saxena S, Dua T, editors. Switzerland: World Health Organization; 2011.

42. WHO. Glossary of terms used in pharmaco vigilance 2011. http://www.who-umc.org/DynPage.aspx?id=22684. Accessed 20 Mar 2015.
43. Ely JW, Osheroff JA, Ebell MH, Bergus GR, Levy BT, Chambliss ML, et al. Analysis of questions asked by family doctors regarding patient care. Br Med J. 1999;319(7206):358–61.
44. Gabbay J, le May A. Evidence based guidelines or collectively constructed "mindlines?" Ethnographic study of knowledge management in primary care. Br Med J. 2004;329(7473):1013.

Anatomical Principles of the Circulatory System

2

Raisa Cristina Teodoro da Silva, Patric Emerson Oliveira Gonçalves, and Ligia de Loiola Cisneros

Abstract

The circulatory system comprises two interrelated systems: the cardiovascular and the lymphatic vascular systems. The cardiovascular system is composed by the heart and its distribution network: arteries, veins, and capillaries [Color textbook of histology, Philadelphia, 2007]. Its ramifications are depicted inside this chapter. In parallel, the lymphatic system consists of an extensive network of vessels similar to veins that are spread throughout the body. These plexuses contain nodes in its path that are responsible for filtering and carrying back to the blood stream fluids from organs and tissues that did not return to the blood capillaries [Color textbook of histology, Philadelphia, 2007; Gray's anatomy: the anatomical basis of clinical practice, Edinburgh, 2008]. For a better understanding of the main problems and diseases related to this system it is extremely important to review the anatomy of the vessels and the heart before going to the next chapters.

Introduction

The circulatory system comprises two interrelated systems: the cardiovascular and the lymphatic vascular systems. The cardiovascular system is composed of the heart and its distribution network: the arteries, veins, and capillaries [1]. It is

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essential that the practitioner understands that this system plays a crucial role mediating different and complexes interactions, i.e., delivery, removal, transport, maintenance, and prevention. This system ensures a continued blood transport to meet the demands of oxygen, nutrients as well as working as a buffer removing carbon dioxide and metabolic products from cells, maintaining its pH levels under different circumstances (e.g., during physical activity) [1, 2]. Moreover, blood transports hormones from glands to target cells as well as it works to regulate the body's temperature. In parallel, the lymphatic system consists of an extensive network of vessels similar to veins that are spread throughout the body. These plexuses contain nodes in its path that are responsible for filtering and carrying back to the blood stream fluids from organs and tissues that did not return to the blood capillaries [1, 3].

We will first review the cardiovascular system: heart, vessel's anatomy, arterial and venous system. At the end of this chapter we will also revise the lymphatic system.

The Cardiovascular System

The Heart

As a central piece and the pump of the cardiovascular system, the heart is conical shaped and located between the lungs and right behind to the sternum inside the rib cage. Although the heart is a hollow organ, its wall is thick and made of involuntary muscle. This wall is divided into four layers that are disposed in the following order from outside the heart to the hollow part: pericardium, epicardium, myocardium, and endocardium (Fig. 2.1). The myocardium composes the greatest part of the heart's wall and it is made of cardiac striated muscle [4]. The sinuatrial (SA) node, the heart's natural pacemaker, is located in the epicardium between the superior vena cava and the right atrium and is responsible for starting the stimulation of the heart through the atria. After discharging the stimuli, the depolarization is transmitted to the AV node and its bundle to contract the ventricles [5].

This hollow organ is divided into four different chambers, two atria and two ventricles that are respectively responsible for receiving and pumping blood. Moreover, one can separate the blood flow into two circuits: pulmonary and systemic circuit that are responsible, consecutively, for the blood convey between heart and lungs, and heart and tissues [1] (Fig. 2.2).

Because the left ventricle is responsible for pumping blood at much higher pressure to the systemic than to the pulmonary circuit, it usually has the greatest hypertrophied wall of the ventricles [5].

Vessels' Wall: The Endothelium

The walls of vessels differ based on whether it is carrying blood from or towards the heart. Arteries are exposed to a much higher internal pressure and so are thicker and morphologically more complex than veins, which carry blood from tissues to the heart at a lower pressure [1].

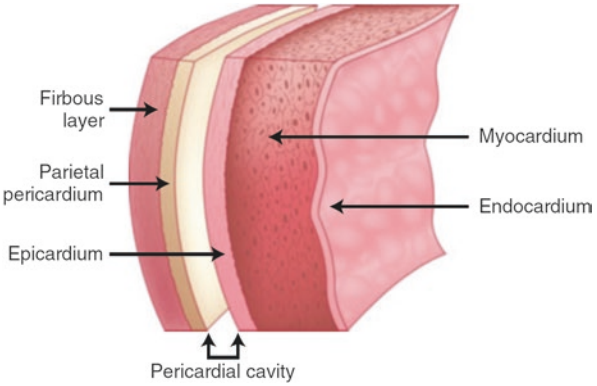


Fig. 2.1 Layers of the heart wall. Reprinted from *Davies A and Scott A. Cardiac Anatomy and Electrophysiology. In: Starting to Read ECG. Springer. 2015*

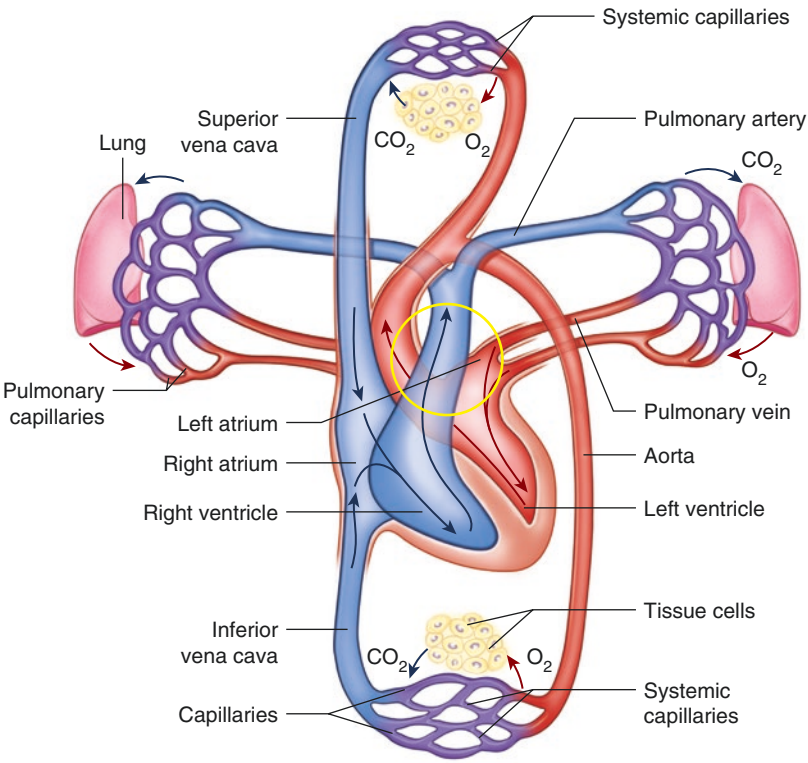


Fig. 2.2 Overview of pulmonary and systemic circuits

The endothelium is the inner cellular lining of all blood vessels, which come into direct contact with circulating blood or lymph [6] (Fig. 2.3). Endocardium is the endothelium of the interior surfaces of the heart chambers. Vascular endothelial

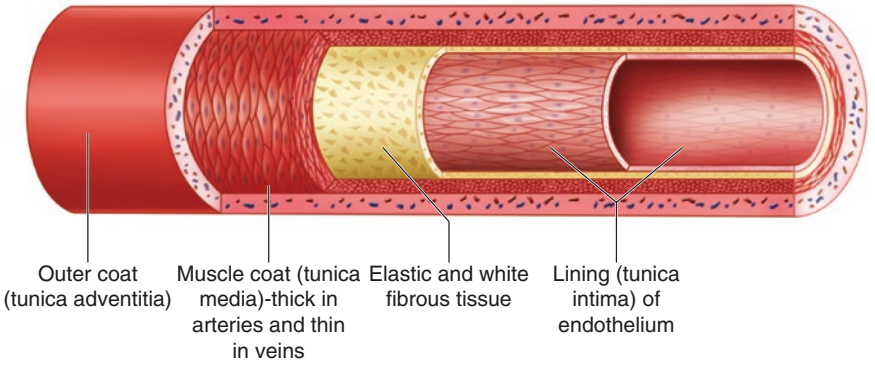


Fig. 2.3 Structure of vessels' wall

cells are those in direct contact with blood whereas those in direct contact with lymph are known as lymphatic endothelial cells. The endothelium acts also as a barrier and regulates the exchange of small and large molecules [7].

Endothelial cells are located on the inner layer of the blood vessels, the tunica intima. Endothelium has a substantial role in regulating the function of vasomotion by its ability to metabolize circulating vasoactive substances and responding to neurotransmitters and vasoactive factors [7, 8].

Endothelial cells are typically aligned in the direction of blood flow, overlapping immediately adjacent cells. They may be continuous (fenestrated or nonfenestrated) and discontinuous. Nonfenestrated continuous endothelium can be found in arteries, veins, and capillaries of the brain, lung, heart, or skin. In arteries and veins, they appear more continuous and thicker than those in capillaries [8]. Fenestrated endothelium occurs in locations of increased filtration or transendothelial transport, such as exocrine and endocrine glands, such as gastric and intestinal mucosa, choroid plexus, glomeruli, and renal tubules. Discontinuous endothelium exists in the liver [6]. The endothelium is indispensable for body homeostasis. It participates in both physiologic and pathologic processes including atherosclerosis, hypertension, pulmonary hypertension, sepsis, and inflammatory syndromes [7].

Coronary Irrigation

As a muscle pump, the external portion of the heart's wall requires its own blood supply, which is provided by arteries and veins surrounding its wall. Apart from that, the inner portion of the heart's wall, i.e., the endocardium, receives nutrients and oxygen supply directly from the chambers and so does not need vessels for its irrigation. Therefore, the atria and ventricles have both, arterial and venous supply [5].

There are two main coronary arteries composing the arterial supply of the heart, the **right coronary artery** (RCA) and the left coronary artery. The right coronary artery originates from the right aortic sinus of the ascending aorta and runs within the coronary sulcus between atria and ventricles (Figs. 2.4 and 2.5). It is responsible

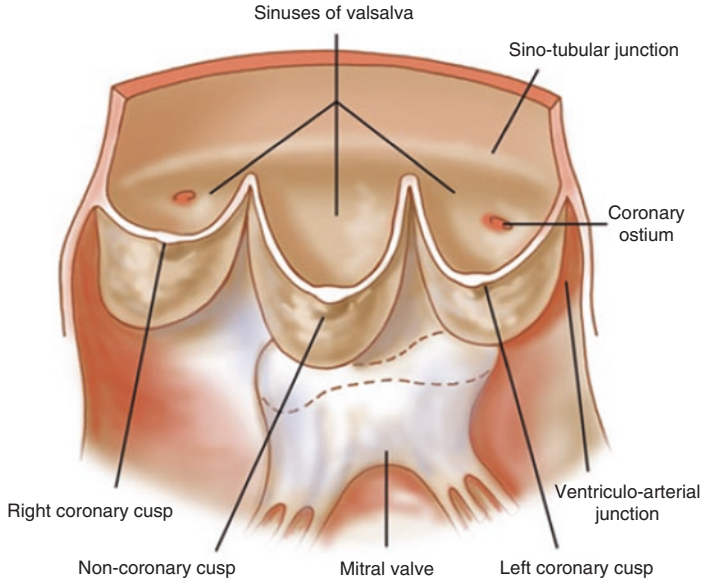


Fig. 2.4 Aortic sinuses of the heart. Reprinted from *Devarajan and Subramaniam. Applied Anatomy of the Aorta. In: Subramaniam K, Park KW and Subramaniam B. Anesthesia and Perioperative Care for Aortic Surgery. Springer. 2011*

for irrigating the right atrium, **sinuatrial** (SA) and **atrioventricular** (AV) **nodes** as well as the interventricular septum. Accordingly, from the right coronary artery arises a sinuatrial nodal branch to supply the heart's pacemaker, the SA node. However, in 40 % of people, the circumflex branch of the left coronary artery is that gives off the SA nodal branch. In its turn, the AV node is also supplied by a subdivision of the right coronary artery, the atrioventricular nodal branch. That arm arises from the right coronary artery in the posterior portion of the heart at the crux of the heart i.e., the meeting point between the four chambers. Moreover, a so-called right marginal branch emerges from the right coronary artery in its path within the sulcus towards the apex. The right border of the heart is supplied by the right marginal branch and does not reach its apex [5].

The ventricles area is supplied by the posterior interventricular branch, which also comes from the right coronary artery. The right coronary artery supplies most of the right ventricle and the diaphragmatic surface of the left ventricle.

In its turn, the **left coronary artery** (LCA) originates from the left aortic sinus running with the right coronary artery in the coronary sulcus on the left side of the pulmonary trunk (Fig. 2.4). Then, the left coronary artery splits into two arms: the circumflex branch and the anterior interventricular branch. As mentioned previously in this section, the SA nodal branch often emerges from the right coronary artery precisely from the circumflex branch of the left coronary artery. The circumflex branch arises from the right coronary artery and follows towards the posterior portion of the heart and to the left within the coronary sulcus [5]. It is then responsible for irrigating the left atrium and left ventricle. This comes to a great importance as

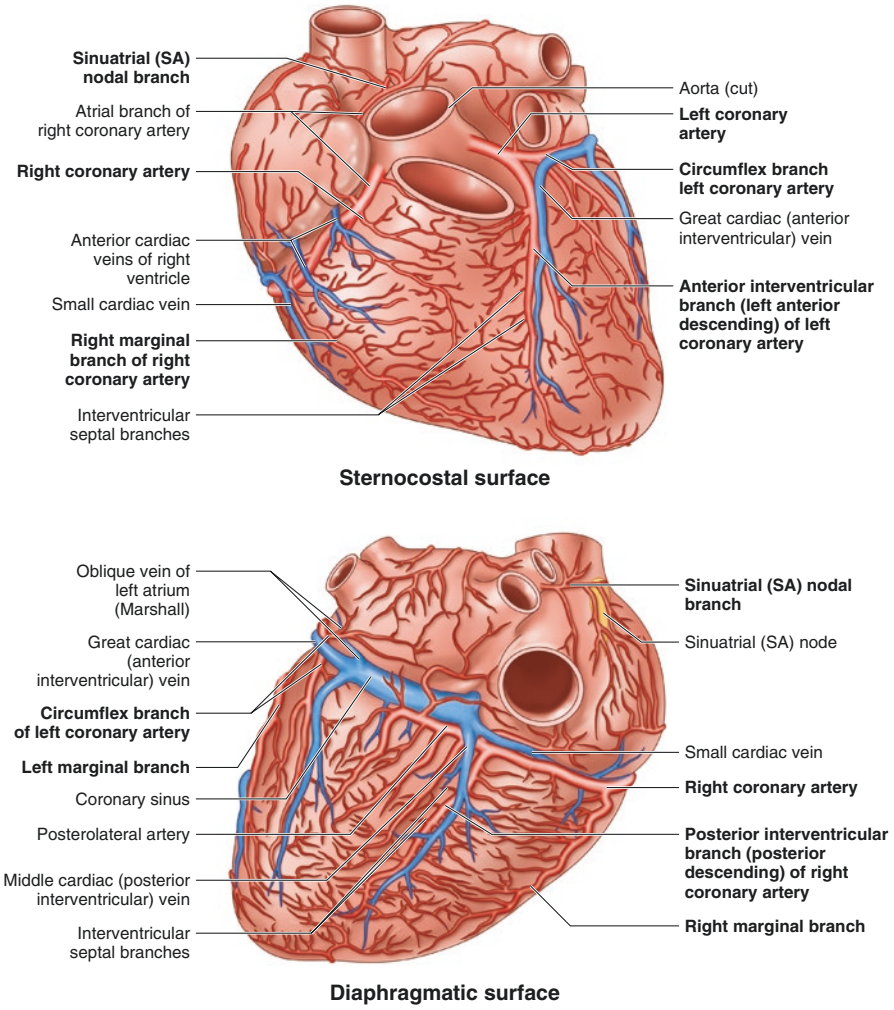


Fig. 2.5 Heart supply with overview of arteries and veins

anomalies of the circumflex branch have been reported. The second branch of the left coronary artery, the anterior interventricular, runs in the anterior interventricular sulcus towards the apex. It is the blood supply for the ventricles [5].

It is common that one's heart develops a collateral circulation should any closure in any main coronary artery occur (e.g., atherosclerosis). It occurs in the so-called functional end arteries [5].

When it comes to the venous supply, one needs to consider that the heart is greatly drained through veins that combine into a greater vessel, the coronary sinus. The second main drain course is through small veins that return blood to the right atrium [5]. Refer to Table 2.1 for details on venous supply of the heart.

Table 2.1 Main cardiac venous system [5, 10]

Vein	Origin	Path	Fuses into the	Drain
Great cardiac vein	Apex of heart ascending with the anterior interventricular branch of the left coronary artery	First: turns left at the coronary sulcus	Coronary sinus (opens into the right atrium)	Areas supplied by the left coronary artery
		Second: surrounds the left side of the heart together with the circumflex branch of the left coronary artery		
Middle cardiac vein (or posterior interventricular vein)	Cardiac apex	Ascends to the coronary sinus		Areas supplied by right coronary artery
Small cardiac veins (or Thebesius' vein)[a]	Between right atrium and ventricle	Follows the right marginal branch of the right coronary artery. Often merges with the right marginal vein		
Oblique veins of the left atrium[b]	Left atrium	Runs obliquely on the posterior wall of left atrium. Later fusing into the great cardiac vein		

Adapted from: *"Moore K, Dalley A, Agur A. Thorax. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014. p. 71-180."* **and** *"Standring S. Heart and great vessels. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone/Elsevier; 2008. p. 959–88."*

[a]Small cardiac vein: it may be absent

[b]Oblique veins of the left atrium: it usually atrophies before birth, but can be present in some adults

Blood returning from coronary walls that is not drained through vessels mentioned in Table 2.1 returns to the right atrium through small veins and the anterior cardiac vein [9].

The Arterial System

Aorta and Its Branches

Authors anatomically divide the aorta into the **ascending aorta, aortic arch, descending thoracic** and **abdominal aorta** [10] (Fig. 2.6).

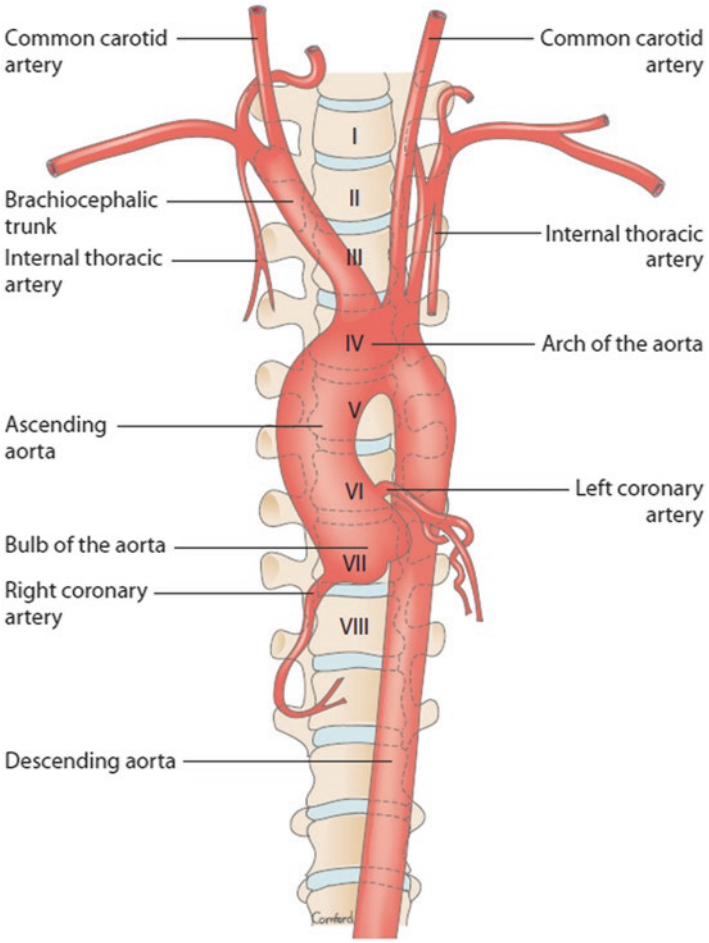


Fig. 2.6 Aorta course and ramifications. Reprinted from *Berdajs D and Turina MI. Surgical Anatomy of the Aorta. In: Operative Anatomy of the Heart. Springer. 2011*

The **ascending aorta** usually lengths 5 cm long [10] and its diameter is 2.5 cm on average [5]. It rises obliquely from the left ventricle, curving forward and to the right, at the level of the lower edge of the third left costal cartilage and it gives origin to the coronary arteries [10].

The transverse part of the aorta is named "**aortic arch**" as it bends to become the descending aorta. The arch begins to the second right sternocostal joint next to the sternal angle and leans to the left, following inferiorly. Three branches emerge from its upper edge: the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery [10].

The **brachiocephalic trunk**, the largest ramification of the aortic arch, is 4–5 cm long [10] and emerges from the curvature of the aortic arch posteriorly. The trunk

surges behind the manubrium and anterior to the trachea, it then goes up diagonally until it positions to the right of the trachea and to the sternum-clavicular joint. Then, it divides into right common carotid and into the right subclavian arteries [5] (Fig. 2.6).

The second branch of the aortic arch, the **left common carotid artery** (Fig. 2.6), arises posterior to the manubrium, posterior and to the left of the brachiocephalic trunk. Subsequently, it rises above the left subclavian artery and enters the neck passing posteriorly to the left subcostal joint [10].

The **left subclavian artery**, the third and last branch of the aortic arch, originates on the left side of the left common carotid artery and rises along the left side of the trachea [5] (Fig. 2.6).

The aortic arch has now turned into the descending thoracic aorta, and it descends approaching the medial plane by moving the esophagus to the right [10].

The **thoracic aorta** runs posteriorly to the root of the left lung, pericardium, and esophagus [10]. It begins on the left side of the inferior border of the T4 vertebra descending posteriorly in the mediastinum on the left sides of T5–T12 vertebrae [5]. It enters the abdomen through the aortic hiatus of the diaphragm where it changes its name to **abdominal descending aorta** (Fig. 2.6), starting close to the 12th thoracic vertebra and splitting at the level of the fourth lumbar vertebra [11].

The primary visceral branches of the abdominal aorta are:

1. The **celiac trunk** that supplies the foregut through its main branches: artery left gastric, artery splenic, and artery common hepatic
2. **Superior mesenteric artery**, which supplies the midgut through the middle colic artery, jejunal-ileal, ileocolic, and right colic
3. The **inferior mesenteric artery,** which supplies the hindgut, with the branches: left colic, sigmoid arteries, and superior rectal arteries

The **abdominal aorta** follows the thoracic aorta and it has its visceral branches in pairs. Its main branches are the renal, testicular or ovarian arteries [10].

Cervical and Intracranial Irrigation

The area between the chest and the neck is an important functional area in which main organs are comprised, such as thyroid, larynx, and glands [12]. Among major structures, we can highlight the carotid arteries, which carry blood supply to brain along the vertebral arteries.

The **internal carotid** and **vertebral arteries** provide the arterial supply to the brain (Fig. 2.7). After the common carotid artery bifurcates, internal carotid arteries rise up in the neck and into the carotid canal in the temporal bone. This system is responsible for irrigating the most anterior cerebral portion. The smallest terminal branch of the internal carotid is the anterior cerebral artery while the middle cerebral artery is the largest (Fig. 2.7) [13, 14].

The **vertebral arteries**, derived from the subclavian arteries, follow upwards in the neck passing through the foramen of the upper cervical vertebrae and pass the cranial opening across the foramen magnum [14]. It supplies major branches of the spinal cord, brainstem and cerebellum, and a significant portion of the posterior

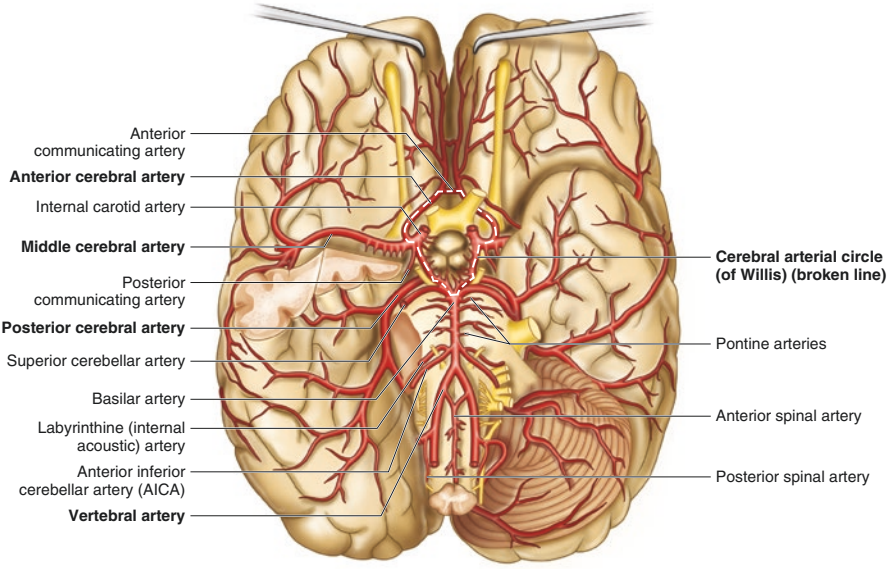


Fig. 2.7 Inferior view of arteries of the brain. Circle of Willis is depicted

cerebral hemispheres. The basilar artery is a large vessel formed by the union of the two vertebral arteries, and the posterior cerebral artery is the terminal branch of the basilar artery [14].

The **circle of Willis** is an arterial anastomosis formed by the branches of both internal carotid arteries and both vertebral arteries (Fig. 2.7) [15]. Should an artery occlusion occurs, this system is capable of redirecting blood to that area that is lacking irrigation. Therefore, that patient could remain asymptomatic as blood flow is reestablished [15].

Thorax and Upper Limb

The **subclavian artery** provides blood supply to the upper extremity (Fig. 2.8). After this artery crosses the side edge of the first rib, it becomes the axillary artery [16].

The **axillary artery** converts into the brachial artery near the lower border of the teres major muscle, thus following in the flexor compartment in the medial arm region [16]. The subscapular artery is the largest branch of the axillary artery [17], and the main branches of the axillary artery are illustrated in Fig. 2.8.

The **brachial artery** is divided into the radial and ulnar arteries distally to the elbow. These arteries have branches that form a rich network of anastomoses that carry blood to the hand, especially to the palmar face [17].

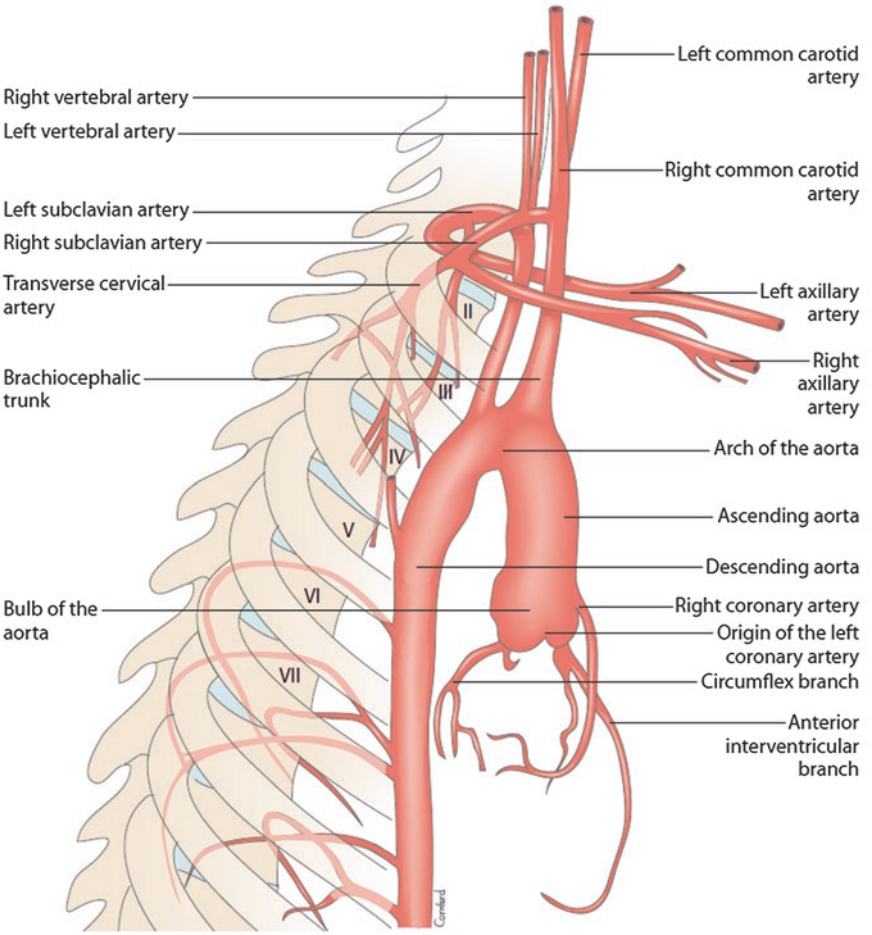


Fig. 2.8 Thorax overview of aorta ramifications. Reprinted from *Berdajs D and Turina MI. Surgical Anatomy of the Aorta. In: Operative Anatomy of the Heart. Springer. 2011*

Lower Limb

The lower limbs are responsible for creating propulsive force through the gait as well as providing a stable foundation to support body's weight during activities. Thereafter it an efficient irrigation system.

The **femoral artery** is the main arterial supply to the lower limb (Fig. 2.9, Flowchart 2.1). It enters the thigh behind the inguinal ligament as a continuation of the external iliac artery and follows its path almost vertically in relation to the adductor tubercle of the femur. Its distal portion passes through the adductor magnus muscle tunnel (adductor hiatus), entering the popliteal space to become the popliteal artery [18].

The **popliteal artery**, the continuation of the femoral artery, is the deeper structure in the popliteal fossa. It passes inferior-laterally across the tank and ends

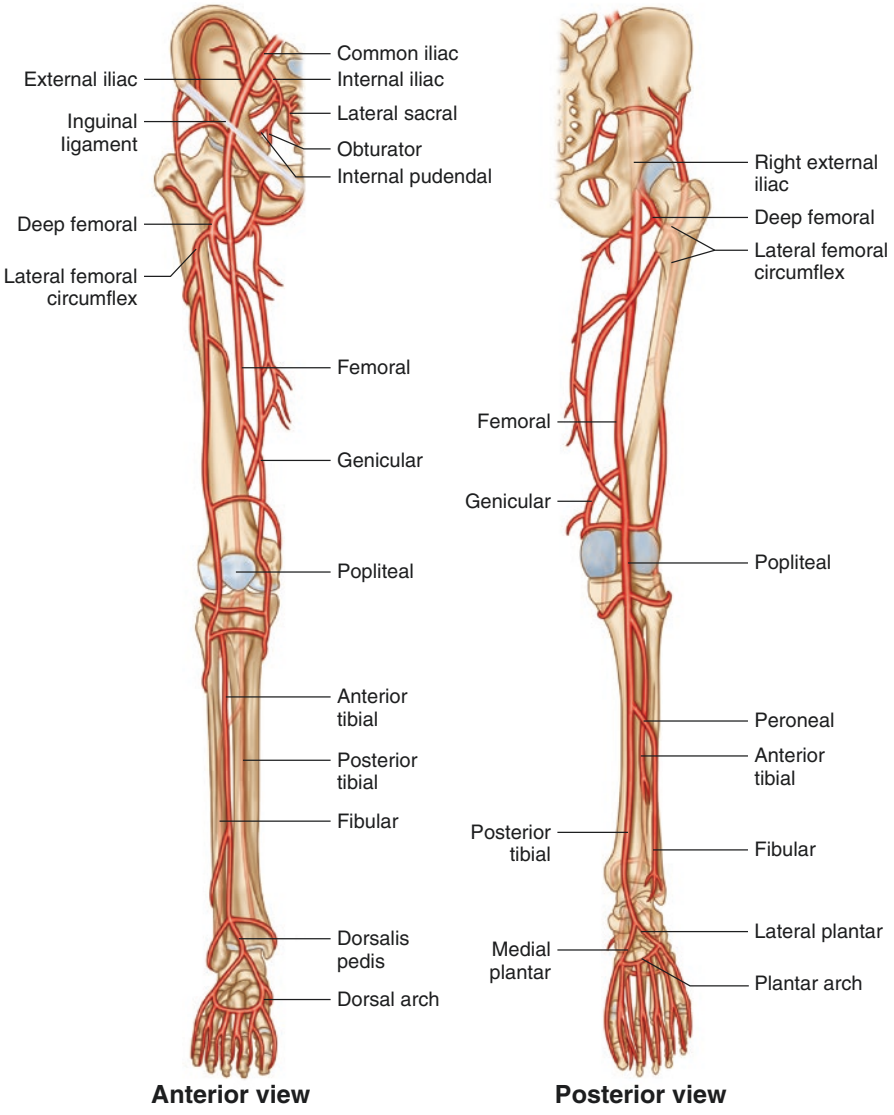
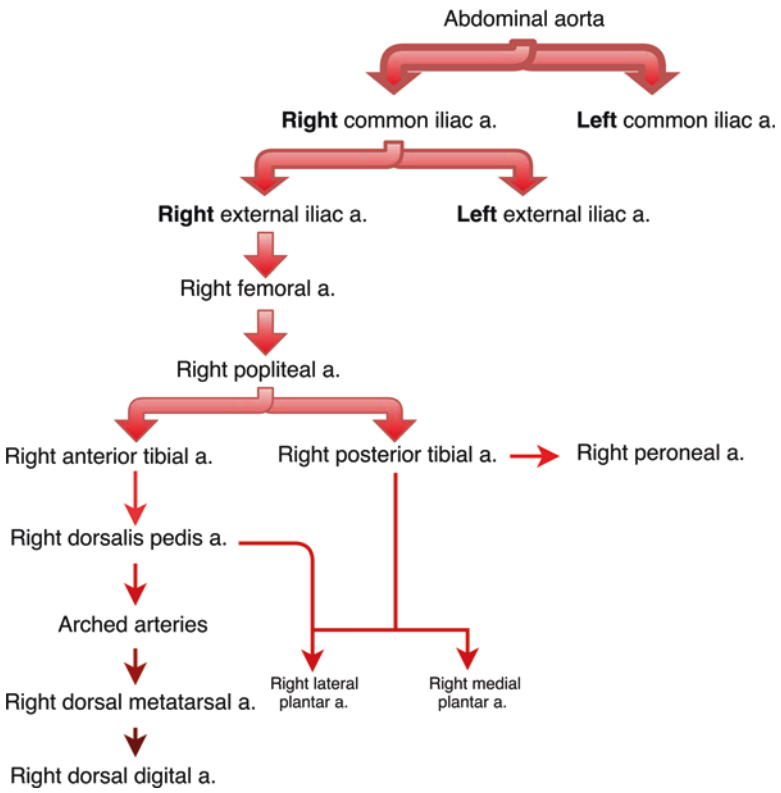


Fig. 2.9 Arteries of the lower limb

at the lower edge of the popliteal muscle divided into anterior and posterior tibial arteries. Five branches of the popliteal artery supply knee structures such as the capsule and ligaments. These branches participate in the formation of periarticular geniculate anastomosis that provides collateral circulation which is capable of



Flowchart 2.1 Scheme of the lower limb arteries

maintaining blood supply to the leg at a full flexion of the knee, which can double the popliteal artery [19].

One of the terminal branches of the popliteal artery, the smaller, is the **anterior tibial artery**, begins at the lower edge of the popliteus muscle, and passes through and above the interosseous membrane to then descend on the anterior surface of the leg. At the level of the ankle joint, the anterior tibial artery becomes the dorsalis pedis artery. The last and largest branch of the popliteal artery is the **posterior tibial artery**. This artery supplies the posterior compartment of the leg and foot, and it originates the peroneal artery, which runs on a parallel and lateral path to the posterior tibial artery. The other terminal branch of the popliteal artery is the posterior tibial artery. It descends with the tibial nerve and vein and supplies the posterior compartment of the leg and to the foot. At the level of the ankle joint, it splits into medial and lateral plantar arteries, as well as in arteries to irrigate the foot sole (Fig. 2.9). The **fibular artery**, the larger branch of the posterior tibial artery, arises at the origin of this artery and runs parallel to it [19].

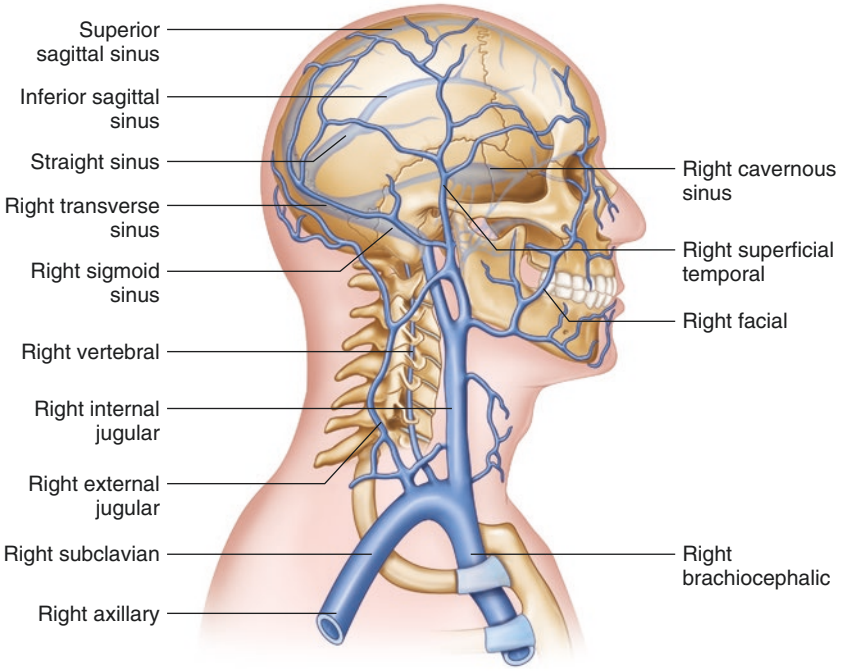


Fig. 2.10 Venous supply to the head. Lateral view of the right side

The Venous System

Cervical and Intracranial

A complex system of deep and superficial veins provides the cerebral venous drainage, which are valveless and have thin walls lacking of muscle tissue. These veins pierce the arachnoid and the inner layer of the dura mater and drain into the dural venous sinuses [14]. The **diploic veins**, developed fully at the age of two, cross the cranial vault and connect the skull's calvaria. The emissary veins connect the scalp veins of the venous sinuses being, hence, a relevant route of infection [15].

The venous sinuses are the upper and lower sagittal sinus, straight sinus, transverse sinus, the sigmoid sinus, the occipital sinus, the cavernous sinuses, upper and petrosal sinuses. They are located between the periosteum and the dura mater (Fig. 2.10) consisting of fibrous and thick walls and receive tributaries from the brain, skull bones, orbit, and inner ear [15].

Posteriorly to the jaw bone's angle, the **external jugular vein** is formed. It follows its course through the sternocleidomastoid muscle, running towards the subclavian vein, where it drains [15] (Fig. 2.10).

As an extension of the sigmoid sinus, the **internal jugular vein** follows inferiorly through the jugular foramen until it leaves the skull towards the heart. This large vein receives blood from the brain, face, and neck, then tracks down on the neck beside to the carotid and ends by joining the subclavian vein behind the collarbone [15].

Thorax and Upper Limb

A group of superficial and deep veins are responsible for the venous drainage of the upper limb.

The superficial group begins with the dorsal arch of the hand, which in its radial portion turns into the cephalic vein. The **cephalic vein** follows its path towards the shoulder rising along the radial portion of the arm and then pierces the fascia emptying into the axillary vein (Fig. 2.11). The **basilic vein** drains from the ulnar part of the dorsal arch of the hand, follows medially in the forearm, and pierces the deep fascia at the elbow to form the axillary vein. At the level of the cubital fossa, the **median cubital vein** connects the cephalic and basilic veins. The deep veins group follows the arteries and drains blood into the axillary vein, which then drains into the subclavian vein [16].

The **intercostal veins** accompany the arteries and intercostal nerves. Eleven posterior intercostal veins anastomoses with the anterior intercostal veins and eleven subcostal veins in each hemithorax. A greater extent of the posterior intercostal veins ends in the azygos/hemiazygos venous system which drains to the superior vena cava while the part of these veins of the first intercostal space drains right into the brachiocephalic (or innominate) vein [5] (Fig. 2.12).

The **right subclavian vein** and the **right internal jugular vein** come together to form the right brachiocephalic vein at the root of the neck. The left brachiocephalic vein has a similar origin and joins the right brachiocephalic vein to form the superior vena cava [9].

The **superior vena cava** is formed by the union of the two brachiocephalic veins and drains venous blood from the head, neck, and upper limbs into the upper part of the right atrium [9]. The azygos veins join the superior vena cava just before it enters the pericardium. They drain the posterior parts of the intercostal space, posterior abdominal wall, pericardium, diaphragm, bronchus, and esophagus.

The **inferior vena cava**, larger than the superior vena cava [9], enters the thorax anteriorly to the eighth thoracic vertebra through the diaphragm and it goes to the right atrium. Whilst, two pulmonary veins leaving the lung arrive in the left atrium carrying oxygenated blood [9].

Lower Limb

The veins of the lower extremities may be divided into three groups: superficial, deep, and perforating veins. The **superficial veins** are located above the fascia and under the skin and it is consisted of the great and small saphenous veins and its tributaries.

The **great saphenous vein** is a superficial vein and originates as an extension of the medial marginal vein of the foot and it ends in the femoral vein close to the

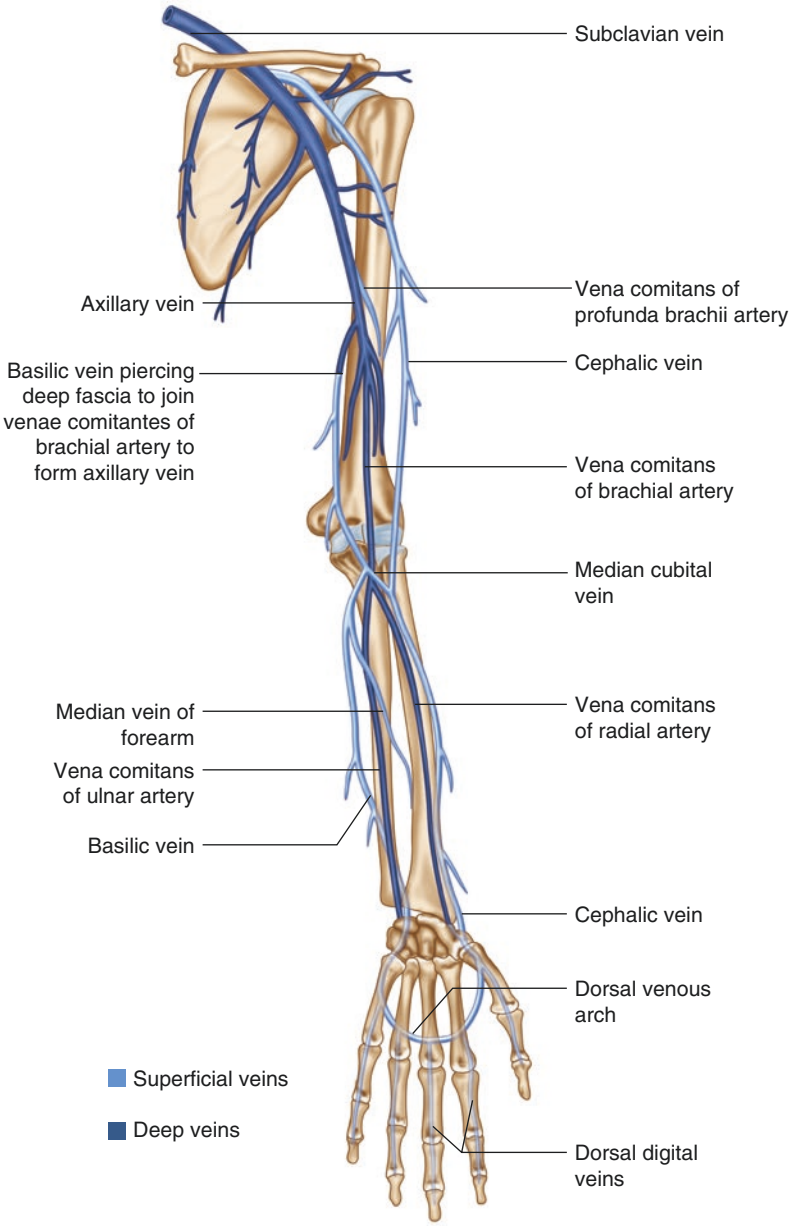


Fig. 2.11 Overview of veins of the left upper limb

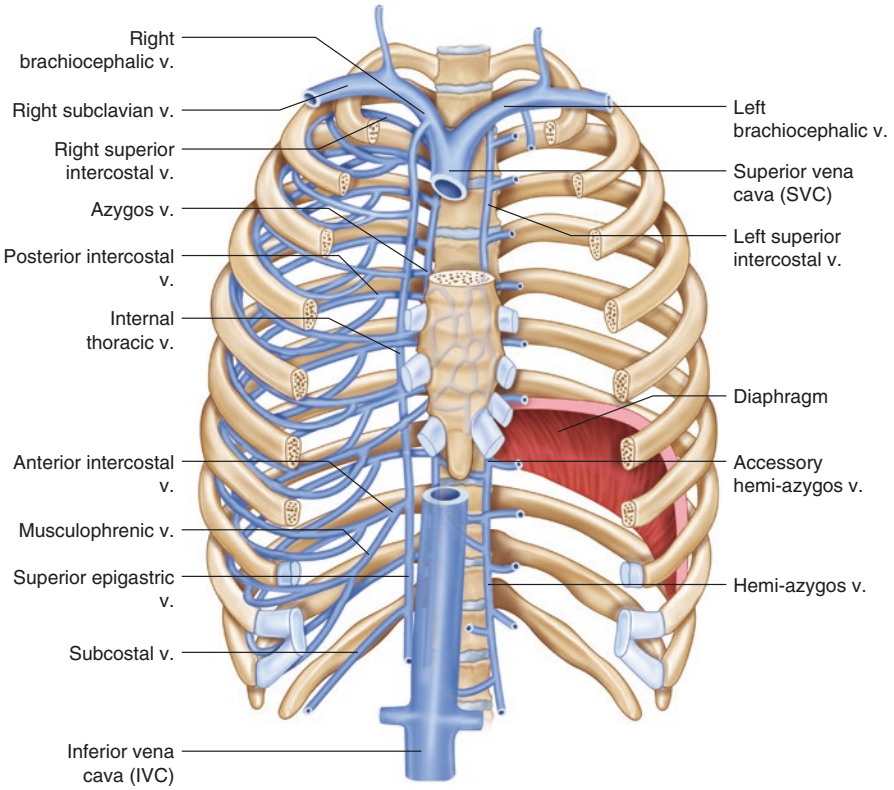


Fig. 2.12 Overview of the thoracic venous circulation

inguinal ligament [20]. It ascends anteriorly to the medial malleolus, crosses the surface of the tibia obliquely, and reaches the medial border of the tibia. Subsequently, it ascends behind to the knee, curves to the front around the medial thigh part, passes through the bottom of the saphenous hiatus in the deep fascia, and joins the femoral vein at approximately 2.5–3.5 cm below and laterally to the pubic tubercle [20].

A single vein is found in the calf in about two-thirds of individuals while the left third has a duplicated system. In most instances, the only great saphenous vein is dominant [21]. The great saphenous vein, the longest vein in the body [20], holds around 10–12 valves. Anatomically, these valves are found to a greater extent in the leg than in the thigh [19].

Branches passing behind the knee connect the great saphenous to the small saphenous vein, and several perforating veins join the saphenous with the deep veins. The superficial iliac circumflex, the superficial epigastric, and the superficial external pudendal veins are tributaries of the saphenous-femoral junction [18].

The **small saphenous vein** has several valves along its course. It arises near to the dorsal venous arch of the foot and rises behind the lateral malleolus, follows the

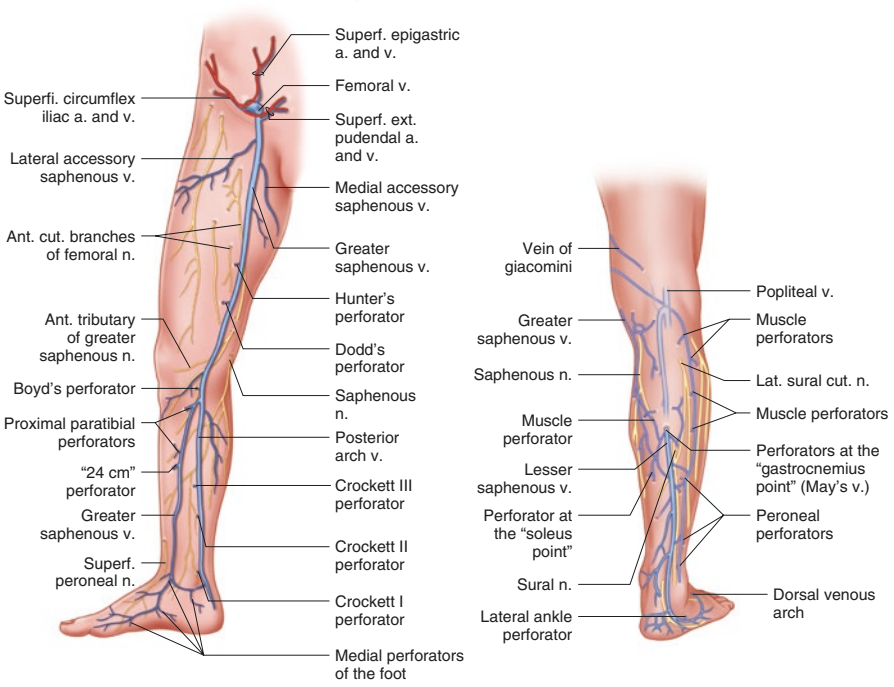


Fig. 2.13 Veins on the lower limb

lateral border of the Achilles' tendon and goes to the back of the leg (Fig. 2.13). This vein ends in the popliteal vein after piercing the deep fascia and passing between the two heads of the gastrocnemius muscle [18].

The deep veins are satellites to the major arteries, running in parallel to its courses, mostly paired. One characteristic of the venous system in the lower limb is that it has a greater amount of venous valves than in the arm [22].

The **posterior tibial veins** follow its course with the posterior tibial **artery**. This group receives tributaries from the calf muscles and connections from superficial veins and the peroneal veins. The peroneal veins run with a similarly named artery and receive tributaries from soleus and superficial veins [22]. The **anterior tibial vein** follows its course to form the dorsalis pedis artery. It leaves the anterior compartment between the tibia and fibula, and passes through the proximal end of the interosseous membrane. Both the anterior and posterior veins drain into the popliteal vein at the distal border of the popliteal [22]. The **profunda femoris vein** (or deep femoral vein) is situated anteriorly to its alongside artery, the femoral artery. Through its tributaries, it binds distally to the popliteal vein and proximally to the inferior gluteal vein. In some cases, the femoral veins drain the medial and lateral circumflex femoral artery [22].

Perforating veins are communicating vessels found mainly around the ankle and the medial side of the lower leg. They link the superficial (great saphenous vein) and deep veins of the lower leg. They have valves that are arranged to prevent the blood flow from deep to superficial veins [18].

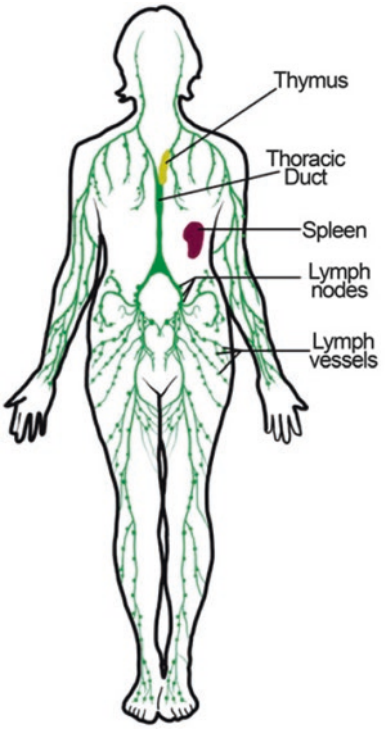


Fig. 2.14 The lymphatic system. Reprinted from *Iaizzo PA. General Features of the Cardiovascular System. In: Handbook of Cardiac Anatomy, Physiology and Devices. Springer. 2009*

The Lymphatic System

The lymphatic system is a blunt-ended linear system that plays a vital part of the transport and immune systems, operating in conjunction with the circulatory system [23]. Lymphatic system moves a clear-to-white fluid derived from interstitial fluid, the lymph. Lymph fluid consists of tissue fluid, proteins, fat, and white blood cells (predominantly lymphocytes). The lymphatic system is composed of a complex network of lymph vessels, termed lymphatics, lymph nodes and lymphoid organs [23, 24] (Fig. 2.14).

Lymphatic vessels are thin-walled capillaries, highly permeable, found in nearly every organ and blood vessel-containing interstitial tissue [24, 25]. They cannot be found in vascular structures and organs such as hair, nails, epidermis, cornea, brain, and retina [24]. Lymphatic vessels serve as a drainage system for excess fluid and large molecules or cells that cannot easily find their way back into venules [25].

Lymphatic capillaries (initial or terminal lymphatics) start blind-ended in the tissue, where they take up lymph. Lymphatic capillaries contain large gaps between their endothelial cells to enable passage of lymph fluid. The interstitial fluid, from the surrounding tissues, enters through the initial lymphatics, connected to collecting vessels by the precollecting lymphatics that combine to form large ducts and trunks [23, 25] (Fig. 2.15). Lymph is drained and transported through propulsion to

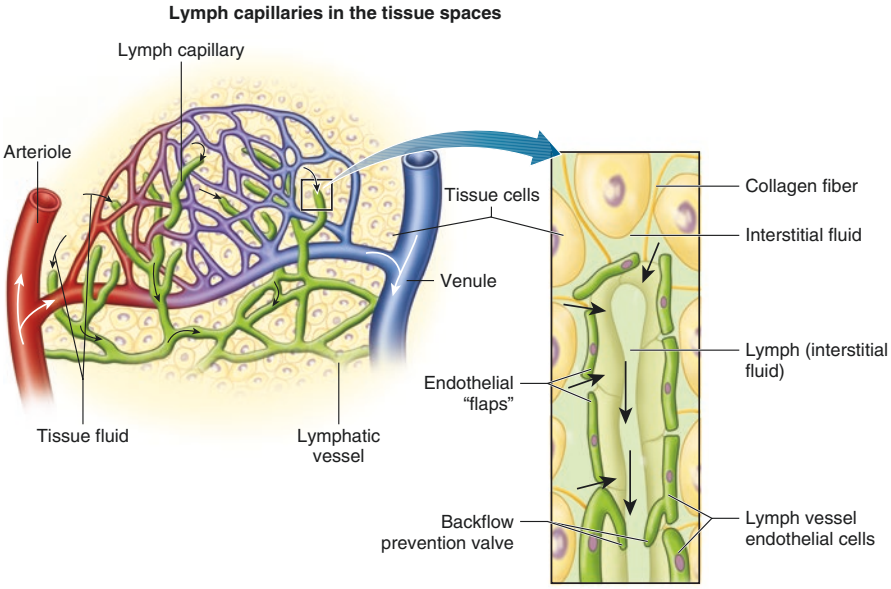


Fig. 2.15 Lymphatic capillaries and the arterioles and venules of the cardiovascular system

lymph nodes, before backing to blood circulation via the thoracic and lymphatic ducts that join to the subclavian veins [25, 26]. Lymph is moved forward by respiratory movement, arterial pulsation, skeletal muscle action, and the rhythmic contractions of smooth muscle in walls of collecting lymphatic vessels and affected by nerve and humoral mediators [6, 23].

Lymphatic Vessels

Initial lymphatic capillaries: The lymphatic system starts in connective tissue spaces in several regions of the body to which they are distributed and are bathed by the intercellular tissue fluids. At this level, a single layer of endothelial cells is present in an irregular wall comprising nonfenestrated endothelial monolayer cells with gaps that provide an entry for interstitial fluid (lymph) into the system. The diameter of initial lymphatics ranges from 10 to 60 μm with a wall thickness of 50–100 nm, blind-ended. Actin filaments support them, which are contractile. This structure allows them to act as a one-way valve system [6, 23].

Precollecting Lymphatics: Precollecting lymphatics drain fluid from the initial lymphatics to collecting vessels. They have segments which contain valves and are surrounded by a basement membrane and one or more layers of smooth muscle cells that may contract and begin the propulsion of lymph through the system [23].

Collecting Lymphatics: Collecting lymphatics are larger and classified as afferent or efferent to specify whether they carry lymph to or from the lymph nodes [27]. At this level, three typical layers of vessel wall are evident: the intima, media, and adventitia. The intima layer is composed of a monolayer of endothelial cells. The

media layer has one to three layers of smooth muscle cells. And the adventitia layer is composed of fibroblasts, connective tissue, and terminal nerves [6, 23].

Lymphoid Organs

Lymph nodes: Lymph nodes are one of a number of organs nodes and the major sites of B cells, T cells, and other immune cells. It is a bean-shaped mass of lymphoid tissue enclosed by a capsule of connective tissue, covered with lymphatic smooth muscles [23]. Lymph nodes are situated in the course of lymphatic vessels so that the lymph passes through them on their way to the blood vessel. Lymph nodes filter the lymphatic fluid and store special cells that can phagocytose molecules and particles such as cancer cells or bacteria that are traveling through the body in the lymph fluid. Lymph nodes are distributed widely throughout the body. Collections of them are present in the inguinal and axillary regions as well as the neck, thorax, and abdomen [6, 27].

Lymphatic trunks and ducts: The lymphatic trunks and ducts are the largest vessels (diameters on the order of 2 mm) that drain lymph. The **trunks** collect fluid from organs, extremities, and trunk. The **ducts** transport lymph into the venous circulation [23]. Lymphatic trunks are formed by confluence of many efferent lymph vessels and drain into one of the two lymph ducts. The thoracic duct is the final branch of the lymphatic system. It receives flow from the left half of the thorax, left arm, and left side of the head and neck. Fluid from the right half of the thorax, right arm, and right side of the head and neck is drained to the right lymph duct [27]. The thoracic duct vessels usually start from the level of the 12th thoracic vertebrae (T12) and extends to the root of the neck. The right lymphatic duct courses along the medial border of the Scalenus anterior muscle, at the root of the neck.

References

1. Gartner L, Hiatt J. Circulatory system. In: Gartner L, Hiatt J, editors. Color textbook of histology. 3rd ed. Philadelphia: Elsevier; 2007. p. 251–72.
2. Wilmore J, Costill D. The cardiovascular system and its control. In: Wilmore J, Costill D, editors. Physiology of sport and exercise. 3rd ed. Champaign: Human Kinetics; 2004. p. 139–62.
3. Standring S. Smooth muscle and the cardiovascular and lymphatic systems. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 127–43.
4. Moore K, Dalley A, Agur A. Introduction to clinically oriented anatomy. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia: Wolters Kluwer; 2014. p. 1–70.
5. Moore K, Dalley A, Agur A. Thorax. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia: Wolters Kluwer; 2014. p. 71–180.
6. Sumpio B, Chin J. Vessel wall biology. In: Cronenwett JL, Johnston KW, editors. Rutherford's vascular surgery. 8th ed. Philadelphia: Elsevier Saunders; 2014. p. 34–48.
7. Galley HF, Webster NR. Physiology of the endothelium. Br J Anaesth. 2004;93:105–13.
8. Sandoo A, van Zanten JJ, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. Open Cardiovasc Med J. 2010;4:302–12.

9. Snell R. The thorax: part II—the thoracic cavity. In: Snell R, editor. Clinical anatomy by regions. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 58–112.
10. Standring S. Heart and great vessels. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 959–88.
11. Standring S. Abdomen and pelvis: overview and surface anatomy. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 1041–54.
12. Moore K, Dalley A, Agur A. Neck. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia: Wolters Kluwer; 2014. p. 981–1052.
13. Standring S. Head and neck: overview and surface anatomy. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 397–408.
14. Standring S. Vascular supply and drainage of the brain. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 247–56.
15. Snell R. The head and neck. In: Snell R, editor. Clinical anatomy by regions. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 527–681.
16. Standring S. Pectoral girdle and upper limb: overview and surface anatomy. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 777–90.
17. Moore K, Dalley A, Agur A. Upper limb. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia: Wolters Kluwer; 2014. p. 670–819.
18. Snell R. The lower limb. In: Snell R, editor. Clinical anatomy by regions. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 435–526.
19. Moore K, Dalley A, Agur A. Lower limb. In: Moore K, Dalley A, Agur A, editors. Clinically oriented anatomy. 7th ed. Philadelphia: Wolters Kluwer; 2014. p. 508–669.
20. Standring S. Pelvic girdle, gluteal region and thigh. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 1349–86.
21. Iafrati M, O'Donnell J, TF. Varicose Veins: Surgical Treatment. In: Cronenwett J, Johnston K, Rutherford R, editors. Rutherford's vascular surgery. 8th ed. Philadelphia: Elsevier; 2014. p. 869–84e.2.
22. Standring S. Pelvic girdle and lower limb: overview and surface anatomy. In: Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 40th ed. Edinburgh: Churchill Livingstone; 2008. p. 1329–48.
23. Margaris KN, Black RA. Modelling the lymphatic system: challenges and opportunities. J R Soc Interface. 2012;9(69):601–12.
24. Oliver G, Detmar M. The rediscovery of the lymphatic system: old and new insights into the development and biological function of the lymphatic vasculature. Genes Dev. 2002;16(7):773–83.
25. Barrett T, Choyke PL, Kobayashi H. Imaging of the lymphatic system: new horizons. Contrast Media Mol Imaging. 2006;1(6):230–45.
26. Choi I, Lee S, Hong YK. The new era of the lymphatic system: no longer secondary to the blood vascular system. Cold Spring Harb Perspect Med. 2012;2(4):a006445.
27. Swartz MA. The physiology of the lymphatic system. Adv Drug Deliv Rev. 2001; 50(1–2):3–20.

Atherosclerosis

3

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Abstract

Atherosclerosis is a chronic inflammatory disease of multifactorial origin that occurs in response to endothelial aggression, affecting mainly the intima of medium and large caliber arteries. It is usually consequent to traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, obesity and smoking. It is related with several cardiovascular morbidities such as cerebrovascular disease, coronary, peripheral arterial and renovascular diseases. According to the World Health Organization, cardiovascular disease is the main cause of disability and premature death worldwide. An estimated 17.5 million people died from this cause in 2005, representing 30 % of all deaths in the world. This can be explained by understanding that people are more exposed to risk factors and less exposed to prevent efforts. Atherosclerosis prevention is less costly than treating its complications; thus, identification of subclinical disease in the asymptomatic phase has emerged as a public health and economic imperative.

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Introduction

Atherosclerosis is a chronic inflammatory disease of multifactorial origin that occurs in response to endothelial injury, affecting mainly the intima of arteries of medium and large caliber. It is usually consequent to traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, obesity and smoking habit. However, more rarely, it can be a consequence of inherited diseases such as familial hypercholesterolemia.

Epidemiology

According to the World Health Organization, cardiovascular disease is the main cause of disability and premature death worldwide [1]. An estimated 17.5 million people died from this cause in 2005, representing 30 % of all deaths in the world. This can be explained by understanding that people are more exposed to risk factors and less exposed to prevent efforts. The prevalence of systemic arterial hypertension in the population over 65 years old is approximately 52.3 %, for diabetes mellitus it is about 21 %, obesity is around 27.5 % and for current smokers it is 11.3 % [2]. However, only 24.8 % of North American adolescents from 12 to 15 years old practice at least 60 min of moderate-vigorous physical activity daily, as recommended by the 2008 physical activity guideline [3].

Pathophysiology

Atherosclerosis starts when monocytes migrate from blood stream to the intima (innermost layer of the arterial blood vessel), constituting the foam cells (macrophages that have engulfed lipoproteins). Over time, foam cells accumulate and form an irregular and thick layer distributed along artery lining. Each thickening zone (called atheroma or atherosclerotic plaque) is consisted of cholesterol, smooth muscle cells and connective tissue. The atheroma tends to be formed at large and medium-sized artery, particularly at vessels bifurcation, presumably due to the altered shear stress of such areas, which injures the arterial wall and predisposes to atheroma formation.

Endothelium dysfunction plays a key role in the atherosclerosis pathophysiology. That Endothelial dysfunction downregulates endothelial nitric oxide synthase, the enzyme that generates nitric oxide, which impairs endothelium-dependent vasodilatation and accelerates atherosclerosis. Arteries affected by atherosclerosis lose their elasticity and become narrower. They become progressively damaged and lose their original elastic structure over the years, which can trigger the formation of a blood clot (thrombus). The clot reduces blood flow through the artery and may even cause its complete occlusion. It can also detach and be carried through the blood stream until it reaches a smaller artery, causing an occlusion (embolism). The

disease development occurs mainly in three territories: cerebrovascular, coronary, and peripheral arteries (Fig. 3.1).

Cerebrovascular Disease

It is a pathological narrowing of the intima of the common or internal carotid artery, typically in focal areas called plaques or atheroma. Although the atheroma can remain stable for many years, its surface may rupture leading to formation of local thrombus with subsequent embolization to the territories of the ophthalmic artery, anterior cerebral, or medial cerebral artery.

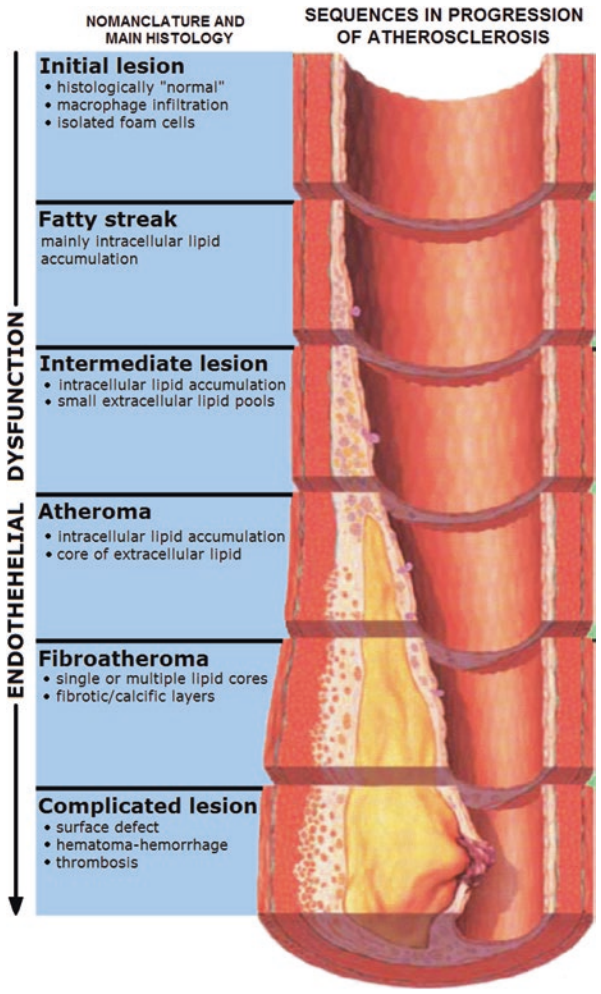

Fig. 3.1 Pathophysiology of atheromatous plaque

The main symptoms depend on the affected territory. At the ophthalmic circulation, symptom of amaurosis fugax or retinal infarction may be seen. On the other hand, the medial cerebral artery embolism can be seen as transient symptoms in the contralateral hemisphere body (called 'transient ischemic attack') or even stroke.

However, it is usually diagnosed on non-invasive imaging studies in asymptomatic individuals [4].

Patients with atrial fibrillation have a threefold to fivefold increased risk of cardioembolic ischemic stroke. Hyperlipidemia is a risk factor for the disease development in this territory, being associated with the presence of atherosclerotic stenosis and the stroke occurrence observed when total cholesterol level is greater than 5.20 mmol/L (200 mg/dL) [5]. Hypertension is an independent risk factor for the development of cardiovascular disease and has a great association with hyperlipidemia [6]. The presence of diabetes mellitus is associated with increased chances of having ischemic stroke in two to three times and its proper control is related to risk reduction [7, 8].

Coronary Artery Disease

Atherosclerosis reduces coronary blood flow leading to symptoms of myocardial ischemia. In recent years, advanced knowledge of the atheroma pathophysiology and the rupture of atherosclerotic plaques was have been achieved. The atheroma is responsible for acute coronary syndromes causes, in more than half of the cases, produces a stenosis lower than 50 % of the vessel diameter. Therefore, they are vulnerable plaques with a large lipid core, inflammatory cells and thin fibrous caps, subject to biomechanical stress. This knowledge of plaques vulnerability has led to change in treatment, with new therapeutic options such as antiplatelet, antithrombotic drugs, statins and beta-blockers drugs [9].

In this territory, the genetic factor is strongly associated with plaque formation and complication, especially in individuals with a history of premature familial disease. This correlation is significant for those with a first-degree relative who had atherosclerotic cardiovascular disease or died due to it before 55 years old for men or 65 years old for women [10]. Dyslipidemia is directly related to the occurrence of coronary artery disease due to its important role in the formation of atherosclerotic plaque. Higher levels of non-high density lipoprotein are associated with higher incidence of coronary events, particularly in patients with earlier manifestations [8, 11, 12]. Nicotine and tar are directly related to deaths from coronary artery disease and higher doses of these toxins are associated with progressive increase in mortality [13]. Patients with diabetes mellitus have higher chance of developing coronary artery disease and developing it in an early age when compared to the general population [14]. Diabetes mellitus also increases the risk of complications. The incidence of acute coronary syndrome is higher in patients with diabetes mellitus when compared to individuals without the disease [15]. Moreover, mortality of patients with diabetes mellitus is mostly related to coronary artery disease complications [16]. A study conducted in 52 countries showed a significant association

between hypertension and coronary artery disease, consistent with the vast data related to the Framingham study. It shows that this is an important target for the reduction of myocardial infarction, especially when it occurs early in life [17, 18].

Peripheral Artery Disease

Atherosclerosis is the leading cause of peripheral arterial disease, in which there is a blockage or stenosis in the arteries that supply lower limbs. Approximately 80 % of patients with peripheral artery disease are asymptomatic. The main symptoms of the ischemia are muscular atrophy, ulcers, pallor and intermittent claudication, and the main finding in the physical examination is the reduction or absence of peripheral pulses. In some cases, the disease can have an acute worsening, characterized by severe pain, sudden onset, associated with reduced limb temperature, decreased temperature and paraesthesia, featuring acute arterial ischemia that must be treated immediately in an attempt to avoid amputation and death.

Advanced age is also a progressive risk for the disease in this territory. However, it becomes significant higher after 40 years. The risk greatly increases in patients older than 70 years, but only part of them present the symptomatic form of peripheral artery disease [20–22]. Smoking is strongly associated with the development of the disease. Studies like Framingham's showed a two times increased risk of developing intermittent claudication among smokers when compared to non-smokers [23]. Such findings were confirmed by other epidemiological studies that also assigned the risk two to six times greater among smokers [24–26]. Diabetes mellitus is directly associated with the incidence and severity of peripheral artery disease. The prevalence is almost five times greater of peripheral artery disease in diabetic patients older than 40 years when compared to people without the comorbidity [27, 28]. Regarding the affected territory, diabetic patients generally have more distal involvement of the vessels, especially in the popliteal and tibial vessels [29, 30]. Regarding the outcome, the association of these two diseases correlates to a higher risk of lower limb amputations in elderly people [31]. It's well known that patients with peripheral artery disease are more likely to have high levels non-high density lipoprotein cholesterol and/or triglycerides [32] as well as reduced levels of high density lipoprotein [33]. In addition, there is a significant association between hypertension and peripheral artery disease both in symptomatic and asymptomatic individuals [22, 34]. Those patients present a two times higher risk of developing symptoms such as claudication when compared to non-hypertensive patients [35].

Reno-Vascular Atherosclerosis

The initial cause of the endothelial lesion not established that yet, though dyslipidemia, diabetes, hypertension and smoking certainly collaborate to the pathogenic process. It is the leading cause of renal artery stenosis in the elderly. This pathologic process is the main cause of renovascular hypertension, responding for 1–10 % of

all hypertensive disease cases in the United States, and contributing importantly to chronic renal failure progression. The lumen of a renal artery with atherosclerosis gradually reduces, leading to decreased blood flow and renal ischemia. The kidney adaptation to atrophy and reduction of tubular cells, inflammation, fibrosis and glomerular atrophy generates a glomerular filtration rate angiotensin II dependent. This adaptation process can maintain a stable renal function until it reaches high grade renal artery stenosis [36].

Diagnosis

The diagnosis of atherosclerosis is usually established after starting its symptoms in at least one of the above mentioned territories. However, the best approach is to diagnose it in a preclinical phase through risk stratification and laboratory tests, enabling the effective secondary prevention with the correct definition of individual therapeutic goals. Atherosclerotic disease risk stratification results from the sum of all potential increased risks identified in patients; therefore, the first step in clinical risk assessment is to identify any high-risk conditions that obviate the need for further risk assessment, these mainly include established atherosclerotic cardiovascular disease and diabetes. If none of such high-risk conditions is present, the second step is to apply a well stablished risk score, such as Framingham.

Determining the Presence of Significant Atherosclerotic Disease or Its Equivalent

The clinical relevance of detecting subclinical atherosclerosis disease rests on improving prediction of cardiovascular disease risk over traditional factors. A systematic review consisted of 25 studies evaluated the link between cardiovascular events and subclinical atherosclerosis findings in imaging tests. It has been found greater chance of fatal and nonfatal cardiovascular events in individuals with calcification in coronary arteries, carotid plaques and incresed thickness in carotid arteries. Individuals with intermediate risk of cardiovascular disease according to traditional risk assessment factor may benefit from additional images studies [37].

Ankle-Brachial Index

The ankle-brachial index test is an easy and non-invasive way to search for peripheral artery disease risk. It's the ratio of Doppler-recorded systolic blood pressure at the ankle divided by systolic blood pressure in the arm (See Appendix A for detailed information). Individuals without clinically significant peripheral artery disease typically have an ankle-brachial index greater than 1, while an ankle-brachial index < 0.9 is 90 % sensitive and 95 % specific for the presence of peripheral artery disease positive on angiography. A peripheral arterial lesion may be revealed with measurement of lower extremity pressures after exercise. Therefore, exercise

treadmill testing may be performed in order to raise ankle-brachial index test sensitivity [38].

Carotid Ultrasonography

Ultrasound methods have the advantages of being feasible in all individuals, relatively accessible and without exposure to radiation. It is useful in detecting flow reduction, obstructive plaques or to measure intima-media thickness, which represents subclinical atherosclerosis and is associated with adverse cardiovascular events. A novel three-dimensional ultrasound-based approach method identified more carotid plaques compared to other methods and its clinical utility as predictor of future cardiovascular events is comparable to coronary artery calcification score [39, 40].

Femoral Ultrasonography

This method may be better than carotid ultrasonography for detection of subclinical atherosclerosis, as showed in a study with 1423 middle-aged men (40–59 years of age) that evaluated the association of subclinical carotid and femoral plaques with risk factors and coronary artery calcification score. The area under the receiver-operating curve for prediction of positive coronary artery calcification score increased from 0.66 when considering only risk factors to 0.71 when adding femoral and carotid plaques ($p < 0.001$). In this model, the femoral odds ratio (2.58) exceeded the carotid odds ratio (1.80) for prediction of positive coronary artery calcification score [41].

Electron-Beam Computed Tomography

It can be used to assess coronary artery calcification score. High coronary artery calcium levels correlates with histological plaque as well as the number of stenosed vessels on studies with invasive angiography [42]. On a study with 6814 participants and over 5.8 years median follow-up, addition of coronary artery calcification score to a prediction model based on traditional risk factors significantly improved the classification of risk. However, this method is limited to detect non calcified plaques and to predict plaque stability [43].

Pressures and Pulse-Volume Recordings

Segmental pressures and pulse-volume recordings are other important tool used to assess the level and extent of obstruction. A series of blood pressure cuffs are placed at multiple levels on the arms or the legs to measure pressures and the amount of blood flow at each level. These tests are performed to localize blockage areas in those territories. An advantage of using pulse volume recording amplitudes is that they are valid when examining calcified vessels, such as in diabetic patients. Exercise test can be necessary to uncover subcritical stenosed sites [44].

Others Cardiovascular Methods of Evaluation

Dobutamine **echocardiography** is more sensitive than adenosine echocardiography, but a positive adenosine echo often represents more severe disease.

A myocardial perfusion **single-photon emission** computed tomography scan of the heart is a non-invasive nuclear imaging test that include perfusion and gated wall motion images. The scans can also be used to accurately determine the left ventricular ejection fraction, the end-systolic volume of the left ventricle, regional wall motion and wall thickening. In addition, solid evidence links these findings to clinical outcomes.

Magnetic resonance imaging offers the advantage of avoiding ionizing radiation and it is capable of identifying specific components of the plaque. However, current magnetic resonance methods suffers from extensive variability of image quality and a longer time for acquiring images.

Utilization of Risk Stratification Scores

Cardiac risk stratification begins with calculating the probability of an incident event using conventional algorithms, such as the Framingham equation.

Framingham Risk Score, for example, estimates the probability of acute myocardial infarction or death from coronary heart disease within 10 years in individuals with no history of clinical atherosclerotic disease and have been validated in multiple countries and populations [45].

Treatment

General Practitioner's Role

Prevention of cardiovascular disease is less costly than treating its complications; thus, identification of subclinical disease in the asymptomatic phase has emerged as a public health and economic imperative. The general practitioner also has an important role in the investigation of peripheral arterial disease through the ankle brachial index (See Appendix A for more details). Behavioral modifications like smoking cessation and exercise has a direct beneficial impact on vascular changes associated with aging. Antiplatelet agents have essential role on prevention of plaque accidents and thrombosis. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE), published in 1996, compared clopidogrel with aspirin in reducing the risk of vascular events in patients with clinical manifestations of atherosclerosis. It found that long-term administration of clopidogrel is more effective than long-term aspirin therapy in reducing the combined risk of ischemic stroke, myocardial infarction or vascular disease. The relative risk reduction provided by clopidogrel is added to the benefit provided by aspirin when compared with placebo. Therefore, rational using of those agents is highly recommended on clinical practice. The pleiotropic effects of statins have beneficial effects on both vascular aging and atherosclerosis. These favorable endothelial effects are attributed to their ability to lower the low-density lipoprotein cholesterol, upregulate endothelial nitric oxide synthase and exert antioxidant activity.

Pharmaceutical agents that block formation of advanced glycation end product have proved efficacious in decreasing vascular stiffness and nephrosclerosis, but clinical trials were halted due to adverse drug effects.

Good medical practice recommends prevent risk factors and behavioral changes associated to pharmacological treatment. Nevertheless, surgical approaches can be necessary.

Medical Specialist Evaluation

The evaluation by the specialist is important when the patient has certain complications of atherosclerosis such as cerebrovascular disease, peripheral arterial disease and other situations. In several cases, surgery becomes necessary. The exact technical procedure will depend on the obstruction grade and its location, but usually some techniques such as open surgery (bypass or endarterectomy) or endovascular surgery can be used. The final objective is to restore the blood flow and stop tissue ischemia. However, the most powerful reduction in atherosclerotic disease results from early recognition and risk factor modification.

References

1. Organization WH, editor. World Health Report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.
2. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. National Center for Health Statistics. Vital Health Stat; 2014;1–171.
3. Fakhouri THI, Hughes JP, Burt VL, Song M, Fulton JE, Ogden CL. Physical activity in U.S. youth aged 12–15 years, 2012. National Health and Nutrition Examination Survey and National Youth Fitness Survey CDC/NCHS; 2014.
4. Thapar A, Jenkins IH, Mehta A, Davies AH. Diagnosis and management of carotid atherosclerosis. Br Med J. 2013;346:f1485.
5. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2013;12(11):1106–14.
6. Qureshi AI, Caplan LR. Intracranial atherosclerosis. Lancet. 2014;383(9921):984–98.
7. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854–65.
8. Cronenwett JL, Johnston KW. Rutherford's vascular surgery. 8th ed. Philadelphia: Saunders; 2014.
9. Goff Jr DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49–73.
10. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B): 2889–934.

11. Roncaglioni MC, Santoro L, D'Avanzo B, Negri E, Nobili A, Ledda A, et al. Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators. Circulation. 1992;85(6):2065–72.
12. Genest Jr JJ, Martin-Munley SS, McNamara JR, Ordovas JM, Jenner J, Myers RH, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation. 1992;85(6):2025–33.
13. Hammond EC, Garfinkel L, Seidman H, Lew EA. "Tar" and nicotine content of cigarette smoke in relation to death rates. Environ Res. 1976;12(3):263–74.
14. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006;368(9529):29–36.
15. American Heart Association. Heart disease and stroke statistics-2004 update. Dallas: American Heart Association; 2004.
16. Centers for Disease Control and Prevention: National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
17. O'Donnell CJ, Elosua R. Cardiovascular risk factors. Insights from Framingham Heart Study. Rev Esp Cardiol. 2008;61(3):299–310.
18. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937–52.
19. Barriocanal AM, Lopez A, Monreal M, Montane E. Quality assessment of peripheral artery disease clinical guidelines. J Vasc Surg. 2016;63(4):1091–8.
20. Ostchega Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. J Am Geriatr Soc. 2007;55(4):583–9.
21. Kroger K, Stang A, Kondratieva J, Moebus S, Beck E, Schmermund A, et al. Prevalence of peripheral arterial disease—results of the Heinz Nixdorf recall study. Eur J Epidemiol. 2006;21(4):279–85.
22. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004;110(6):738–43.
23. Kannel WB, Shurtleff D. The Framingham Study. Cigarettes and the development of intermittent claudication. Geriatrics. 1973;28(2):61–8.
24. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall study. Circulation. 1990;82(6):1925–31.
25. Bowlin SJ, Medalie JH, Flocke SA, Zyzanski SJ, Goldbourt U. Epidemiology of intermittent claudication in middle-aged men. Am J Epidemiol. 1994;140(5):418–30.
26. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992;135(4):331–40.
27. Abbott RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic men and women: experiences from the Framingham Study. Am J Med. 1990;88(4):376–81.
28. Elhadd T, Robb R, Jung R, Stonebridge P, Belch J. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. Pract Diabetes Int. 1999;16(6):163–6.
29. American Diabetes A. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003;26(12):3333–41.
30. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and non-diabetic patients: a comparison of severity and outcome. Diabetes Care. 2001;24(8):1433–7.
31. Centers for Disease C, Prevention. Diabetes-related amputations of lower extremities in the Medicare population—Minnesota, 1993-1995. MMWR Morb Mortal Wkly Rep. 1998;47(31):649–52.

32. Vitale E, Zuliani G, Baroni L, Bicego L, Grego F, Valerio G, et al. Lipoprotein abnormalities in patients with extra-coronary arteriosclerosis. Atherosclerosis. 1990;81(2):95–102.
33. Bradby GV, Valente AJ, Walton KW. Serum high-density lipoproteins in peripheral vascular disease. Lancet. 1978;2(8103):1271–4.
34. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam study. Arterioscler Thromb Vasc Biol. 1998;18(2):185–92.
35. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997;96(1):44–9.
36. Plouin PF, Bax L. Diagnosis and treatment of renal artery stenosis. Nat Rev Nephrol. 2010;6(3):151–9.
37. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart. 2012;98(3):177–84.
38. Kravos A, Bubnic-Sotosek K. Ankle-brachial index screening for peripheral artery disease in asymptomatic patients between 50 and 70 years of age. J Int Med Res. 2009;37(5):1611–9.
39. Sillesen H, Muntendam P, Adourian A, Entrekin R, Garcia M, Falk E, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage study. JACC Cardiovasc Imaging. 2012;5(7):681–9.
40. Baber U, Mehran R, Sartori S, Schoos MM, Sillesen H, Muntendam P, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol. 2015;65(11):1065–74.
41. Laclaustra M, Casasnovas JA, Fernandez-Ortiz A, Fuster V, Leon-Latre M, Jimenez-Borreguero LJ, et al. Femoral and Carotid Subclinical Atherosclerosis Association with risk factors and coronary calcium: the AWHS study. J Am Coll Cardiol. 2016;67(11):1263–74.
42. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2007;49(3):378–402.
43. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA. 2010;303(16):1610–6.
44. Gerhard-Herman M, Gardin JM, Jaff M, Mohler E, Roman M, Naqvi TZ. Guidelines for noninvasive vascular laboratory testing: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. Vasc Med. 2006;11(3):183–200.
45. D'Agostino Sr RB, Grundy S, Sullivan LM, Wilson P, Group CHDRP. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. 2001;286(2):180–7.

Hemostasis and Anticoagulation Therapy

4

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Abstract

The hemostasis consists of all the mechanisms maintaining the vascular blood flow. It acts by balancing factors that generate the interruption of bleeding (hemorrhage) and the inhibition of clot formation (thrombosis), while leading to tissue repair. It is didactically divided into primary hemostasis, with the participation of the endothelium and platelets, forming the platelet plug; and secondary hemostasis, which culminate in the formation of fibrin clot through a chain of enzymatic reactions (whose steps are: initiation, expansion, and propagation). The fibrinolytic system, also part of the hemostasis process, inhibits the formation of intravascular thrombi associated with excessive fibrin formation.

Prophylaxis and treatments for certain diseases, such as deep vein thrombosis and pulmonary thromboembolism, may use anticoagulants acting in different factors of the coagulation cascade to block the clot formation. A number of anticoagulants are available. Heparins, fondaparinux, warfarin, and other coumarins are the traditional group of anticoagulants used widespread worldwide. Unfractionated heparin and low molecular weight heparin are used subcutaneously and act mainly inhibiting thrombin and factor Xa. Fondaparinux is a synthetic and selective anticoagulant which blocks factor Xa. Warfarin and other coumarins are oral anticoagulant drugs that act as vitamin K antagonists. Recently, a number of new agents have been introduced. The new oral anticoagulants include inhibitors of

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factor IIa (dabigatran) and factor Xa (rivaroxaban, apixaban, and edoxaban). The new parenteral direct thrombin inhibitors anticoagulants include argatroban, bivalirudin, danaparoid, lepirudin, and desirudin—both recombinant forms of hirudin. They have some specifications described in this chapter.

Abbreviations

FIXa	Activated factor IX
FVa	Activated factor V
FVIIa	Activated factor VII
FVIIIa	Activated factor VIII
FXa	Activated factor X
kg	Kilogram
mg	Milligrams

Introduction

Hemostasis is the process of the vascular system to prevent and stop blood loss at the site of a vascular injury [1]. It is an actively maintained state, divided into two integrated phases with a high degree of overlap between each other [1]. The two phases of the hemostatic process are named:

1. Primary hemostasis, which occurs rapidly after a vascular injury and leads to platelet plug formation [1].
2. Secondary hemostasis, which leads to the formation of an insoluble fibrin mesh through the action of coagulation factors [1].

A balance between factors acting as thrombogenic (promoting clot formation), nonthrombogenic (preventing clot formation), and fibrinolytic agents (promoting dissolution of clots previously formed) is required. This balance ensures a rapid generation of a localized thrombus at the site of the injury, preventing pathological thrombosis or hemorrhage. For this to happen, each process must develop correctly. The four key components are the vascular endothelium, platelets, coagulation pathway, and fibrinolysis [2].

Primary Hemostasis

Primary hemostasis is the formation of a hemostatic platelet plug and is the first line to prevent blood loss. It requires two main components: the endothelium and platelets. The process evolves with platelets adhesion, activation, and aggregation to the endothelium wall, and finally restoration of the normal blood flow.

Endothelium

The endothelium primarily regulates hemostasis, vascular tone [1], and permeability [2].

Endothelial cells secrete many mediators that prevent both primary and secondary hemostasis [1]. Primary hemostasis is inhibited by the synthesis of nitric oxide, prostacyclin, and ectoADPase membrane protein [1], substances that inhibit platelet action; and anticoagulation is favored by endothelial expression of thrombomodulin, heparin sulfate, and dermatan sulfate [2].

After tissue damage and disruption of the endothelial basement membrane, after stimulation by enzymes such as thrombin or after a vascular intervention (such as angioplasty, stent placement, and bypass), the exposure of von Willebrand factor induces platelet aggregation and activation. The endothelium becomes thrombogenic by expression of tissue factor, which initiates the coagulation pathway leading to fibrin generation and clot formation; and impairs fibrinolysis by secretion of plasminogen activator inhibitor-1, commonly shortened as PAI-1 [2].

Platelets

Platelets are a crucial component of the clotting process and also contribute to the fibrinolysis process. They have a nonthrombogenic surface under controlled circumstances, but after a disruption of the vascular system, the platelet becomes activated, releasing the content of its granules (alpha granules, dense granules, and lysosomes), which contain fibrinogen and factor V, among other procoagulant molecules [1]. Also, activated platelets express receptors and specific binding sites triggering the formation of multiprotein procoagulant complexes.

Platelet Adhesion

Platelet adhesion depends on the connection between the von Willebrand factor and glycoprotein 1b, a platelet surface glycoprotein. This interaction is the initial step [2].

Platelet Activation

The activation occurs when platelets adhere to endothelial cells, leading to secretion of granules [2] that contain thromboxane A2, which stimulates the amplification of the coagulation process [3].

Platelet Aggregation

Platelet aggregation is responsible for the generation of the hemostatic plug, with several layers of platelets, generating a firm thrombus. This process requires

platelet's receptor glycoprotein IIb–IIIa to bind to each other on an activated platelet, using fibrinogen as a link [2].

Secondary Hemostasis

The fibrin clot formation is a critical process for the maintenance of vascular integrity since the platelet plug is insufficient to maintain hemostasis in larger lesions and to contain the pressure of the arterial system. Thus, the formation of fibrin is indispensable to consolidate the platelet thrombus. Simultaneously, the fibrinolytic system is activated to prevent the excessive formation of fibrin that could otherwise lead to vessel obstruction. Therefore, to keep blood flowing inside vessels without hemorrhage or obstruction due to excessive thrombus formation, a dynamic equilibrium between the coagulation system and the fibrinolytic system must be maintained.

Coagulation

In the classic model of the coagulation cascade, fibrin formation is the end point of a chain of enzymatic reactions in which a proenzyme (inactive protease in blood plasma) is activated to form an enzyme. The activated enzyme then activates another proenzyme, with each passage presenting an explosive augmentation system, that is, there is a sequential cascade of events that will culminate in the formation of fibrin and thrombus [4, 5].

The proenzymes are known as coagulation factors, which are numbered from I to XIII, the number corresponding to the order of discovery. The numbers plus the letter "a" is the enzyme (activated proenzyme). However, there is no factor VI; factor III is commonly known as tissue factor, and factor IV is the ionized calcium.

This proposed coagulation cascade divides coagulation in extrinsic pathway, involving blood elements and the presence of tissue factor; and intrinsic pathway, initiated by components present in the intravascular space, which converge into a common pathway after the activation of factor X, resulting in the formation of fibrin [4, 5]. The intrinsic pathway has also been taught as a sequence of reactions occurring in the blood, and the extrinsic pathway would be related to reactions happening in the vessel wall.

This traditional model of explaining the coagulation corresponds to the processing of blood coagulation in vitro, a concept of importance only for laboratory diagnosis. It may also reflect a didactic way to explain the coagulation cascade. However, dividing the coagulation cascade into intrinsic and extrinsic pathways is a flawed model of in vivo hemostasis. The model proposed by Hoffman based on cellular and molecular components, the cell-based model of the hemostasis, reflects more consistently coagulation in vivo and is the currently accepted model [6, 7].

This new coagulation model is considered multifaceted, extremely balanced, involving three phases: initiation, amplification, and propagation. All these steps occur together in different cell surfaces, which locate the wound and ensure that the entire system is turned on, and is restricted to the site of tissue injury [6, 7].

The Initiation Phase

The coagulation initiation phase occurs on the surfaces of cells containing tissue factor, which are stromal fibroblasts, mononuclear cells, macrophages, and endothelial cells. Tissue factor is activated by vascular injury or cytokines in an inflammatory response [6, 7].

The exposed tissue factor activates factor VII present in blood plasma (FVIIa) and forms the complex tissue factor−/−factor VIIa, which consequently activates factors X and IX. The FXa activates factor V forming a complex FXa−/−FVa called prothrombinase. Prothrombinase is capable of converting prothrombin (factor II) into thrombin (factor IIa) [6, 8].

This conversion of prothrombin into thrombin is insufficient to complete the process of formation of the fibrin clot but is of fundamental importance for the amplification phase of coagulation [6, 7].

The Amplification Phase

The amplification phase occurs on the surface of platelets. Despite the low generation of thrombin in the initiation phase, this will have the following functions in this next phase:

1. Platelet activation, exposing receptors and binding sites for activated clotting factors, in addition to releasing factor V partly activated [6].
2. Activation of factor VIII, factor V, and factor XI on the surface of activated platelets [6].

Factor VIII, which is initially bound to von Willebrand factor, dissociates when activated, allowing von Willebrand factor to mediate platelet adhesion and aggregation at the site of vascular injury [6, 8]. Simultaneously, the factors on the surface of activated platelets rapidly initiate the propagation phase [6].

The Propagation Phase

This final phase is characterized by recruitment of big amounts of platelets and formation of the complexes: tenase and prothrombinase at the platelet surface. The activated factor Xa in the initiation phase joins the factor VIIIa released in the amplification stage and forms the complex FIXa/FVIIIa, called tenase complex, which activates factor X. This factor associates with factor V and forms complex FXa/FVa, called prothrombinase. Thus, large amounts of prothrombin are converted to thrombin, cleaving the fibrinogen into fibrin monomers, which polymerise and result in the formation of a stable fibrin clot [6, 7].

The coagulation system needs to be confined to the injury site to prevent thrombotic occlusion of the vessel. Thus, this system is restrained and inhibited by specific anticoagulants that include: tissue factor pathway inhibitor, protein C, protein S, and antithrombin [9].

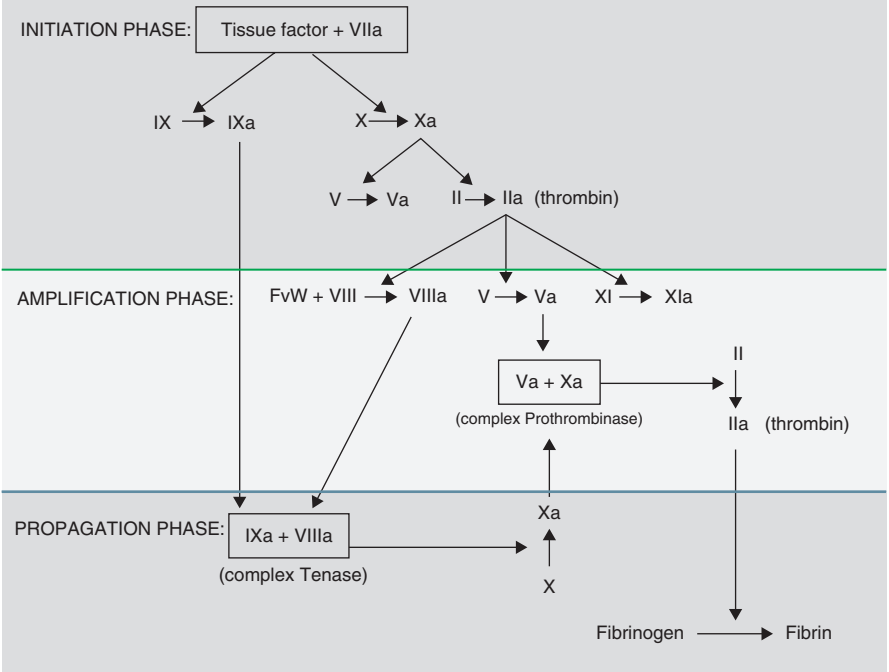

Fig. 4.1 Secondary hemostasis. Cell-based model representation of coagulation with three phases: initiation, amplification, and propagation, leading to the formation of fibrin. *vWF:* von Willebrand Factor [6, 7, 9]. **Adapted from:** "*Vine AK. Recent advances in haemostasis and thrombosis. Retina. 2009;29(1):1–7.*" [10]

In the initiation phase, the excessive thrombin generation is controlled by inhibition of the tissue factor pathway [9].

The activation of protein C (natural anticoagulant) occurs after connection of thrombin to thrombomodulin, an endothelial cell receptor. The activated protein C inhibits coagulation by cleaving and inactivating factors Va and VIIIa. This process is potentialized by protein S, which acts as a cofactor in the inactivation of nonenzymatic reactions [9].

The amplification and propagation phases are controlled primarily by the action of antithrombin, which inhibits thrombin and factors: IXa, Xa, XIa. A substance present in the membrane of the endothelial cells, heparan sulfate, catalyzes the antithrombin reactions [9] (Fig. 4.1).

Fibrinolysis

The fibrinolytic system aims degradation of fibrin, because after thrombus formation, its excess must be removed to restore blood flow [11].

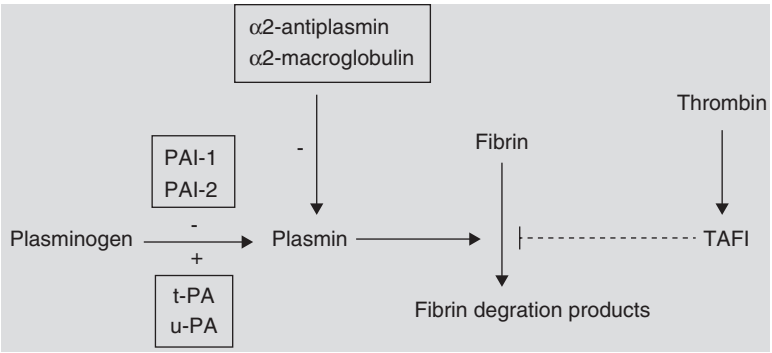

Fig. 4.2 Fibrinolysis and its natural inhibitors system. Tissue plasminogen activator and urokinase-type plasminogen activator activates the fibrinolytic system by converting plasminogen to plasmin, thus leading to a degradation of fibrin into fibrin degradation products. This process is modulated by plasminogen activators 1 and 2, α2-antiplasmin, α2-macroglobulin, and thrombin-activatable fibrinolysis inhibitor [9, 11, 12]. **Adapted from:** "*Batty P, Smith G. Anticoagulation. Surgery (Oxford). 2010;28(6):243–7.*"**,** *"Vaughan D, Declerck P. Fibrinolysis and its regulation. 1998."* **and** *"Rau J, Beaulieu L, Huntington J, Church F. Serpins in thrombosis, hemostasis and fibrinolysis. Journal of Thrombosis and Haemostasis. 2007;5(s1):102–15."*

The activation of plasminogen, a circulating inactive precursor to plasmin, is the beginning of fibrinolysis. This activation can occur via two pathways: one mediated by tissue plasminogen activator and urokinase-type plasminogen activator, substances released by endothelial cells after activation of coagulation, limiting unnecessary progression of thrombus [11, 12].

Plasmin does not restrict its action on fibrin. Plasmin is also able to break the degrading fibrinogen, factor V, and factor VIII [12].

The fibrinolytic process is regulated by natural inhibitors system: (1) plasminogen activator inhibitor 1 and plasminogen activator inhibitor 2, which act directly on plasminogen; (2) α2-antiplasmin and α2-macroglobulin, which inhibit plasmin. In addition to the thrombin-activatable fibrinolysis inhibitor, tissue plasminogen activator act by preventing to bind to the fibrin, thereby decreasing fibrinolysis [9, 12] (Fig. 4.2).

Anticoagulant Treatment

Parenteral Anticoagulants

Unfractionated Heparin

What is it? Unfractionated heparin, known as standard heparin or simply heparin, is an anticoagulant drug, heterogeneous with respect to molecular size, anticoagulant action, and pharmacokinetic aspects [13]. This drug is composed of proteins of various molecular weights, which have different kidney clearance. Only one-third of heparin molecules contain the high-affinity pentasaccharide required for

anticoagulant activity. These are some aspects that justify the heterogeneous activity of the drug. Heparin acts mainly by indirect inhibition of thrombin and factor Xa [13].

Indications: Heparin is a commonly used medication worldwide since it is essential in the prophylaxis and treatment of thromboembolic disorders. It is indicated for the prevention and treatment of venous thromboembolism and treatment of acute coronary syndrome and other arterial conditions as well [14].

Dose: Heparin must be given parenterally. It is usually administered subcutaneously or by continuous intravenous infusion. When it is used for therapeutic purposes, the intravenous route is most often used [15, 16, 17]. To prescribe the appropriate heparin dose, the physician should consider the patient's weight and associated comorbidities, as the dose of heparin depends on these factors. The initial dose of heparin for treatment of venous thromboembolism is weight based: 80 U/kg bolus and 18 U/kg/h infusion [13]. The most used commercial presentation of unfractionated heparin for intravenous use is 5000 U/mL [17].

Monitoring: Since heparin has a variable anticoagulant response**,** the anticoagulant effect of heparin must be monitored when therapeutic doses are employed, and doses should be adjusted accordingly. The activated partial thromboplastin time (aPTT) or anti-factor Xa assay is the appropriate laboratory test. The goal is to reach an activated partial thromboplastin time within the therapeutic range of 1.5–2.5 times higher than control [13, 18–26]. The activated partial thromboplastin time should be measured approximately 6 h after the initial dose, and the continuous intravenous dose of heparin is altered in agreement with the result of the test (Table 4.1).

Adverse effects: Main adverse effect of heparin is bleeding. The risk of extensive bleeding with hemodynamic consequences increases with higher doses and interaction with other medications, such as antiplatelet or fibrinolytic agents. Heparin's antidote is protamine sulfate, and it should be used in patients experiencing major bleedings during heparin treatment: 1 mg protamine intravenous neutralizes approximately about 100 U of heparin [28]. Another important adverse effect is heparin-induced thrombocytopenia. Heparin-induced thrombocytopenia is a dangerous

Table 4.1 Heparin dose adjustment according to activated partial thromboplastin time (aPTT) [26, 27]

Initial dose	80 U/kg bolus, then 18 U/kg/h
aPTT, <35 s	80 U/kg bolus, then increase 4 U/kg/h
aPTT, 35–45 s	40 U/kg bolus, then increase 2 U/kg/h
aPTT, 46–70 s	No change
aPTT, 71–90 s	Decrease infusion rate by 2 U/kg/h
aPTT, >90 s	Hold infusion 1 h, then infusion rate by 3 U/kg/h

aPTT activated partial thromboplastin time, *s* seconds, *kg* kilograms

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adverse drug reaction that promotes antibody-mediated-platelet activation. It is defined as a relative reduction in platelet count of 50 % occurring within 5–14 days after initiation of the therapy. The diagnosis of heparin-induced thrombocytopenia is challenging and is based on the clinical probability and laboratory tests for the detection of heparin-induced thrombocytopenia antibodies. Heparin must be discontinued immediately in case of a clinical suspicion for heparin-induced thrombocytopenia [29]. Heparin-induced thrombocytopenia has been estimated to develop in 1–5 % of the postoperative patients receiving unfractionated heparin [30]. Ambulatory patients develop heparin-induced thrombocytopenia in frequencies lower than 1 % [29].

Other adverse effects are osteoporosis, which has been reported in up to 30 % of patients given long-term heparin treatment [31–34], and elevated levels of transaminases, which occur in approximately 15 % of the patients [35].

Contraindications/precautions: Important limitations are the deficient bioavailability in small doses, dose-dependent clearance, and variable anticoagulant response. The use of heparin is limited in patients with osteopenia [36].

Heparin is contraindicated in the presence of active bleeding or disease states with an increased risk of bleeding. Patients using other drugs that can affect the clotting process should be monitored closely since the interaction between drugs may increase the chance of bleeding. In cases of spinal injection or puncture, it is necessary to seek specialist advice before considering intrathecal, epidural analgesia, anesthesia, or lumbar puncture, due to the risk of epidural hematoma, which may cause paralysis. Heparin is also contraindicated in cases of severe hepatic disease. All heparins are Australian category C in pregnancy because they are medicines that cause or may cause harmful effects to the human fetus and neonate. However, they do not cause malformations [14, 37, 38]

Low Molecular Weight Heparins

What is it? Low molecular weight heparins consist of smaller fragments of heparin and are prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. Low molecular weight heparins have a mean molecular weight of 4000–5000 (about one-third of the molecular weight of unfractionated heparin) [13, 39]. Low molecular weight heparins have advantages over heparin: better bioavailability, dose-independent clearance, predictable anticoagulant response, lower risk for heparin-induced thrombocytopenia and osteoporosis. Therefore, heparin is replaced for most indications. Low molecular weight heparins act inhibiting antithrombin and, mainly, factor Xa. Enoxaparin, dalteparin, and tinzaparin are representatives of this class of drug.

Indication: Low molecular weight heparin has the same indications of heparin: prevention and treatment of venous thromboembolism, acute pulmonary embolism, acute coronary syndromes, and other arterial conditions.

Dose: Low molecular weight heparin is typically administrated in fixed doses, subcutaneously, for thromboprophylaxis, or in body weight-adjusted doses for full therapeutic effect. For prophylaxis purposes, once-daily doses of 2500 U are recommended for moderate risk patients and 5000 U for high-risk patients. Treatment of venous

thromboembolism requires doses of 100 U/kg once-daily for 5–10 days [14]. Laboratory monitoring is generally not necessary, except in patients with kidney disease and severe obesity [40–43]. The test that evaluates the anticoagulant activity is the dosage anti-Xa activity. A more globally responsive test is the Heptest [43, 44].

Adverse effects: Main adverse effect of low molecular weight heparins is also bleeding. Heparin-induced thrombocytopenia and osteoporosis are less common with low molecular weight heparins than with unfractionated heparin (less than 1 % of patients exposed to low molecular weight heparin develop heparin-induced thrombocytopenia) [39, 45–47].

Bleeding complications can be handled with protamine sulfate. Protamine is an antidote to heparin, but it has incomplete action on low molecular weight heparins because protamine sulfate binds only the longer fragments of the chemical structure of the substance [48]. Protamine neutralizes approximately 60 % of the anti-factor Xa activity of low molecular weight heparin [49–52].

Currently, the following scheme has been recommended [53]:

1. If low molecular weight heparin was administered for less than 8 h: 1 mg of protamine per 100 anti-factor Xa units low molecular weight heparin (1 mg of low molecular weight heparin equals approximately 100 anti-factor Xa units). If the bleeding continues a second dose is recommended: 0.5 mg of protamine per 100 anti-factor Xa units.
2. If low molecular weight heparin was administered more than 8 h: smaller doses are needed for neutralization.

Contraindications/precautions: The use of low molecular weight heparins in patients with creatinine clearance < 30 mL/min should be carefully monitored with anti-factor Xa. The treatment dose in cases of patients with a creatinine clearance < 30 mL/min who have acute coronary syndromes or venous thromboembolism or another acute arterial condition is half of usual dose [54]. Severe thrombocytopenia or heparin-induced thrombocytopenia induced by heparin contraindicates the use of low molecular weight heparins. The medication is also contraindicated in case of active bleeding or disease states with an increased risk of bleeding. The concomitant use with others drugs that increase the bleeding risk should be avoided. Caution is also required in patients with thrombocytopenia, severe uncontrolled hypertension, and spinal injection or puncture. Low molecular weight heparins are also contraindicated in cases of a severe hepatic disease. In surgical patients, unless prophylactic doses are used, the risk of excessive bleeding during the procedure is increased for up to 12 h after intravenous heparin administration and up to 36 h after low molecular weight heparin administration [14]. All heparins are Australian category C in pregnancy because they are medicines that cause or may cause harmful effects to the human fetus and neonate. However, they do not cause malformations [14, 37].

Fondaparinux

What is it? Fondaparinux is a synthetic and selective anticoagulant which blocks factor Xa. It is an alternative to heparin and low molecular weight heparins for

thromboprophylaxis and treatment or venous thromboembolism [54]. Fondaparinux has higher bioavailability and plasma half-life after subcutaneous administration in comparison to low molecular weight heparin [55, 56].

Indications: Fondaparinux is indicated for the prevention and treatment of venous thromboembolism and is accepted in the treatment of unstable angina and acute myocardial infarction [57, 58]. It has also been used in patients with heparin-induced thrombocytopenia [58]. For initial treatment of patients with deep vein thrombosis or pulmonary embolism, it appears as effective as standard treatment (heparin or low molecular weight heparin followed by oral anticoagulation with vitamin K antagonists) with similar rates of bleeding [59, 60].

Dose: Fondaparinux is administered subcutaneously. Dosages and treatment duration varies depending on the therapeutic objectives. For venous thromboembolism prophylaxis in abdominal and orthopedic surgery, a dose of 2.5 mg once daily is recommended, initiating at least 6–8 h after surgery and continued for at least 5–9 days. For prophylaxis in high-risk medical patients, the same dose is given once daily for 6–14 days [58].

The dose used for the treatment of venous thromboembolism is presented in Table 4.2. Treatment is usually continued for 5–9 days and followed by oral anticoagulation [58].

The doses of fondaparinux may need to be reduced in patients with renal impairment [58].

The treatment does not require laboratory control. Unlike heparin, there is no specific antidote for fondaparinux [58].

Adverse effects: Main adverse effect of fondaparinux is bleeding. Hemorrhagic complications imply the discontinuation of treatment and, if necessary, consider blood or fresh plasma transfusion and plasma exchange. Thrombocytopenia and allergic reactions are infrequent side effects occurring in <1 % [57].

Contraindications/precautions: Fondaparinux is eliminated renally and should be used with caution in patients with renal impairment. It is contraindicated in patients with creatinine clearance (CC) below 30 mL/min, and in patient with CC between 30 and 50 mL/min this drug should be used with caution [58].

It is also contraindicated for treatment and prophylaxis in cases of severe active bleeding, severe uncontrolled hypertension, and severe thrombocytopenia [57].

Table 4.2 Doses of fondaparinux for the treatment of venous thromboembolism [58]

Patient body weigh	Fondaparinux doses
<50 kg	Single dose 5 mg/day
>50 and <100 kg	Single dose 7.5 mg/day
>100 kg	Single dose 10 mg/day

mg milligrams, *kg* kilograms
Adapted From: "*Fondaparinux Sodium.(2015). In S. Sweetman (ed.) Martindale: The complete drug reference [Internet]. 2015. Available from: London Pharmaceutical Press:www.medicinescomplete.com.*"

Caution is recommended when treating patients with bodyweight below 50 kg and elderly patients due to a higher risk of bleeding [58]. It is category C used in pregnancy because they are medicines that cause or may cause harmful effects to the human fetus and neonate. However, they do not cause malformations [37].

Fondaparinux should be used cautiously in those with a history of heparin-induced thrombocytopenia, and it should not be given to patients who had thrombocytopenia with heparin and who also have a positive in vitro platelet aggregation test (i.e., cross-reactivity) in the presence of fondaparinux itself [61].

Direct Thrombin Inhibitors

Direct thrombin inhibitors include Argatroban, Bivalirudin Danaparoid and Lepirudin and Desirudin- both recombinants forms of Hirudin. These medicine agents bind directly to thrombin and block its interaction with its substrates. Table 4.3 shows some important aspects of these drugs.

Oral Anticoagulants

Vitamin K Antagonists

What is it? Principal representatives of this class are warfarin and acenocoumarol. These oral anticoagulant drugs act by modulating the synthesis of blood clotting factors dependent of vitamin K, which results in the synthesis of blood clotting factors partially active or inactive by the liver. The blood clotting factors vitamin K dependents are factors II, VII, IX, and X [66, 67].

Warfarin

The anticoagulation effect of warfarin occurs 24 h after the administration of the medicine, and the peak of the anticoagulant effect occurs 72–96 h after the administration. A single dose of warfarin exhibits an anticoagulation effect which lasts 2–5 days [68]. In the first days of use, warfarin acts inhibiting the production of natural anticoagulants (such as C protein and S protein) leading to a hypercoagulable state favoring the occurrence of thromboembolic events. For this reason, heparin should be started simultaneously with warfarin and maintained until the INR (International Normalized Ratio) reaches anticoagulant therapy charge [69].

Indication: Warfarin is indicated for the prophylaxis and treatment of (1) thromboembolic events (venous thrombosis and pulmonary embolism), (2) thromboembolic complications (associated with cardiac valve and atrial fibrillation), (3) recurrent myocardial infarction, and their thromboembolic complications [68].

Dose: Warfarin is administered orally. Intravenous route is an alternative for patients who cannot receive oral drugs, but it is not commonly used [68].

Warfarin dosage and administration should be individualized by monitoring patients through prothrombin time/International Normalized Ratio (PT/INR) [70–74]. Elderly patients have increased sensitivity to the anticoagulant effects of warfarin, so lower doses of warfarin are usually required to produce a safe therapeutic level of anticoagulation. No dosage adjustment is necessary for patients with renal failure. Most patients are satisfactorily maintained at doses of 2–10 mg daily.

Therapy duration should be individualized. In general, anticoagulant therapy should be continued while the risk factors for thromboembolic events have not been

Table 4.3 Dose, use, and considerations about the parenteral direct thrombin inhibitors

Drug	Dose	Considerations
Argatroban	Initial dose of 1–2 mg/kg/min and the dose is adjusted to maintain the aPTT ratio in the 1.5–2.5 range	– Licensed for treatment and prevention of HIT-associated thrombosis and for anticoagulation during percutaneous coronary interventions when heparin is contraindicated because of a recent history of HIT
		– Use with caution in patients with hepatic insufficiency because it has hepatic metabolism [62]
		– It is not renally excreted, so it is particularly useful in patients with HIT with severe renal impairment
		– It has a plasma half-life about 45 min
		Dose should be adjusted to maintain aPTT 1.5–3 times the control
		– Can also prolong the INR [63]
Bivalirudin	Bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure	– Licensed as an alternative to heparin in patients undergoing percutaneous interventions for unstable angina or non-ST-elevation or ST-elevation myocardial infarction and in patients with HIT (with or without thrombosis) who require percutaneous coronary interventions [64]
		– It has a plasma half-life of about 25 min [62]; excreted via the kidneys
Danaparoid		– Danaparoid is the only agent that has been evaluated for HIT in a randomized clinical trial, wherein it was reported to be significantly better than dextran
		– It acts catalyzing the inhibition of factor Xa in an AT-dependent fashion
		– Danaparoid does not prolong the INR
Hirudin recombinant form: **Desirudin**	15 mg twice daily without monitoring	– Approved in Europe and the United States for postoperative thromboprophylaxis in patients undergoing elective hip arthroplasty
		– Cleared via the kidneys (dose must be reduced when the CrCl is 60 mL/min and it is contraindicated in patients with renal failure)
		– It has a plasma half-life of 60 min

(continued)

Table 4.3 (continued)

Drug	Dose	Considerations
Hirudin recombinant form: **Lepirudin**	0.15 mg/kg/h with or without an initial bolus of 0.4 mg/kg	– Licensed for the treatment of thrombosis complicating HIT – Cleared via the kidneys (dose must be reduced when the CrCl is 60 mL/min and it is contraindicated in patients with renal failure) – Plasma half-life of 60 min – Some patients developing antibodies against the drug that, in rare cases, can cause serious bleeding [65] – Can be monitored through aPTT (dose should be adjusted to maintain aPTT 1.5–2.5 times the control)

Source: [54, 62–65]
IV intravenous, *SC* subcutaneously, *aPTT* activated partial thromboplastin time, *HIT* heparin-induced thrombocytopenia, *INR* international normalized ratio, *CrCl* creatinine clearance, *mg* milligrams, *kg* kilograms, *h* hour, *min* minute, *mL* milliliters
Adapted From: *"Garcia DA, Baglin TP, Weitz JI, Samama MM, American College of Chest P. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e24S-43S."* **and** *"Weitz JI, Buller HR. Direct Thrombin Inhibitors in Acute Coronary Syndromes Present and Future. Circulation. 2002;105(8):1004–11."* **and** *"Sheth S, DiCicco R, Hursting M, Montague T, Jorkasky D. Interpreting the International Normalized Ratio (INR) in individuals receiving argatroban and warfarin. Thromb Haemost. 2001;85(3):435–40."* **and** *"White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. Expert opinion on drug metabolism & toxicology. 2009;5(5):529–38."* **and** *"Eichler P, Friesen H-J, Lubenow N, Jaeger B, Greinacher A. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. Blood. 2000;96(7):2373–8."*

Table 4.4 Duration of the treatment of venous thromboembolism with warfarin

Clinical condition of patient	Duration of the therapy
First episode DVT or PE secondary to a transient (reversible) risk factor	3 months
Patients with a first episode of idiopathic DVT or PE	6–12 months
Patients presenting with two or more episodes of documented DVT or PE	Indefinite treatment

Source [68]
DVT deep venous thromboembolism, *PE* pulmonary embolism

resolved [70, 72, 73, 75, 76]. Recommendation of warfarin for the treatment of the venous thromboembolism and pulmonary embolism are explained below (Table 4.4):

In cases of excessive anticoagulation, warfarin administration should be discontinued and if necessary, oral or parenteral vitamin K should be administrated. In a case of

small bleeding that progress, it is recommended the use of 5–25 mg of parenteral vitamin K [70, 71]. The necessity of complementary treatments should be considered.

The warfarin has erratic bioavailability and anticoagulant action and therefore should be monitored carefully. It is important to adjust the dose of warfarin to maintain a target International Normalized Ratio of 2.5 (International Normalized Ratio range, 2.0–3.0) during all treatment period [70, 72, 75, 76].

After the initial dose of warfarin, the Prothrombin Time/International Normalized Ratio (PT/INR) should be determined daily until its results stabilize in the target therapeutic range. Subsequent dosages interval is upon the physician's judgment of the patient's reliability and response to the medication.

Adverse effects: The use of warfarin has been associated with many adverse effects. Hemorrhage in tissues and organs is the most important one. There is a higher bleeding risk in the starting period and with higher doses. The risk factors for bleeding include high intensity of anticoagulation (International Normalized Ratio ≥ 4.0), elderly patient (age ≥ 65), highly variable values of International Normalized Ratios, the presence of comorbidity, trauma, and long duration of warfarin therapy [68].

Other adverse reactions include: Necrosis of skin and other tissues, hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, hypotension, vasculitis, edema, anemia, pallor, fever, rash, dermatitis, angina syndrome, chest pain, abdominal pain, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, headache, dizziness, loss of consciousness, syncope, coma, taste perversion, pruritus, alopecia, cold intolerance, and paresthesia [68].

Contraindications/precautions: Warfarin is contraindicated in (1) pregnancy; (2) hemorrhagic tendencies or blood dyscrasias; (3) recent or contemplated complex surgery; (4) active ulceration or bleeding injury in gastrointestinal, genitourinary, or respiratory tracts; (5) cerebrovascular hemorrhage; (6) dissecting aorta; (7) pericarditis and pericardial effusions; (8) bacterial endocarditis; (9) threatened abortion; (10) eclampsia and preeclampsia; (11) inadequate laboratory facilities; (12) unsupervised patients with senility, alcoholism, or psychosis or other lack of patient cooperation; (13) spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding; (14) malignant hypertension; and (15) known hypersensitivity to warfarin or to any other components of this product [68].

The anticoagulation effect of warfarin can be affected by factors such as other drugs like antiarrhythmics, antibiotics, anticonvulsants, antidepressants, antineoplastics, diuretics, hypnotics, hypolipidemics, vitamins, steroids, antithyroid drugs, nonsteroidal anti-inflammatory drugs; cancer; diarrhea, infections; comorbidities like congestive heart failure, hepatic disorders, hyperthyroidism, poor nutritional state; and unusual dietary intake of vitamin K [68].

Acenocoumarol

Acenocoumarol has a similar mechanism of action and anticoagulation effect of warfarin. Indications, adverse effects, and contraindications are also similar. Acenocoumarol is given in a single dose at the same time daily. The initial dose is 2–4 mg daily for 2 days and maintenance dose is usually 1–8 mg daily. Doses should be adjusted according to the anticoagulation response [77].

New Oral Anticoagulants

The new anticoagulants consist of the direct thrombin inhibitor dabigatran, and the direct factor Xa inhibitors rivaroxaban, edoxaban, and apixaban. These new oral anticoagulants have been developed as an alternative to warfarin, and knowledge has been accumulated to support a better understanding of the efficacy and safety of these agents. These drugs have a rapid onset of action and a prolonged half-life. Due to their bioavailability, they can be taken at fixed doses without the need for frequent monitoring, and they suffer little dietary and drug interaction [78].

Dabigatran

What is it? Dabigatran is an oral anticoagulant exhibiting its effect directly and reversibly inhibiting thrombin. The inhibition of thrombin avoids the conversion of fibrinogen to fibrin, and thus prevents the thrombus formation. It also acts inhibiting thrombin-induced platelet aggregation [79].

Indications: Dabigatran has been used (1) to prevent venous thromboembolism in patients undergoing elective orthopedic surgery, (2) in patients with non-valvular atrial fibrillation with a high risk of stroke or systemic embolism, and (3) to treat deep vein thrombosis and pulmonary embolism. Treatment of deep vein thrombosis and pulmonary embolism with dabigatran is recommended to be introduced after 5–10 days of the parenteral anticoagulation [79, 80].

Dose: Dabigatran dose is 150 and 220 mg once daily to prevent postoperative venous thromboembolism, 150 mg bid for the treatment of venous thromboembolism, and 110 and 150 mg bid in patients with atrial fibrillation. Studies about clinically important effects of age, gender, or renal function on efficacy or safety of dabigatran have provided little evidence [81]; however, the dose adjustment in elderly patients (>75 years) and patients with renal impairment is recommended [79, 80].

Adverse effects: Gastritis, dyspepsia, nausea, diarrhea, and gastrointestinal bleeding are the most frequently adverse effects of dabigatran. Jaundice, fatigue, and anorexia, with raised liver enzyme values, can occur, mainly in elderly [80] Bleeding and signs of bleeding like anemia are adverse effects commonly induced by direct thrombin inhibitors [79, 80]. There is no antidote to dabigatran [80].

Contraindications/precautions: Dabigatran increases the risk of gastrointestinal hemorrhage when compared with warfarin. Dabigatran is therefore contraindicated in gastrointestinal bleeding within previous 12 months. The use of this medicine is

also contraindicated in patients with a prosthetic heart valve, renal impairment with creatinine clearance <30 mL/min, hepatic disease, severe active bleeding, severe uncontrolled hypertension, severe thrombocytopenia, pregnancy (category C), breastfeeding, spinal injection, or puncture. It is recommended to stop the use of dabigatran 1–3 days (if creatinine clearance >50 mL/min) or 3–5 days (if creatine clearance 30–50 mL/min) before elective surgery or procedures.

Some drugs interact in dabigatran action and their concomitant use should be avoided: verapamil, ketoconazole, cyclosporine, tacrolimus, and itraconazole [79].

Rivaroxaban

What is it? Rivaroxaban prevents the conversion of prothrombin to thrombin by selectively inhibiting factor Xa. The absence of thrombin precludes the conversion of fibrinogen to fibrin, thus preventing thrombus formation [82].

Indications: Rivaroxaban has been used to prevent venous thromboembolism in patients with non-valvular atrial fibrillation with elevated risk of systemic embolism or stroke (same indications of dabigatran) [82].

Dose: Rivaroxaban is approved for the prevention of venous thromboembolism in patients undergoing total and total knee replacement surgeries in the dose of 10 mg once daily. Drug administration should be started between 6 and 10 h after surgery, and the duration of treatment should vary from 2 weeks (total knee replacement surgery) to 5 weeks (total hip replacement surgery). Rivaroxaban is currently not approved for use in patients with severe renal failure, a hepatic disease associated with coagulopathy, those who are receiving concomitantly systemic treatment with azole-antimycotics or human immunodeficiency virus (HIV) protease inhibitors, children or adolescents, and pregnant women [83]. It does not require routine laboratory monitoring [82, 84].

Hemorrhagic complications related to overdose should be treated with standard measures. In cases of severe hemorrhage, the use of factor VIIa may be considered although the clinical experience is lacking. There is a specific antidote to factor Xa inhibitors, the Andexanet alfa; it is under investigation [84].

Adverse effects: The most frequent adverse effects are bleeding, peripheral edema, itch, skin blisters, and muscle spasm. Nausea and increase in liver enzyme values may also occur [84]. Bleeding and signs of bleeding like anemia are common adverse effects [82].

Contraindications/precautions: Rivaroxaban is contraindicated in patient with severe renal impairment with creatine clearance <15 mL/min, hepatic disease [84], and pregnancy (Category C—that are medicines that cause or may cause harmful effects to the human fetus and neonate). However, they do not cause malformations [37]), breastfeeding, severe active bleeding, severe uncontrolled hypertension, severe thrombocytopenia, and spinal injection or puncture (the same contraindications of dabigatran) [82]. Renal function should be monitored during the use of rivaroxaban, especially in elderly patients [82].

Rivaroxaban should not be administered concomitantly with azoles such as ketoconazole**,** itraconazole, posaconazole, and voriconazole and human immunodeficiency virus-protease inhibitors [82, 84].

Apixaban

Apixaban is a medicine from the same class of rivaroxaban. The initial dose for the treatment of acute deep vein thrombosis or pulmonary embolism is 10 mg twice daily for 7 days, preceded by 5 mg twice **for at least 6 months.** After the treatment period is recommended, the use of 2.5 mg twice daily to prevent recurrence of thromboembolic events [85]. The main important side effects are bleeding and nausea. It is not recommended in patients with weight < 60 kg, age > 80 years, and severe renal injury. Indication, adverse effects, precautions, and contraindications are similar to rivaroxaban and are detailed above [85, 86].

Edoxaban

It is an oral anticoagulant indicated for the treatment of deep vein thrombosis, pulmonary embolism, and to reduce the risk of patients with non-valvular atrial fibrillation developing systemic embolism events and stroke [87].

The recommended dose of the treatment of deep vein thrombosis is 60 mg, once daily, following 5–10 days of initial therapy with a parenteral anticoagulant. Common adverse effects are bleeding, rash, abnormal liver function tests, and anemia. Renal clearance accounts for approximately 50% of the total clearance of edoxaban. It is necessary to reduce the dose in pacients with CrCL 15-50 mL/min, and it is not recommended its use in patients with CrCL < 15 mL/min. Category C in pregnancy are medicines that cause or may cause harmful effects to the human fetus and neonate. However, they do not cause malformations [37, 87].

References

1. Batty P, Smith JG. Haemostasis. Surgery (Oxford). 2010;28(11):530–5.
2. Austin SK. Haemostasis. Medicine. 2009;37(3):133–6.
3. Clemetson KJ. Platelets and primary haemostasis. Thromb Res. 2012;129(3):220–4.
4. Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. Science. 1964;145(3638):1310–2.
5. Macfarlane R. An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. Nature. 1964;202:498–9.
6. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. Blood Rev. 2003;17:S1–5.
7. Hoffman M, Monroe DM. A cell-based model of hemostasis. Thromb Haemost. 2001;85(6):958–65.
8. Pérez-Gómez F, Bover R. La nueva cascada de la coagulación y su posible influencia en el difícil equilibrio entre trombosis y hemorragia. Rev Esp Cardiol. 2007;60(12):1217–9.
9. Batty P, Smith G. Anticoagulation. Surgery (Oxford). 2010;28(6):243–7.
10. Vine AK. Recent advances in haemostasis and thrombosis. Retina. 2009;29(1):1–7.
11. Vaughan D, Declerck P. Fibrinolysis and its regulation. In: Loscalzo J, Schafer A, editors. Thrombosis and hemorrhage. Philadelphia: Lippincott Williams and Wilkins; 1998. p. 155–70.

12. Rau J, Beaulieu L, Huntington J, Church F. Serpins in thrombosis, hemostasis and fibrinolysis. J Thromb Haemost. 2007;5(s1):102–15.
13. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest J. 2004;126(3_Suppl):188S–203S.
14. Australian Medicines Handbook. Dalteparin: Drug Monography. ClinicalKey; 2015.
15. Prandoni P, Carta M, Cogo A, Ruol A, Vigo M, Casara D, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet. 1992;339(8791):441–5.
16. Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. Arch Intern Med. 1991;151(2):333–7.
17. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S–453S.
18. Olson JD, Arkin CF, Brandt JT, Cunningham MT. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med. 1998;122(9):782.
19. Brandt J, Triplett D. Laboratory monitoring of heparin. Effect of reagents and instruments on the activated partial thromboplastin time. Am J Clin Pathol. 1981;76(4 Suppl):530–7.
20. Zanke B, Shojania A. Comparison of two n methods of monitoring heparin therapy. APTT ratio and heparin response of pooled normal plasma. Am J Clin Pathol. 1990;93(5):684–9.
21. Bain B, Forster T, Sleigh B. Heparin and the activated partial thromboplastin time—a difference between the in-vitro and in-vivo effects and implications for the therapeutic range. Am J Clin Pathol. 1980;74(5):668–73.
22. Kitchen S, Jennings I, Woods T, Preston F. Wide variability in the sensitivity of APTT reagents for monitoring of heparin dosage. J Clin Pathol. 1996;49(1):10–4.
23. Shojania AM, Tetreault J, Turnbull G. The variations between heparin sensitivity of different lots of activated partial thromboplastin time reagent produced by the same manufacturer. Am J Clin Pathol. 1988;89(1):19–23.
24. Volles DF, Ancell CJ, Michael KA, Mullins DM, Humphries JE. Establishing an institution-specific therapeutic range for heparin. Am J Health Syst Pharm. 1998;55(19):2002–6.
25. Rosborough TK. Comparison of anti-factor Xa heparin activity and activated partial thromboplastin time in 2,773 plasma samples from unfractionated heparin-treated patients. Am J Clin Pathol. 1997;108(6):662–8.
26. Van den Besselaar A, Meeuwisse-Braun J, Bertina R. Monitoring heparin therapy: relationships between the activated partial thromboplastin time and heparin assays based on ex-vivo heparin samples. Thromb Haemost. 1990;63(1):16–23.
27. Raschke RA, Gollihare B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. Arch Intern Med. 1996;156(15):1645–9.
28. Sulfate P. Antiheparin agents 20: 12.08. AHFS drug information. 1999:1265–7.
29. Linkins L-A. Heparin induced thrombocytopenia. Br Med J. 2015;350:g7566.
30. Junqueira DR, Perini E, Penholati RR, Carvalho MG. Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2012;9:CD007557.
31. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol. 1993;168(4):1265–70.
32. Barbour LA, Kick SD, Steiner JF, LoVerde ME, Heddleston LN, Lear JL, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol. 1994;170(3):862–9.
33. Dahlman TC, Sjöberg HE, Ringertz H. Bone mineral density during long-term prophylaxis with heparin in pregnancy. Am J Obstet Gynecol. 1994;170(5):1315–20.
34. Douketis J, Ginsberg J, Burrows R, Duku E, Webber C, Brill-Edwards P. The effects of long-term heparin therapy during pregnancy on bone density. A prospective matched cohort study. Thromb Haemost. 1996;75(2):254–7.

35. Guevara A, Labarca J, Gonzalez-Martin G. Heparin-induced transaminase elevations: a prospective study. Int J Clin Pharmacol Ther Toxicol. 1993;31(3):137–41.
36. Shaughnessy SG, Young E, Deschamps P, Hirsh J. The effects of low molecular weight and standard heparin on calcium loss from fetal rat calvaria. Blood. 1995;86(4):1368–73.
37. Prescription MO. Australian categorisation system for prescribing medicines in pregnancy; 1997.
38. Australian categorisation system for prescribing medicines in pregnancy; 1997.
39. Wood AJ, Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688–99.
40. Litin SC, Heit JA, Mees KA, Investigators TC, editors. Use of low-molecular-weight heparin in the treatment of venous thromboembolic disease: answers to frequently asked questions. Mayo Clin Proc. 1998;73(6):545–51.
41. Kessler CM, editor. Low molecular weight heparins: practical considerations. Semin Hematol. 1997;34:3542-5.
42. Abbate R, Gori AM, Farsi A, Attanasio M, Pepe G. Monitoring of low-molecular-weight heparins in cardiovascular disease. Am J Cardiol. 1998;82(5B):33L–6L.
43. Samama MM, Poller L. Contemporary laboratory monitoring of low molecular weight heparins. Clin Lab Med. 1995;15(1):119–23.
44. Kessler CM, Esparraguera IM, Jacobs HM, Druy E, Fortune WP, Holloway DS, et al. Monitoring the anticoagulant effects of a low molecular weight heparin preparation. Correlation of assays in orthopedic surgery patients receiving ardeparin sodium for prophylaxis of deep venous thrombosis. Am J Clin Pathol. 1995;103(5):642–8.
45. Junqueira DRG, Carvalho M, Perini E. Heparin-induced thrombocytopenia: a review of concepts regarding a dangerous adverse drug reaction. Rev Assoc Med Bras. 2013;59(2):161–6.
46. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med. 1999;130(10):800–9.
47. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2004;140(3):175–83.
48. Muir JM, Andrew M, Hirsh J, Weitz J, Young E, Deschamps P, et al. Histomorphometric analysis of the effects of standard heparin on trabecular bone in vivo. Blood. 1996;88(4):1314–20.
49. Racanelli A, Fareed J, Walenga JM, Coyne E, editors. Biochemical and pharmacologic studies on the protamine interactions with heparin, its fractions and fragments. Semin Thromb Hemost. 1985;11(2):176–89.
50. Lindblad B, Borgström A, Wakefield TW, Whitehouse WM, Stanley JC. Protamine reversal of anticoagulation achieved with a low molecular weight heparin. The effects on eicosanoids, clotting and complement factors. Thromb Res. 1987;48(1):31–40.
51. Massonnet-Castel S, Pelissier E, Bara L, Terrier E, Abry B, Guibourt P, et al. Partial reversal of low molecular weight heparin (PK 10169) anti-Xa activity by protamine sulfate: in vitro and in vivo study during cardiac surgery with extracorporeal circulation. Pathophysiol Haemost Thromb. 1986;16(2):139–46.
52. Wolzt M, Weltermann A, Nieszpaur-Los M, Schneider B, Fassolt A, Lechner K, et al. Studies on the neutralizing effects of protamine on unfractionated and low molecular weight heparin (Fragmin) at the site of activation of the coagulation system in man. Thromb Haemost. 1995;73(3):439–43.
53. Sampaio LO, Tersariol IL, Lopes CC, Bouças RI, Nascimento FD, Rocha HA, et al. Heparins and heparans sulfates. Structure, distribution and protein interactions. Insights into carbohydrate structure and biological function. Kerala: Transworld Research Network; 2006. p. 51–61.
54. Garcia DA, Baglin TP, Weitz JI, Samama MM, American College of Chest P. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e24S–43S.
55. Grouzi E, Kyriakou E, Panagou I, Spiliotopoulou I. Fondaparinux for the treatment of acute heparin-induced thrombocytopenia: a single-center experience. Clin Appl Thromb Hemost. 2009;16(6):663–7.

56. Lobo B, Finch C, Howard A, Minhas S. Fondaparinux for the treatment of patients with acute heparin induced thrombocytopenia. Thromb Haemost. 2008;99(1):208–14.
57. Australian Medicines Handbook. Fondaparinux: Drug Monography. ClinicalKey; 2015.
58. Fondaparinux Sodium. In: Sweetman S, editor. Martindale: the complete drug reference [Internet]. 2015. London Pharmaceutical Press. www.medicinescomplete.com
59. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004;140(11):867–73.
60. Büller H, Davidson B, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349(18):1695–702.
61. Blackmer AB, Oertel MD, Valgus JM. Fondaparinux and the management of heparin-induced thrombocytopenia: the journey continues. Ann Pharmacother. 2009;43(10):1636–46.
62. Weitz JI, Buller HR. Direct thrombin inhibitors in acute coronary syndromes present and future. Circulation. 2002;105(8):1004–11.
63. Sheth S, DiCicco R, Hursting M, Montague T, Jorkasky D. Interpreting the international normalized ratio (INR) in individuals receiving argatroban and warfarin. Thromb Haemost. 2001;85(3):435–40.
64. White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. Expert Opin Drug Metab Toxicol. 2009;5(5):529–38.
65. Eichler P, Friesen H-J, Lubenow N, Jaeger B, Greinacher A. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects on aPTT, and clinical relevance. Blood. 2000;96(7):2373–8.
66. Malhotra O, Nesheim M, Mann K. The kinetics of activation of normal and gamma-carboxyglutamic acid-deficient prothrombins. J Biol Chem. 1985;260(1):279–87.
67. Friedman P, Rosenberg R, Hauschka P, Fitz-James A. A spectrum of partially carboxylated prothrombins in the plasmas of coumarin-treated patients. Biochim Biophys Acta. 1977;494(1):271–6.
68. Coumadin F. Tablets (Warfarin Sodium Tablets, USP) Crystalline; COUMADIN® FOR INJECTION (Warfarin Sodium for Injection, USP). 2007 [updated 2007; cited 2008 11-23]; FDA (Food and Drug Administration).
69. Nicolaides A, Fareed J, Kakkar A, Comerota A, Goldhaber S, Hull R, et al. Prevention and treatment of venous thromboembolism international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost. 2013;19(2):116–8.
70. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic: the Seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest J. 2004;126(3_Suppl):457S-82S.
71. Committee AGSCP. The use of oral anticoagulants (warfarin) in older people. American Geriatrics Society guideline. J Am Geriatr Soc. 2002;50(8):1439.
72. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest J. 2004;126(3_Suppl):429S–56S.
73. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. Cleve Clin J Med. 2003;70(4):361–71.
74. Jaffer AK, Brotman DJ, Chukwumerije N. When patients on warfarin need surgery. Cleve Clin J Med. 2003;70(11):973–84.
75. Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med. 1997;336(6):393–8.
76. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348(15):1425–34.
77. Acenocoumarol. In: Sweetman S, editor. Martindale: complete drug reference [Internet]. London Pharmaceutical Press; 2015. www.medicinescomplete.com
78. Rb R. Vascular surgery. 8th ed. Philadelphia: Elsevier; 2014. p. 1018.

79. Australian Medicines Handbook. Dabigatran: Drug Monography. ClinicalKey; 2015.
80. Dabigatran. In: Sweetman S, editor. Martindale: complete drug reference [Internet]. London: Pharmaceutical Press; 2014. http://www.medicinescomplete.com
81. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest J. 2012;141(2_Suppl):e44S–88S.
82. Australian Medicines Handbook. Rivaroxaban: Drug Monography. ClinicalKey; 2015.
83. AG BSP. Xarelto® summary of product characteristics; 2011.
84. Rivaroxaban. In: Sweetman S, editor. Martindale: the complete drug reference [Internet]. London: Pharmaceutical Press; 2015. http://www.medicinescomplete.com
85. Apixaban. In: Sweetman S, editor. Martindale: the complete drug reference [Internet]. London: Pharmaceutical Press; 2015. Http://www.medicinescomplete.com
86. Australian Medicines Handbook. Apixaban: Drug Monograph. ClinicalKey; 2015.
87. FDA. Highlights of prescribing information savaysa (edoxaban); 2015.
88. Chan EL, Bardin JA, Bernstein EF. Inferior vena cava bypass: experimental evaluation of externally supported grafts and initial clinical application. J Vasc Surg. 1984;1(5):675–80.

Peripheral Artery Disease

5

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Abstract

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis that leads to reduction of limb's blood supply, leading to acute or critical ischemia. In the United States, this condition affects 4.3 % of the general population. In about 90 % of the chronic cases, it is caused by atherosclerosis, and it is an important marker of cardiovascular risk and death. The remaining cases are caused by a varied group of pathologies, such as arteritis and neuropathies. Peripheral arterial disease's risk factors are advanced age, hypertension, diabetes mellitus, smoking, and hyperlipidemia. Its most common symptom is intermittent claudication, but the patient may also be asymptomatic (the largest group of patients), experiencing pain at rest or ulceration. The gold standard test to determine the presence of peripheral vascular disease is calculation of the ankle-brachial index. Treatment is divided into lifestyle, medical, and surgical

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revascularization therapies, and it is aimed at pain relief, healing of ulcerations, prevention of limb loss, independent walking maintenance, risk factors control, and survival increasing.

Abbreviations

BASIL	Bypass versus angioplasty in severe ischemia of the leg
m	Meters
LDL	Low-density lipoprotein
mg/dL	Milligrams per deciliter
mmHg	Millimeters of mercury
PTFE	Polytetrafluoroethylene

Introduction

Peripheral arterial disease is the presence of obstruction or narrowing in the arteries that supply the members in one or more of the segments, leading to ischemia. It mainly affects the lower limbs, in one or more territories of the aortoiliac, femoropopliteal, and infrapopliteal arteries. The etiology, in about 90 % of the cases, is atherosclerosis, and it is an important clinical marker of cardiovascular risk and death [1].

Epidemiology

In the United States, the peripheral arterial disease affects 4.3 % of the general population. The prevalence and incidence increase with age: about 20 % of the population aged over 60 have some degree of the condition. It is more frequent in non-Hispanic black population (7.8 %) than in the white population (4.4 %). It is slightly more prevalent in males [2].

The main risk factors of atherosclerosis are those of diabetes *mellitus*, smoking, high blood pressure, hypercholesterolemia, and age, and its risk is related to the severity and duration of diabetes. Nonetheless, the link between diabetes and critical ischemia is also well documented [3–5]: the prevalence is 20–30 % higher in diabetic patients than in the general population [6]. The severity of peripheral arterial disease is proportional to the degree of tobacco exposure, measured on pack-years [7]. Hypertension increases the risk of developing symptoms and is present in 55 % of patients with peripheral arterial disease [8].

The treatment of dyslipidemia reduces the progression of the disorder and the claudication [9]. Each additional risk factor increases, independently, the risk of developing symptomatic disease [10]. Chronic renal failure appears to be an independent factor, but it can also be causal [11].

Peripheral arterial disease is promptly diagnosed by ankle-brachial index measurements, obtained with a handheld continuous wave Doppler. Index lesser than 0.9 or greater than 1.4 confirms the condition. Besides, it is an independent risk

factor for cardiovascular events and to all causes of death. Thus, patients older than 65 years, older than 50 who are smokers and/or diabetic or with peripheral arterial diseases symptoms should have their ankle-brachial index checked [12].

Natural History and Clinical Presentation

Peripheral arterial disease patients may be asymptomatic or present with intermittent claudication or critical limb ischemia. Critical ischemia includes pain at rest and/or those with ischemic ulcers [Table 5.1] [13].

Asymptomatic

They constitute the largest group. The diagnosis is made by the ankle-brachial index. Despite the absence of symptoms, individuals with peripheral arterial disease (ankle-brachial index <0.9) have higher morbidity rates than patients with normal index. The risks are inversely proportional to the daily physical activity. This group of patients should be conducted medically in the same manner as the symptomatic [14].

Intermittent Claudication

Intermittent claudication patients have fatigue or muscle pain while walking. It is most common in the calf but may be present in the buttock or thigh, according to the site of arterial obstruction. Symptoms cease with rest and restart with the next effort [15].

The pain results from ischemic neuropathy and local intramuscular acidosis [16]. The pain intensity depends on physical activity degree. Therefore, some patients may be asymptomatic due to poor clinical conditions and/or low functional capacity. Elderly patients usually walk indoors, not completing the necessary distance to elicit symptoms. At the same time, a workman that needs to walk more than 1000 m to perform their labor activities will complain of limiting symptoms [15].

The intermittent claudication causes functional disability. It is marked by slow progression, rarely leading to critical limb ischemia. In 75 % of cases, it stabilizes

Table 5.1 Peripheral arterial disease—Rutherford's clinical classification [13]

Fontaine Grade	Rutherford Grade	Rutherford stages	Clinical presentation
I	0	0	Asymptomatic
IIa		1	Mild claudication
IIb	I	2	Moderate claudication
		3	Severe claudication
III	II	4	Pain at rest
IV	III	5	Minor tissue loss
		6	Major tissue loss

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or alleviates symptoms. Only 25 % deteriorate, most commonly in the first year (6–9 % in the first year and 2–3 % per year) [17].

A low ankle-brachial index (<0.5) is a predictor of clinical worsening. The best single predictor, however, is a reduced ankle absolute pressure, between 40 and 60 mmHg. Amputation is rare, with rates as low as 2 % in 5 years [18]. Mortality, on the other hand, is high, reaching 42 % at 5 years and 65 % at 10 years [19].

Critical Limb Ischemia

Critical limb ischemia is the most severe presentation of peripheral arterial disease. It affects 1 % of all symptomatic cases. It is divided into two groups: rest pain and ischemic trophic lesion [20].

Rest pain is described as burning sensation or uncomfortable cold or numbness, sufficiently intense to interfere with sleep. The discomfort is aggravated by leg elevation, relieving in standing position or dangling the leg over the edge of the bed [21, 22]. Pain always affects the limb most distal segment, the forefoot or at the amputation stump. Rest pain does not affect the calf or thigh, except for patients with acute limb ischemia [23].

The degree of sleep interference informs about its intensity. The patient is woken up by the pain, returning to sleep soon after. With the progression of the ischemia, they only can sleep dangling the leg over the edge of the bed leading to leg edema [21, 22].

Ulcers and gangrenes occur when blood flow to the limb is insufficient to maintain cell viability at rest. They predominate in the toes but also can be present in the ankle and heel. The pain can be increased by ischemic neuropathy, skin loss, exposure of subcutaneous sensory nerves, osteomyelitis, and ascending infection. Diabetes is an important risk factor for gangrene, present in 40 % versus 9 % in nondiabetic patients with critical limb ischemia [24].

Patients with critical limb ischemia have a poor prognosis. About 25 % will undergo amputation immediately; 25 % will have medical treatment and 50 % will be revascularized. After 1 year, only 25 % will have the critical limb ischemia resolved; 20 % will remain with symptoms, 25 % will be dead, and 30 % will be amputees. Critical limb ischemia can be the first peripheral arterial disease presentation in most patients, which hinders therapies for prevention [13].

Due to atherosclerosis's systemic involvement, a severe peripheral arterial disease is often associated with advanced coronary artery and cerebrovascular diseases. Thus, all patients with this disease require strict control of the modifiable risk factors, to slow atherosclerosis progression, besides improvement of the benefits, duration, and safety of vascular intervention [25].

Diagnosis

It is based on medical history and physical examination. Peripheral arterial disease must be confirmed by noninvasive tests since its prevalence is underestimated when based solely on symptoms, and overestimated if based exclusively on pulses

palpation. The diagnosis is confirmed by hemodynamic measurements with a handheld Doppler (ankle-brachial index <0.9) [26].

On physical examination, one should search for the absence of pulses, changes on foot color and temperature, muscular atrophy (by disuse), reduction of the amount of hair, slow toe's nail growth, and nail hypertrophy [26].

Imaging exams such as duplex scan, computed angiography, magnet resonance angiography, and digital subtraction angiography are not required for diagnosis. They are necessary for anatomical details and revascularization planning and may be useful on atypical presentation or doubtful situations [13]. The differential diagnosis is made with peripheral neuropathy conditions (burning or tingling sensations especially in hands and feet); nerve root compression (pain, weakness, and loss of sensation in the posterior aspect of the lower limb); night cramps (muscle pain located in the calf and foot); Buerger's disease (ischemia of the distal part of extremities in young smokers); gout (severe pain in the joints of the feet, ankles, hands, and wrists); plantar fasciitis (pain, stiffness, and burning in the sole of the foot); neuroma (numbness and pain in the forefoot); and rheumatoid arthritis (pain and swelling in small joints, particularly in hands) [13]. Such groups of disease simulating peripheral arterial disease are called pseudoclaudication.

Treatment

Treatment of peripheral arterial disease is aimed at pain relief, healing of ulcerations, prevention of limb loss, independent walking maintenance, risk factors control, and survival increasing.

Risk Factors Control

It is recommended smoking cessation [27, 28]; lipid control (Low-density lipoprotein [LDL] <100 mg/dL, or, in case of patients at high risk of ischemic events, <70 mg/dL) [29]; rigorous glycemic control and blood pressure control (<140/90 or 130/80 mmHg for diabetic or chronic renal failure patients) [30].

Drugs aimed at modifying risk factors, such as statins and antiplatelet agents, are used in all stages of peripheral arterial disease, aiming at slowing atherosclerosis progression [9].

Treatment of Intermittent Claudication

Intermittent claudication therapy targets pain relief and better daily physical performance. The patient has to be advised to walk to the limit of pain's tolerance, followed by a short rest period. Then, must return to walking, redoing all this cycle for at least 30 min, three times a week [31].

Some patients are able to accomplish this training by themselves. Most, however, require support, being referred to a supervised exercise program. This consists of performing physical activities monitored and guided by a physiotherapist, to increase patient's adherence and intervention's effectiveness [32].

Cilostazol is a phosphodiesterase III inhibitor drug with vasodilatory, metabolic, and antiplatelet activity. It is the only drug with proven efficacy for intermittent claudication symptoms' relief [33–36]. That said, it should be prescribed for all these individuals, for about 3–6 months [13, 33].

The lack of response to exercise and/or drug therapy leads to limb's revascularization evaluation. However, patients who present with proximal lesions, i.e., aortoiliac obstruction manifested by buttocks' claudication and femoral pulse reduction, revascularization can be considered earlier [13].

Treatment of Critical Limb Ischemia

Critical limb ischemia implies the imminent risk of limb loss. This risk is only reduced by limb's blood supply reestablishment. Thus, patients with this condition should be promptly referred to a vascular surgery team for a proper approach [13].

Bypass surgery consists on the diversion of blood flow from an area of normal blood flow to an area with low flow, distal to the arterial obstructed segment, with the aid of tubular grafts. These can be autologous, such as the great saphenous vein, or synthetic, such as polytetrafluoroethylene, commonly shortened as PTFE, or polyester grafts [37].

The endovascular surgery is a minimally invasive image-guided approach, used for restoring the patency of the arteries. First, an arterial puncture is made, usually on the femoral or brachial artery, through which catheters, guidewires, and other endovascular devices are introduced. After crossing the vascular obstruction with a guidewire, the angioplasty with a balloon catheter is performed. Angioplasty is the compression of the atherosclerosis plaque against the artery wall to reopen the vessel lumen. According to the lesion type and location and the angioplasty results, a stent, which is a tubular metal cylinder, is delivered. Its function is to maintain the plaque compacted and fixed against the artery wall, allowing the free blood circulation.

The choice between one method and the other is made according to the extension of the lesion, the comorbidities of the patient, operative risk, the patient life span, availability of local resources and surgeon preference [13]. The BASIL (Bypass versus angioplasty in severe ischemia of the leg) trial compared results of surgery and angioplasty in patients presenting with severe limb ischemia due to infrainguinal disease and observed that patients with expected survival of less than 2 years, whenever possible, should be treated with angioplasty [38]. On the other hand, patients with expected survival of more than two years are better treated with surgery, particularly if performed with autologous vein [39]. A recent good systematic review showed that primary patency for vein bypass grafts is significantly improved compared with PTFE grafts in the above-knee setting [40].

There are also some recent publications using mostly observational data for the treatment of aortoiliac disease reporting that endovascular procedures were associated with lower cost, shorter hospital stay, and lower complication rates compared to surgery [41]. However, a meta-analysis showed superior durability of conventional surgery compared to the endovascular treatment, althoug surgery resulted in higher risk of complications and mortality, and longer hospital stay [42].

When the revascularization is not possible, due to anatomical factors or patient characteristics such as high surgical risk, extensive and irreversible tissue loss, septic gangrene, no walking capacity, and bedridden, then primary amputation may be the best treatment [43]. Intensive wound care, sometimes, may prevent amputation in selected cases [13]. Furthermore, amputation is usually necessary in case of revascularization failure, in exchange for pain relief, allowing sleep and keeping the patient without wounds. Besides, patients with better functional capacity can be rehabilitated, restoring walking capacity, autonomy, and quality of life [44].

Questions

- What can the nonexpert do for the patient?
- In asymptomatic patients and in patients with intermittent claudication, control of the modifiable risk factors for atherosclerosis.
- When to refer to the expert?
- Symptomatic patients with critical limb ischemia (rest pain or ulceration) and patients with intermittent claudication refractory to risk factor modification and exercise therapy.

References

1. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg. 1986;4(1):80–94.
2. National Institute for Health and Clinical Excellence. Lower limb peripheral arterial disease: diagnosis and management. Manchester; 2012.
3. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham study. J Am Geriat Soc. 1985;33(1):13–18.
4. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992;135(4):331–40.
5. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997;96(1):44–9.
6. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. J Am Coll Cardiol. 2006;47(5):921–9.
7. Powell JT, Edwards RJ, Worrell PC, Franks PJ, Greenhalgh RM, Poulter NR. Risk factors associated with the development of peripheral arterial disease in smokers: a case-control study. Atherosclerosis. 1997;129(1):41–8.
8. Lane DA, Lip GY. Treatment of hypertension in peripheral arterial disease. Cochrane Database Syst Rev. 2009;(4):CD003075.

9. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78.
10. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006;47(6):1239–312.
11. O'Hare AM, Vittinghoff E, Hsia J, Shlipak MG. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). J Am Soc Nephrol. 2004;15(4):1046–51.
12. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. Crit Pathw Cardiol. 2005;4(4):198–203.
13. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5–67.
14. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, et al. Metabolic syndrome and risk of incident peripheral artery disease the cardiovascular health study. Hypertension. 2014;63(2):413–9.
15. Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014;10, CD003748.
16. Sluka KA. Pain mechanisms involved in musculoskeletal disorders. J Orthop Sports Phys Ther. 1996;24(4):240–54.
17. Dormandy J, Heeck L, Vig S. The natural history of claudication: risk to life and limb. Semin Vasc Surg. 1999;12(2):123–37.
18. Kannel WB, Skinner JJ, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. Circulation. 1970;41(5):875–83.
19. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1996;25(6):1172–81.
20. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg. 2000;31(1 Pt 2):S1–296.
21. Weinberg DH, Simovic D, Isner J, Ropper AH. Chronic ischemic monomelic neuropathy from critical limb ischemia. Neurology. 2001;57(6):1008–12.
22. Jamieson C. The definition of critical ischaemia of a limb. Br J Surg. 1982;69 Suppl:S1.
23. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517–38.
24. Kannel WB. Risk factors for atherosclerotic cardiovascular outcomes in different arterial territories. J Cardiovasc Risk. 1994;1(4):333–9.
25. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol. 1991;20(2):384–92.

26. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation. 1985;71(3):516–22.
27. Kabir Z, Connolly GN, Clancy L, Koh HK, Capewell S. Coronary heart disease deaths and decreased smoking prevalence in Massachusetts, 1993-2003. Am J Public Health. 2008;98(8):1468–9.
28. Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Büller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. J Vasc Surg. 2005;42(1):67–74.
29. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Arterioscler Thromb Vasc Biol. 2004;24(8):e149–61.
30. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomisedcontrolled trial. Lancet. 2005;366(9493):1279–89.
31. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. N Engl J Med. 2002;347(24):1941–51.
32. Lane R, Ellis B, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev. 2014;7, CD000990.
33. Regensteiner JG, Ware JE, McCarthy WJ, Zhang P, Forbes WP, Heckman J, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc. 2002;50(12):1939–46.
34. Dawson DL, Cutler BS, Hiatt WR, Hobson RW, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000;109(7): 523–30.
35. Barnett AH, Bradbury AW, Brittenden J, Crichton B, Donnelly R, Homer-Vanniasinkam S, et al. The role of cilostazol in the treatment of intermittent claudication. Curr Med Res Opin. 2004;20(10):1661–70.
36. Pande RL, Hiatt WR, Zhang P, Hittel N, Creager MA. A pooled analysis of the durability and predictors of treatment response of cilostazol in patients with intermittent claudication. Vasc Med. 2010;15(3):181–8.
37. Merrell GA, Gusberg RJ. Infrainguinal bypass conduit: autogenous or synthetic—a national perspective. Vasc Endovascular Surg. 2002;36(4):247–54.
38. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet. 2005;366(9501):1925–34.
39. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg. 2010;51(5 Suppl):69S–75.
40. Twine CP, McLain AD. Graft type for femoro-popliteal bypass surgery. Cochrane Database Syst Rev. 2010;5, CD001487.
41. Indes JE, Mandawat A, Tuggle CT, Muhs B, Sosa JA. Endovascular procedures for aorto-iliac occlusive disease are associated with superior short-term clinical and economic outcomes compared with open surgery in the inpatient population. J Vasc Surg. 2010;52(5):1173–9, 9.e1.
42. Indes JE, Pfaff MJ, Farrokhyar F, Brown H, Hashim P, Cheung K, et al. Clinical outcomes of 5358 patients undergoing direct open bypass or endovascular treatment for aortoiliac occlusive disease: a systematic review and meta-analysis. J Endovasc Ther. 2013;20(4):443–55.
43. Taylor SM, Kalbaugh CA, Blackhurst DW, Cass AL, Trent EA, Langan EM, et al. Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. J Vasc Surg. 2006;44(4):747–55; discussion 55–6.
44. Taylor SM, Kalbaugh CA, Blackhurst DW, Hamontree SE, Cull DL, Messich HS, et al. Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: an analysis of 553 consecutive patients. J Vasc Surg. 2005;42(2):227–35.

Acute Limb Ischemia

6

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Abstract

Acute ischemia is the sudden reduction of limb perfusion due to acute interruption of blood flow, endangering its viability. It may be secondary to an embolic event or arterial thrombosis, each with its own distinct characteristics and prognosis. The symptoms are known as the six P's: Pain, Pallor, Paresthesia, Paralysis, Pulseless, and Poikilothermia. Time of ischemia defines the prognosis. Treatment requires an expert since it involves urgent revascularization surgery in many cases. The degree and time of ischemia helps determine the best choice of treatment.

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Introduction

Acute ischemia is the sudden reduction of limb perfusion due to acute interruption of blood flow, endangering its viability. It is considered acute when presented within 2 weeks after the occlusive event [1, 2].

The etiology of the occlusion may be an embolic event or arterial thrombosis, each one with its own distinct characteristics and prognosis. The most frequent cause currently is arterial thrombosis, usually associated with atherosclerosis. The main source of arterial embolism is the heart in cases of presence of intracavitary thrombi. Less common causes are arterial dissections, hypercoagulable states, and vascular dysfunction causing vasospasms [3–6].

Arterial Thrombosis

Thrombosis results in the formation of blood clot inside the arterial lumen, leading to its obstruction. It is usually caused by endothelial disruption of a pre-existing atherosclerotic plaque. The rupture follows sudden plaque's expansion due to atherosclerotic intraplaque hemorrhage. The most common cause therefore correlates with disease aterosclertotic disease. Other causes are thrombosis of peripheral aneurysms (particularly popliteal artery aneurysms), thrombosis of a previous revascularization procedure, whether endovascular or open conventional, and hypercoagulable states [3–5].

Arterial Embolism

Arterial embolism is the obstruction of an artery, determined by the migration of emboli—a blood immiscible material—through the arterial tree. The emboli are generally a thrombi's fragment that lodges in natural arterial narrowing. In the lower limbs, the most affected sites are the bifurcation of the common femoral and popliteal arteries [5, 7–9].

The majority of emboli originate at the heart [7]. Of all intracardiac thrombi, 55–87 % will reach peripheral arteries [7, 9]. The remaining cardiac emboli may also reach the viscera, particularly the superior mesenteric artery causing acute mesenteric ischemia, and some reaches the brain causing strokes [7]. Arrhythmias are the main cause of heart thrombi's formation, and atrial fibrillation is the most frequent one [7, 10, 11]. Heart failure and valvar heart diseases are predisposing conditions as well. Besides, some post-myocardial infarction patients may present with mural thrombus [12, 13]. Paradoxical embolism is the clinical situation where emboli formed in the venous circulation—as a consequence of deep vein thrombosis—reach the arterial circulation through an atrial septal defect, usually persistence of patent *foramen ovale* [14]. Other arterial embolism from cardiac sources are: septic emboli, secondary to bacterial endocarditis, and emboli from tumoral vegetations, such as an atrial myxoma [7]. Non-cardiac sources of embolus may originate from peripheral aneurysms and unstable atherosclerotic plaques, but are less frequent [8].

Epidemiology

The profile of patients at risk for arterial thrombosis is the same as those for peripheral arterial disease, since atherosclerosis is the main cause, which includes patients with *diabetes mellitus*, smoking, high blood pressure, hypercholesterolemia, and advanced age [15]. Nonatherosclerotic causes may be related to hypercoagulable states, such as thrombophilia and malignancies [16].

In contrast, the main risk factors for arterial embolism are heart disease—arrhythmias, valvular disease, myocardial infarction, and cardiomyopathy—peripheral aneurysms, and patients with malignancies. Therefore, many of such patients do not report previous peripheral arterial disease symptoms [5, 7, 17].

Clinical Presentation

The clinical picture depends on the time of onset of the symptoms. Also, the presence or absence of collateral network is of critical importance, once it may assist in limb perfusion. It tends to be more severe in patients with arterial embolism and more insidious in case of thrombosis, once the latter have some degree of previous ischemia.

Pain is always present in the early stages and it is very intense. The limb is cold and pale and distal pulses cannot be palpated. With the persistence of the ischemia, neurological damage installs. Initially, sensory injury with some degree of paresthesias may be related by the patients, starting at the toes and progressing to the foot and ankle afterwards.

In more advanced cases of ischemia, motor impairment is reported. Initially, motor weakness (paresthesia) is objectively seen as reduction of the dorsoflexion amplitude of the foot. Afterwards, no movement of the ankle joint is reported, characterizing paralysis. Such neurological symptoms are linked to high risk of limb loss and death, in case a revascularization procedure cannot be accomplished promptly [5, 7, 18].

Diagnosis

Diagnosis is based on clinical history, physical examination, and ankle-braquial index measurements [19].

These data allow the classification of patients according to the degree of ischemia (Table 6.1).

CLASS 1—VIABLE LIMB

Pain and pallor, without sensory loss or muscle weakness. Distal pulse is not palpable. Arterial and venous sounds are audible to doppler [1, 13].

CLASS 2—THREATENED LIMB

2A: Marginally threatened—Pain, pallor, and minimal sensory loss. No muscle weakness. Absence of arterial doppler sound, but with audible venous sounds. Member may be saved if treated promptly.

2B: Immediately threatened—Pain, pallor, and greater sensory loss. Mild to moderate muscle weakness. Tenderness of the calf. Absence of arterial doppler sound, but keeps audible venous sounds. Imminent risk of limb loss that can be saved if immediately revascularized [1, 13].

CLASS 3—IRREVERSIBLE

Permanent damage with massive sensory loss and profound muscle weakness or paralysis. Absence of arterial and venous sound on doppler. Muscle stiffening like *rigor mortis*. At this point, ischemia is irreversible [1, 13].

Therefore, this classification shows the severity and guides the therapy—whether medical, revascularization procedures, or limb amputation—and its urgency [7] (Table 6.1).

The acute limb ischemia symptoms are memorized by the six P's: Pain, Pallor, Paresthesia, Paralysis, Pulseless, and Poikilothermia. Laboratory tests are used to quantify both local and systemic impairment. Muscle necrosis leads to increase in creatine phosphokinase levels. Furthermore, leukocytosis, metabolic acidosis, hemoconcentration, and impairment of renal function may be present [21].

Imaging exams such as duplex scan, computerized tomography, magnet resonance angiography, and digital subtraction angiography are not required for diagnosis. They are useful in atypical presentation or in doubtful situations and should be done for anatomical details and revascularization planning, if the patient can wait due to the ischemia severity [15, 22].

Arterial Duplex Scan helps to identify the level of occlusion, checking also the patency of other distal arteries, which may be useful in surgical planning. It may suggest the age of the thrombus as well by its echogenicity. It also can diagnose thrombosed aneurysm as the cause of ischemia. It is a fast and cheap method that can be used at bedside and is very accurate before and after intervention [23].

Table 6.1 Classification of acute limb ischemia occlusion [20]

Class	Category	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler	Venous Doppler
I	Viable	No immediate limb threat	None	None	Audible	Audible
IIA	Threatened: marginal	Salvageable if treated promptly	Minimal-none	None	+/– audible	Audible
IIB	Threatened: immediate	Salvageable if treated immediately	More than just toes	Mild-moderate	Rare audible	Audible
III	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

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Arteriography defines the site of obstruction, the quality of the distal arteries, the concomitant presence of atherosclerotic disease, and collateral circulation, obtaining relevant data for surgical planning and technique adoption. It may be performed intraoperatively [1].

Other imaging methods such as computed tomography angiography and magnetic resonance angiography can be useful, but is time-consuming and may delay the treatment leading to bad outcome. Therapy delay may be determinant for limb loss and death [1].

Echocardiography is useful in identifying potential embolic sources, but it is not essential for diagnosis or for the revascularization procedure [3, 4].

Differential Diagnosis

Other conditions that may mimic acute limb ischemia are: hemodynamic shock, phlegmasia cerulea dolens, acute compressive neuropathy, aortic dissection, ergotism, HIV's arteriopathy, compartmental syndrome, and vasculitis. In these patients, imaging exams help to elucidate the diagnosis [1, 15, 24–27].

Treatment

Initial treatment aims to prevent thrombus's progression and relies on systemic anticoagulation. Best initial choice is continuous intravenous infusion of unfractioned heparin, keeping activated partial thromboplastin time between two and three times above the baseline time [3]. Direct thrombin inhibitors may be used if heparin is not possible, but they are not approved by the US Food and Drug Administration (FDA) for this propose. It is indicated in reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [28].

All patients with suspected acute limb ischemia should be immediately evaluated by a vascular specialist, especially when neurological symptoms are present, particularly muscle weakness. Waste of time can lead to limb damage, sometimes irreversible. The surgeon will define the need and timing of revascularization and which way should be the best approach: open or endovascular surgery [29, 30].

Endovasculartherapy

There are two endovascular techniques for flow restoration on patients with acute limb ischemia: catheter-directed thrombolysis and mechanical thrombectomy [31].

Catheter-directed thrombolysis is intra-thrombus infusion of thrombolytic drugs through a multi-perforated catheter. The clot dissolution is slow and may take more than 24 h. Therefore, it should not be used in advanced ischemia, i.e., with loss of motor function, where immediate reperfusion is mandatory. It is indicated for the categories I and IIa patients, with better results if accomplished preferably in the

first 15 days. It carries increased risk of bleeding due to thrombolytic drugs use. Thrombolytic agents include streptokinase, urokinase, pro-urokinase, and recombinant tissue plasminogen activators [32–34].

The mechanical thrombectomy devices are endovascular catheters able to promote immediate clot lysis [2, 31]. The mechanism of action consists of mechanical thrombi's fragmentation, followed by aspiration and removal, quickly reestablishing blood flow. Some devices allow the injection of a thrombolytic agent, under pressure, into the thrombi, which is called pharmaco-mechanical thrombolysis. This aims to accelerate the dissolution of the thrombus with a lower dose of thrombolytic agents, in order to decrease the risk of bleeding. Mechanical thrombectomy, contrary to catheter-directed thrombolysis, can be used in selected patients with advanced ischemia, i.e., when muscle weakness is already established [31, 35, 36].

After thrombus dissolution, completion angiography is mandatory to investigate and identify the unstable injury that caused the occlusion. The endovascular approach allows correction of these lesions, by angioplasty, with or without stent, at the same procedure [37].

In general, endovascular techniques are preferred for arterial thrombosis within 15 days of evolution. Furthermore, they work better for infra inguinal arteries [37–39].

Conventional Open Surgery

Open surgery is more appropriate for patients with embolic occlusion and/or for those with aortoiliac involvement. In the event of failure of the endovascular therapy, open surgery may still be an option [3, 4]. Conventional surgery can be done by two ways: thromboembolectomy and/or arterial bypass.

The first consists of thrombus extraction with a catheter with a balloon at its end—embolectomy catheter (Fogarty catheter). Arteriotomy is performed near the site of occlusion; the catheter is introduced, under direct vision and, when the catheter reaches the distal arterial segment, the balloon is inflated and pulled back, dislodging and bringing out the thrombi. This technique is the first choice for patients with embolic acute limb ischemia and for those with previous bypass or angioplasty occlusion [40].

The second method, arterial bypass, has been described before and follows the same principles for peripheral arterial disease patients. It is performed when thromboembolectomy fails, inadequate removal of thrombi, or insufficient flow restoration [18]. It is very useful for peripheral aneurysm occlusion repair [41].

In situations of irreversible damaged limb (acute limb ischemia class III patients), the best treatment choice is primary amputation at a proper level. Attempt to revascularize such patients can trigger severe inflammatory and metabolic responses, due to reperfusion syndrome, adding high rates of morbidity and mortality [9, 30].

Complications

Syndrome of Reperfusion

The most feared complication of revascularization is reperfusion syndrome, and its severity is closely associated with the intensity of ischemia and its duration. Systemic and regional metabolic changes are triggered by rhabdomyolysis. It is characterized by metabolic acidosis, hyperkalemia, increased creatine phosphokinase serum level, increased blood partial pressure of CO_2, decreased blood partial pressure of O_2, and myoglobinuria, leading to myocardial depression, respiratory failure, and acute renal failure. If untreated, can lead quickly to death [21, 42, 43].

Muscle compartment syndrome occurs, due to severe swelling of the muscles inside the inextensible muscle fascia after revascularization, increasing the pressure inside this compartment. If the pressure equals or exceeds the diastolic pressure, muscle perfusion is jeopardized and ischemia installs. The treatment of compartment syndrome is through fasciotomy, a long longitudinal surgical opening of muscular fascia for decompression [44–46].

Questions

- What can the non-expert do for the patient?
- Identify the problem and initiate systemic anticoagulation with intravenous heparin for suspected acute ischemia to prevent thrombus's progression until the patient reaches the specialist [3].
- When to refer to the expert?
- Since acute limb ischemia is an emergency medical condition with imminent risk of limb loss and death, all patients should be referred for expert evaluation at once [29, 30].

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5–67.
2. Walker TG. Acute limb ischemia. Tech Vasc Interv Radiol. 2009;12(2):117–29.
3. Berridge DC, Kessel D, Robertson I. Surgery versus thrombolysis for acute limb ischaemia: initial management. Cochrane Database Syst Rev. 2002;(3):CD002784.
4. Graor R, Comerota A, Douville Y, Turpie A, Froehlich J, Hosking J, et al. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower-extremity-the stile trial. Ann Surg. 1994;220(3):251–68.
5. Mutirangura P, Ruangsetakit C, Wongwanit C, Sermsathanasawadi N, Chinsakchai K. Clinical differentiation between acute arterial embolism and acute arterial thrombosis of the lower extremities. J Med Assoc Thai. 2009;92(7):891–7.
6. O'Donnell TF. Arterial diagnosis and management of acute thrombosis of the lower extremity. Can J Surg. 1993;36(4):349–53.

7. Lyaker MR, Tulman DB, Dimitrova GT, Pin RH, Papadimos TJ. Arterial embolism. Int J Crit Illn Inj Sci. 2013;3(1):77–87.
8. Saric M, Kronzon I. Aortic atherosclerosis and embolic events. Curr Cardiol Rep. 2012;14(3):342–9.
9. Dag O, Kaygın MA, Erkut B. Analysis of risk factors for amputation in 822 cases with acute arterial emboli. ScientificWorldJournal. 2012;2012:673483.
10. Wasilewska M, Gosk-Bierska I. Thromboembolism associated with atrial fibrillation as a cause of limb and organ ischemia. Adv Clin Exp Med. 2013;22(6):865–73.
11. Campbell WB, Ridler BM, Szymanska TH. Two-year follow-up after acute thromboembolic limb ischaemia: the importance of anticoagulation. Eur J Vasc Endovasc Surg. 2000;19(2):169–73.
12. White DC, Grines CL, Grines LL, Marcovitz P, Messenger J, Schreiber T. Comparison of the usefulness of enoxaparin versus warfarin for prevention of left ventricular mural thrombus after anterior wall acute myocardial infarction. Am J Cardiol. 2015;115(9):1200–3.
13. Nunes MC, Kreuser LJ, Ribeiro AL, Sousa GR, Costa HS, Botoni FA, et al. Prevalence and risk factors of embolic cerebrovascular events associated with Chagas heart disease. Glob Heart. 2015;10(3):151–7.
14. Windecker S, Stortecky S, Meier B. Paradoxical embolism. J Am Coll Cardiol. 2014;64(4):403–15.
15. Sontheimer DL. Peripheral vascular disease: diagnosis and treatment. Am Fam Physician. 2006;73(11):1971–6.
16. Alfirević Z, Alfirević I. Hypercoagulable state, pathophysiology, classification and epidemiology. Clin Chem Lab Med. 2010;48 Suppl 1:S15–26.
17. Andersen LV, Lip GY, Lindholt JS, Frost L. Upper limb arterial thromboembolism: a systematic review on incidence, risk factors, and prognosis, including a meta-analysis of risk-modifying drugs. J Thromb Haemost. 2013;11(5):836–44.
18. O'Connell JB, Quiñones-Baldrich WJ. Proper evaluation and management of acute embolic versus thrombotic limb ischemia. Semin Vasc Surg. 2009;22(1):10–6.
19. Haigh KJ, Bingley J, Golledge J, Walker PJ. Barriers to screening and diagnosis of peripheral artery disease by general practitioners. Vasc Med. 2013;18(6):325–30.
20. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997;26(3):517–38.
21. Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. Semin Vasc Surg. 2009;22(1):29–33.
22. Lavanier GL, Sacks D, Robinson ML. Acute limb ischemia. Emerg Med Clin North Am. 1992;10(1):103–19.
23. Hodgkiss-Harlow KD, Bandyk DF. Interpretation of arterial duplex testing of lower-extremity arteries and interventions. Semin Vasc Surg. 2013;26(2–3):95–104.
24. Schoder M. Acute peripheral arterial ischemia: diagnosis and interventional therapy. Wien Med Wochenschr. 2001;151(21–23):541–5.
25. Zeboulon C, Amy de la Bretèque M, Bilan P, Sin C, Linder JF, Dakhil B, et al. [Phlegmasia cerulea dolens]. Ann Dermatol Venereol. 2014;141(11):682–4.
26. Ayarragaray JE. Ergotism: a change of perspective. Ann Vasc Surg. 2014;28(1):265–8.
27. Brand M, Woodiwiss AJ, Michel F, Nayler S, Veller MG, Norton GR. Large vessel adventitial vasculitis characterizes patients with critical lower limb ischemia with as compared to without human immunodeficiency virus infection. PLoS One. 2014;9(8):e106205.
28. Roca B, Roca M. The new oral anticoagulants: reasonable alternatives to warfarin. Cleve Clin J Med. 2015;82(12):847–54.
29. Saarinen Anders Albäck E, Albäck A. [Lower limb pain of arterial origin]. Duodecim. 2013;129(17):1813–9.
30. Rutherford RB. Clinical staging of acute limb ischemia as the basis for choice of revascularization method: when and how to intervene. Semin Vasc Surg. 2009;22(1):5–9.

31. Ouriel K. Endovascular techniques in the treatment of acute limb ischemia: thrombolytic agents, trials, and percutaneous mechanical thrombectomy techniques. Semin Vasc Surg. 2003;16(4):270–9.
32. Ouriel K. Randomized comparison of thrombolysis and surgery. TOPAS investigators. Thrombolysis or peripheral arterial surgery. J Vasc Interv Radiol. 1995;6(6 Pt 2 Suppl):83S.
33. Giannini D, Balbarini A. Thrombolytic therapy in peripheral arterial disease. Curr Drug Targets Cardiovasc Haematol Disord. 2004;4(3):249–58.
34. Acosta S, Kuoppala M. Update on intra-arterial thrombolysis in patients with lower limb ischemia. J Cardiovasc Surg (Torino). 2015;56(2):317–24.
35. Ouriel K. Current status of thrombolysis for peripheral arterial occlusive disease. Ann Vasc Surg. 2002;16(6):797–804.
36. Baumann F, Sharpe E, Peña C, Samuels S, Benenati JF. Technical results of vacuum-assisted thrombectomy for arterial clot removal in patients with acute limb ischemia. J Vasc Interv Radiol. 2016;27(3):330–5.
37. Costantini V, Lenti M. Treatment of acute occlusion of peripheral arteries. Thromb Res. 2002;106(6):V285–94.
38. Ouriel K. Comparison of surgical and thrombolytic treatment of peripheral arterial disease. Rev Cardiovasc Med. 2002;3 Suppl 2:S7–16.
39. Storck M, Wagner HJ. Peripheral arterial obstruction and acute lower limb ischemia. Chirurg. 2007;78(7):611–9.
40. Hu HD, Chang Q, Chen Z, Liu C, Ren YY, Cai YC, et al. Management and prognosis of acute arterial embolism: a multivariable analysis of 346 patients. Zhonghua Yi Xue Za Zhi. 2011;91(41):2923–6.
41. de Donato G, Setacci F, Galzerano G, Borrelli MP, Mascolo V, Mazzitelli G, et al. Endovascular treatment of popliteal aneurysm. J Cardiovasc Surg (Torino). 2015;56(4):587–97.
42. Blaisdell FW. The reperfusion syndrome. Microcirc Endothelium Lymphatics. 1989;5(3–5):127–41.
43. Trummer G, Brehm K, Siepe M, Heilmann C, Schlensak C, Beyersdorf F. The management of acute limb ischemia. Minerva Chir. 2010;65(3):319–28.
44. Sellei RM, Hildebrand F, Pape HC. Acute extremity compartment syndrome: current concepts in diagnostics and therapy. Unfallchirurg. 2014;117(7):633–49.
45. Percival TJ, White JM, Ricci MA. Compartment syndrome in the setting of vascular injury. Perspect Vasc Surg Endovasc Ther. 2011;23(2):119–24.
46. Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. Cardiovasc Surg. 2002;10(6):620–30.

Cerebrovascular Disease

7

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Abstract

Stroke is the acute development of a focal neurologic deficit due to ischemia or hemorrhage, persisting for a period equal or greater than 24 h. The ministroke is a focal ischemia with symptoms lasting less than 24 h and no evidence of ischemia (on imaging test). The importance of this clinical condition is the potential predictor of new neurological events in sequence. According to the literature, about 87 % of strokes are ischemic in etiology, 10 % are due to intracerebral hemorrhage, and 3 % result from subarachnoid hemorrhage. Extracranial causes of brain ischemia can be due to atherosclerosis with internal carotid artery stenosis, embolization of cardiac origin (mainly atrial fibrillation), among others. Stroke is among the major causes of mortality and disabilities in the world. Every year about 800,000 people in the United States have a new stroke episode. Atherosclerotic disease is responsible for about 90 % of cases of cerebrovascular

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disease. The carotid bulb is the site of frequent involvement by atherosclerotic plaques. On physical examination, it must be evaluated the strength and sensibility of limbs, speech, and vision. Depending on the severity of the ischemia patient may present with plegia or member weakness, associated with reduced or no sensitivity. Ultrasonography with duplex scan is the first test for the detection of extracranial carotid stenosis. The medical treatment should be indicated for all patients with extracranial carotid disease. The primary endpoint of carotid surgery is to reduce the risk of cerebral ischemia. The surgery does not improve existing sequelae of prior ischemia.

Concept

Stroke is the acute development of a focal neurologic deficit due to ischemia or hemorrhage, persisting for a period equal or greater than 24 h or until death [3].

Ischemic stroke is characterized by a focal infarction with cellular death in the brain, spinal cord, or retina; clinically characterized symptoms lasting for a period greater than 24 h; and/or ischemia signs on an imaging test. Hemorrhagic stroke is characterized by vascular rupture, followed by hemorrhage, which has an inflammatory effect and can lead to intracranial mass effect [3].

The ministroke is a focal ischemia with symptoms lasting less than 24 h and no evidence of ischemia (on imaging test). The importance of this clinical condition is the potential predictor of new neurological events in sequence [1], since approximately 30 % of these patients develop ischemic stroke within the first 5 years [2].

According to the literature, about 87 % of strokes are ischemic in etiology, 10 % are due to intracerebral hemorrhage, and 3 % result from subarachnoid hemorrhage [3].

Extracranial causes of brain ischemia can be due to atherosclerosis with internal carotid artery stenosis, embolization of cardiac origin (mainly atrial fibrillation), carotid aneurysms, carotid artery kinking, spontaneous or posttraumatic dissection of carotid artery, fibromuscular dysplasia, Takayasu arteritis and aortic arch atheroembolism, among others [3]. However, up to 40 % of cases may have no definite causes.

Adams JR et al. suggest that only about 8 % of all ischemic diseases are associated with extracranial carotid artery stenosis and about 3.5 % is secondary to its occlusion [4]. However, other authors suggest that the extracranial carotid disease may be responsible for at least 20 % of all stroke episodes [3].

The importance of setting the stroke etiology is due to the differing prognoses and different recurrence rates. The extracranial carotid stenosis is the ischemic stroke etiology which has higher recurrence rates and is removable, while those secondary to cardioembolic disease have more limited survival rates and cannot be removed [5]. Thus, in some situations, the treatment of extracranial carotid artery stenosis has an impact in preventing new stroke episodes.

Epidemiology

Stroke is among the major causes of mortality and disabilities in the world [6]. It is the third leading cause of death in the United States for decades, but in 2010 the Centers for Disease Control and Prevention announced its fall to fourth position [7, 8]. The Framingham cohort study also found that the incidence of stroke has been declining over the past 50 years [9].

The overall stroke prevalence, relative to the population as a whole in the United States, during the years 2005–2008 was approximately 3.0 %. Projections show that by 2030, an additional four million people will have had a stroke, a 24.9 % increase in prevalence comparing to 2010 [10, 11].

Every year about 800,000 people in the United States have a new stroke episode and about 185,000 are recurrent episodes [10]. Although women have a lower age-adjusted stroke incidence than men, women have a higher lifetime risk of stroke than men because of longer life expectancy [12, 13]. The risk of first-ever stroke in blacks is twice that in whites [14].

In stroke survival, patients' quality of life is worse due to severe motor and psychological sequelae. It is estimated that in the United States this disease is the leading cause of functional loss.

Approximately half of the survivors remain with hemiparesis and 25–30 % of them require assistance to perform daily activities. About 25 % of survivors become institutionalized [10].

The treatment costs of stroke were estimated at 71.55 billion dollars in 2012 and it is estimated that this spending will triplicate by 2030. Associated with this, the indirect costs totaled 33.65 billion dollars in 2012 and will increase to 56 billion in 2030 [15].

Clinical Presentation

The precise characterization of signs and symptoms is important in determining treatment and prognosis. Most patients with extracranial carotid artery stenosis are asymptomatic and are incidentally diagnosed through carotid bruit on physical examination or a routine neck imaging [3].

The carotid artery is responsible for the supply of the anterior brain circulation. The common carotid artery is divided into internal carotid artery and external carotid artery at the level of the thyroid cartilage. The external carotid artery supplies part of the face and scalp and internal carotid artery supplies the anterior portion of the brain. This is divided into anterior cerebral artery and middle cerebral artery. Once the middle cerebral artery has a larger diameter, it has a higher probability of an embolism. The middle cerebral artery supplies the parietal lobe and the central gyrus of the brain. Due to the pyramids decussation, the right cerebral hemisphere irrigated by the right carotid artery is responsible for the innervation of the left side of the body (motor and sensory) and vice versa [3].

Thus, the most common symptoms in the middle cerebral artery ischemia due to stenosis of the internal carotid artery are:

- Paresis or plegia in contralateral members to the affected hemisphere (hemiparesis or contralateral hemiplegia).
- Hypoesthesia or anesthesia in contralateral members to the affected hemisphere (hemiparestesis or contralateral hemianesthesia).
- Fleeting amaurosis characterized by sudden and transient loss (about 5 min) of all visual field of the ipsilateral eye in relation to the internal carotid artery. This symptom is usually predictor of carotid disease [16] and is often associated with the presence of unstable atherosclerotic plaques.
- Dysarthria/aphasia: because the speech center is located most commonly in the parietal lobe of the left hemisphere, ischemia on this region commit speech in varying degrees, from mild to total loss, and is generally associated with right hemiparesis, hemiparestesis, hemiplegia, or hemianesthesia.

Other symptoms alone are not characteristic of carotid disease such as seizures, vertigo, dizziness, tinnitus, migraine, headache, scotoma, paresthesia or bilateral paresis, fecal or urinary incontinence. Therefore, in these cases, patients may be regarded as asymptomatic [3].

Natural History

Atherosclerotic disease is responsible for about 90 % of cases of cerebrovascular disease. The carotid bulb is the site of frequent involvement by atherosclerotic plaques.

This atherosclerotic plaque can lead to stroke or ministroke by two mechanisms: embolization or hypoperfusion. The embolization is the most frequent. The hypoperfusion usually occurs in cases of severe and diffuse obstruction in the territory of both carotid and vertebral arteries [3].

The major predictor for the risk of a future stroke is recent neurological symptoms (as described above). The NASCET [17] and ECST [18] studies showed that the risk of stroke is higher in the first month after an initial neurological event and approach the risk of an asymptomatic patient 6 months after the event. The risk of new neurological events within 6 months in these patients reaches 25 %, that is, one in four symptomatic patients will have a new ischemia episode and this time the possibilities of death and sequel is twice bigger [3].

Moreover, patients with asymptomatic carotid stenosis have lower risk of developing a neurological event when compared to symptomatic patients. The probability of neurological events in these patients is 1–2 % per year, and is approximately 10 % at 5 years according to ACAS study [19].

The severity of stenosis in carotid artery is also associated with risk of ischemic stroke in *symptomatic* patients. After the presence of symptoms, stenosis severity is the most important predictor of recurrent ischemia [3].

In symptomatic patients with significant carotid stenosis (70–99 % obstruction), the relationship between stenosis and risk of stroke is well established. In cases of

symptomatic patients with carotid stenosis between 50 and 69 %, this benefit of carotid intervention is not so clear [3].

The presence of contralateral carotid occlusion is associated with increased risk of stroke in patients with significant carotid stenosis [3].

Other independent risk factors that can be identified on imaging studies are the ulceration on the board and/or unstable aspect of plaque with high lipid content, which favors the occurrence of bleeding inside the plaque [3].

Diagnosis

In patient assessment, the history of symptoms onset, duration and resolution of symptoms, if no longer present. It should be further evaluated the comorbidities, particularly heart disease [3].

On physical examination, it must be evaluated the strength and sensibility of limbs, speech, and vision. Depending on the severity of the ischemia patient may present with plegia or member weakness, associated with reduced or no sensitivity. It is important to investigate the presence of arrhythmic pulse (as in atrial fibrillation), once it may suggest cardioembolic causes. The discrepancy in blood pressure in the upper limbs may suggest occlusion or severe stenosis of the innominate artery or the left subclavian artery. If reduction or absence of carotid pulses is present, it may indicate proximal carotid occlusion or heart valve disease. Neck auscultation may reveal a bruit [3].

The severity of the stroke is proportional to the affected brain volume, since the higher brain loss the worse the prognosis is.

Patients with extensive global ischemia are usually brought to the emergency unconscious.

Lacunar infarcts can manifest as pure hemiparesis, pure sensory syndrome, sensory motor syndrome, ataxia, and dysarthria. But it is silent in 89 % of cases and is usually caused by intracranial atherosclerosis, and therefore not a removable cause [3].

The most common symptoms of vertebrobasilar insufficiency are vertigo and diplopia, and they rarely occur isolated.

Every patient with symptoms of stroke should be investigated with imaging to confirm the mechanism of injury (ischemic, hemorrhagic) [3].

Ultrasonography with duplex scan is the first test for the detection of extracranial carotid stenosis. This test is low cost, noninvasive, and has no radiation. The high accuracy of the test can help prevent further strokes [20].

Unstable plaque features in the duplex are hypoechoic (with high fat content) and/or heterogeneous (with irregular surface, signs of ulceration or intra-plaque hemorrhage) [3].

The stable plaque has hyperechoic content and more homogeneous appearance, more fibrous and/or calcified content. The heterogeneous aspect has been associated with increased risk of stroke. However, the lack of standardization of plaque feature takes this finding be relegated to the background in making therapeutic decisions.

The evaluation of disease in the vertebral territory is limited. Atherosclerotic disease of the vertebral arteries affects more often the ostium of these vessels in its origin

from the subclavian arteries. This region is difficult to be accessed by ultrasound due to lung apex [21]. Also, it is injured by the arterial course through the vertebral bones.

The duplex scan has not been indicated as a screening test for extracranial carotid stenosis in asymptomatic patients, as the tendency to conservative approach in this situation. However, cardiologists advocate its use to quantify the average intima-media thickness in screening atherosclerotic predictors, aimed at secondary prevention [22].

Other complementary methods are necessary when the duplex ultrasonography results are inconclusive [21].

In patients with focal and acute ischemic neurological symptoms, it is recommended to perform the magnetic resonance angiography or computed tomography angiography when the ultrasonography is inconclusive [23].

Computed tomographic angiography is not considered a method of screening. It is not mandatory in the preoperative planning of carotid endarterectomy. However, it is considered the first choice in preoperative planning for carotid angioplasty and stenting. This test is especially useful in cases of excessive calcification, as it evaluates the morphology of the supra-aortic trunks, is rapidly done, is cheaper than magnetic resonance providing high resolution, allows performing high-quality reconstructions in two and three dimensions, visualizes soft tissues, bones and vessels simultaneously, and shows vascular abnormalities such as occlusion and tortuosity. As disadvantages, it may underestimate the stenosis, use ionizing radiation, does not show the direction of blood flow, and is at risk for allergy and nephrotoxicity due to the use of iodinated contrast [3].

The digital subtraction angiography was considered the gold standard for preoperative evaluation of intra- and extracranial circulation. However, today, angiography is indicated especially in cases of severe stenosis or tortuosity in distal internal carotid artery, in which computed tomography or magnetic resonance may show artifacts [21]. Some of its complications are such as bruising at the puncture site (4 %), permanent or transient neurological deficit (2.6 %), and death (0.06 %)[24].

Magnetic resonance is seen as having high sensitivity and specificity, similar to duplex, for carotid stenoses between 70 and 99 %. However, as well as duplex, it is less sensitive and specific to 50 % to 69 % stenosis. It has the advantage of not exposing the patient to radiation. Its disadvantages are the cost, the difficulty of access, and impossibility of realization in people with claustrophobia. Technically magnetic resonance features artifacts especially in the presence of calcifications and has the possibility to overestimate the degree of stenosis [3]. However, it is considered the best noninvasive imaging method for diagnosis of carotid stenosis [20]. Care must be taken in the use of this test in patients with chronic kidney disease at risk of systemic fibrosis development by the use of magnetic gadolinium enhancer [3].

Positron emission tomography (PET scan) has no role as a preoperative evaluation routine. However, due to its capacity to measure cerebral blood flow and the oxygen extraction fraction, PET scan remains the gold standard in evaluation of hemodynamic effects of cerebrovascular disease as self regulatory failure and reduced cerebrovascular reserve [25].

When there is no suspicion of carotid disease, or it was excluded, echocardiography should be performed to search for the source of cardiogenic embolism.

Treatment

Medical Treatment

The medical treatment should be indicated for all patients with extracranial carotid disease, regardless of the degree of stenosis or presence of symptoms, in order to promote secondary prevention of atherosclerosis and reduce the risk of stroke and death [3].

It should be assessed the patient's clinical condition, its comorbidities, and life expectancy. Several medical conditions have been associated with increased risk of stroke, among them hypertension, diabetes mellitus, dyslipidemia, smoking, and alcohol consumption. The clinical control of these conditions leads to reduced risk of stroke and death. In addition, treatment with antiplatelet agents and statins reduces the risk of stroke as well as cardiovascular mortality and morbidity (Tables 7.1, 7.2, and 7.3) [3].

Table 7.1 Effect of modifying risk factors—drugs [3]

Antiplatelet agents	One or two associated drugs	Reduces risk of stroke and CV mortality
Antihypertensive agents	Reduction in systolic BP by 10 mmHg/diastolic by 5 mmHg or reduction to 120/80 mmHg in hypertensive	Reduces risk of stroke and CV mortality
Statins	Reduction of LDL by 50 % or to a value <70 mg/dL	Reduces risk of stroke and CV mortality. Even in normolipidemic patients

CV cardiovascular, *BP* blood pressure, *LDL* low density cholesterol
Adapted from: "*Caron B. Rockman TSM. Cerebrovascular Disease: General Considerations. In: Jack L. Cronenwett KWJ, editor. Rutherford's Vascular Surgery. 1. Eight ed. Philadelphia, PA 19103-2899: Elsevier Saunders; 2014. p. 1456–72*"

Table 7.2 Effect of modifying risk factors—diseases [3]

Diabetes mellitus	$HgbA_{1c} < 7$	Reduces risk of stroke and CV mortality
Atrial fibrillation	Anticoagulation	Reduces risk of stroke

HbA1c glycated hemoglobin, *CV* cardiovascular
Adapted from: "*Caron B. Rockman TSM. Cerebrovascular Disease: General Considerations. In: Jack L. Cronenwett KWJ, editor. Rutherford's Vascular Surgery. 1. Eight ed. Philadelphia, PA 19103-2899: Elsevier Saunders; 2014. p. 1456–72*"

Table 7.3 Effect of modifying risk factors—changing lifestyle habits [3]

Smoking	Total abstinence	Reduces risk of stroke and CV mortality
Alcohol	Avoid excessive consumption	There is a reported increased risk of ischemic stroke with "irregular" drinking, including heavy and binge drinking. However, moderate drinking may be associated with a decreased risk of ischemic stroke [3]

CV cardiovascular
Adapted from: "*Caron B. Rockman TSM. Cerebrovascular Disease: General Considerations. In: Jack L. Cronenwett KWJ, editor. Rutherford's Vascular Surgery. 1. Eight ed. Philadelphia, PA 19103-2899: Elsevier Saunders; 2014. p. 1456–72*"

Statins have action in lowering cholesterol levels and anti-inflammatory effect. It has been shown to reduce the risk of subsequent neurological events in symptomatic patients after carotid surgery [26–28].

The acetylsalicylic acid is the most studied antiplatelet agent. It was demonstrated its benefit in the secondary prevention of stroke. It is effective in doses of 50–1500 mg, although higher doses lead to more frequent gastrointestinal effects. It is recommended dose of 81–325 mg/day [29].

Clopidogrel is an alternative for antiplatelet therapy and was superior to aspirin in preventing cardiovascular events [30]. However, the availability and low cost of aspirin made this drug choice for most patients with atherosclerotic disease and stroke [31]. The isolated use of aspirin, the isolated use of clopidogrel (75 mg/day), or aspirin use associated with extended release dipyridamole (25 and 200 mg/twice daily) is recommended in preference the combination of aspirin with clopidogrel (level of evidence A) in patients with extracranial carotid disease, occlusive and unocclusive who have suffered stroke or ministroke [32].

Surgical Treatment

To indicate the surgical treatment one should assess the risk of cerebral ischemia, compared to the risk of the proposed intervention.

As mentioned above, the most important indicator of future risk of brain ischemia is the presence of focal neurological symptoms in the last 6 months, particularly in the first month after the event.

In symptomatic patients with carotid stenosis from 70 to 99 %, the risk of new neurological events at 6 months is about 25 %. Moreover, in patients with symptomatic carotid stenosis from 50 to 69 %, the benefit from a carotid surgery is not so evident. In these cases, other causes of neurological symptoms should be investigated, such as, for example, pistons of cardiac origin [17, 18].

In asymptomatic patients, a linear relationship between the degree of stenosis and increased risk of stroke was not found, and in these patients, the risk of a neurological event per year is 1–2 % [33, 34]. Therefore, the benefit of surgical intervention is very low, with an NNT of about 20, and should be performed in vascular services with stroke and death rates less than or equal to 3 %.

The primary endpoint of carotid surgery is to reduce the risk of cerebral ischemia. The surgery does not improve existing sequelae of prior ischemia.

Therefore, in patients with non-disabling stroke or transient ischemic cerebral symptoms with low or moderate surgical risk, you can better indicate endarterectomy in the presence of stenosis of the internal carotid artery ipsilateral greater than or equal to 70 % [17, 18].

The endarterectomy was assessed by systematic review as beneficial procedure for symptomatic patients with 50–69 % of carotid stenosis and highly beneficial to those with 70–99 % stenoses [35, 36]; however, it does not add any benefit to asymptomatic patients [37].

Surgical intervention should preferably be done in the first 2 weeks after the neurological event, unless there are contraindications. It has excellent clinical and anatomical results in long term, with a survival rate of 82 % and stroke-free survival at 5 years of 92 % [38].

The American Heart Association recommends that only vascular services with a combined risk of stroke and mortality lower than 6 % for symptomatic patients and 3 % for asymptomatic patients should conduct carotid endarterectomy [39]. It is not indicated revascularization in patients with chronic occlusion of the internal carotid artery [40].

Acute myocardial infarction is responsible for most postoperative deaths (25–50 % of deaths) [41–43].

Angioplasty and stenting can be recommended as an alternative to carotid endarterectomy for symptomatic patients with low or moderate risk of complications associated with endovascular procedure in the presence of internal carotid artery stenosis greater than 70 % and in service with advance rate of stroke and operative mortality lower than 6 % [44]. Angioplasty is considered an alternative technique to endarterectomy in patients with decompensated heart disease, changes in cervical anatomy that increase the risk of cranial nerve injury, irradiated neck, prior radical neck surgery, tracheostomy, and high carotid bifurcation (above the mandibular angle) [40].

This is due to the fact that angioplasty was considered inferior to endarterectomy when compared the incidence of stroke or death, even if it is associated with less myocardial infarction rate [45].

Age greater than or equal to 68 years is associated with stroke risk increase and death in patients undergoing carotid angioplasty [46, 47].

What Generalist Doctor Can Do for This Patient?

The nonspecialist may be responsible for the conservative treatment of asymptomatic and symptomatic patients with carotid disease. Treatment is focused on control of modifiable risk factors for atherosclerosis, with emphasis on blood pressure and glycemic control, prescription of statins and antiplatelet, and quit smoking.

When Is the Time to Refer to Specialist?

Should be referred to specialists those patients who have surgical treatment indication ou dubious situations. Symptomatic patients—stroke (in recovery and not disabling) or ministroke—with internal carotid artery stenosis greater than 70 % should be referred for specialist assessment preferably within 2 weeks after onset of symptoms. Thus, it is possible for reduction of stroke and death rates [48].

References

1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064–89.
2. Albers GW, Hart RG, Lutsep HL, Newell DW, Sacco RL. AHA Scientific Statement. Supplement to the guidelines for the management of transient ischemic attacks: a statement

from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. Stroke. 1999;30(11):2502–11.
3. Caron B, Rockman TSM. Cerebrovascular disease: general considerations. In: Jack L, Cronenwett KWJ, editors. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier; 2014. p. 1456–72.
4. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35–41.
5. Petty GW, Brown Jr RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31(5):1062–8.
6. Mukherjee D, Patil CG. Epidemiology and the global burden of stroke. World Neurosurg. 2011;76(6 Suppl):S85–90.
7. Byrnes KR, Ross CB. The current role of carotid duplex ultrasonography in the management of carotid atherosclerosis: foundations and advances. Int J Vasc Med. 2012;2012:187872.
8. Kochanek KD, Xu J, Murphy SL, Miniño AM, Kung H-C. Deaths: preliminary data for 2009. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. Natl Vital Stat Syst. 2011;59(4):1–51.
9. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. J Am Med Assoc. 2006;296(24):2939–46.
10. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–220.
11. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933–44.
12. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke. 2006;37(2):345–50.
13. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. Lancet Neurol. 2008;7(10):915–26.
14. Lung NH, Institute B. Incidence and prevalence: 2006 chart book on cardiovascular and lung diseases. Bethesda: National Heart. Lung, and Blood Institute; 2006.
15. Total expenses and percent distribution for selected conditions by source of payment [Internet]. Medical expenditure panel survey household component data. 2008. http://meps.ahrq.gov/mepsweb/data_stats/tables_compendia_hh_interactive.jsp?_SERVICE=MEPSSocket0&_PROGRAM=MEPSPGM.TC.SAS&File=HCFY2008&Table=HCFY2008%5FCNDXP%5FD&_Debug=
16. McCullough HK, Reinert CG, Hynan LS, Albiston CL, Inman MH, Boyd PI, et al. Ocular findings as predictors of carotid artery occlusive disease: is carotid imaging justified? J Vasc Surg. 2004;40(2):279–86.
17. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991;325(7):445–53.
18. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet (London, England). 1998;351(9113):1379–87.
19. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol. 2010;9(7):663–71.
20. Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. Health Technol Assess (Winchester, England). 2006;10(30):iii–iv, ix–x, 1–182.

21. Markose ARNG. Cerebrovascular disease: diagnostic evaluation. In: Jack L, Cronenwett KWJ, editors. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier; 2014. p. 1473–95.
22. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2007;147(12):854–9.
23. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Catheter Cardiovasc Interv. 2013;81(1):E76–123.
24. Kaufmann TJ, Huston 3rd J, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients. Radiology. 2007;243(3):812–9.
25. Powers WJ, Zazulia AR. The use of positron emission tomography in cerebrovascular disease. Neuroimaging Clin N Am. 2003;13(4):741–58.
26. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan 3rd A, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke. 2007;38(12):3198–204.
27. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology. 2006;105(6):1260–72; quiz 89–90.
28. Verzini F, De Rango P, Parlani G, Giordano G, Caso V, Cieri E, et al. Effects of statins on early and late results of carotid stenting. J Vasc Surg. 2011;53(1):71–9; discussion 9.
29. Johnson ES, Lanes SF, Wentworth 3rd CE, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose-response effect of aspirin on stroke. Arch Intern Med. 1999;159(11):1248–53.
30. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet (London, England). 1996;348(9038):1329–39.
31. Ricotta JJ, Ricotta JJ. Carotid artery disease: decision making including medical therapy. In: Cronenwett JL, Johnston KW, editor. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier; 2014. p. 1496–513.
32. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke. 2008;39(5):1647–52.
33. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. J Am Med Assoc. 1995;273(18):1421–8
34. Mohammed N, Anand SS. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. MRC asymptomatic carotid surgery trial (ACST) collaborative group. Lancet 2004;363:1491–502. Vasc Med (London, England). 2005;10(1):77–8.
35. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2011;(4):Cd001081.
36. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet (London, England). 2003;361(9352):107–16.

37. Guay J, Ochroch EA. Carotid endarterectomy plus medical therapy or medical therapy alone for carotid artery stenosis in symptomatic or asymptomatic patients: a meta-analysis. J Cardiothorac Vasc Anesth. 2012;26(5):835–44.
38. Jacobowitz GR, Adelman MA, Riles TS, Lamparello PJ, Imparato AM. Long-term follow-up of patients undergoing carotid endarterectomy in the presence of a contralateral occlusion. Am J Surg. 1995;170(2):165–7.
39. Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott T, et al. Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the Ad Hoc Committee, American Heart Association. Circulation. 1995;91(2):566–79.
40. Cao P, De Rango P. Carotid artery: stenting. In: Cronenwett JL, Johnston KW, editor. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier; 2014. p. 1544–67.
41. Kazmers A, Cerqueira MD, Zierler RE. The role of preoperative radionuclide left ventricular ejection fraction for risk assessment in carotid surgery. Arch Surg (Chicago, Ill : 1960). 1988;123(4):416–9.
42. Hertzer NR, Lees CD. Fatal myocardial infarction following carotid endarterectomy: three hundred thirty-five patients followed 6-11 years after operation. Ann Surg. 1981;194(2): 212–8.
43. O'Donnell Jr TF, Callow AD, Willet C, Payne D, Cleveland RJ. The impact of coronary artery disease on carotid endarterectomy. Ann Surg. 1983;198(6):705–12.
44. Brott TG, Hobson 2nd RW, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1): 11–23.
45. Liu Z-J, Fu W-G, Guo Z-Y, Shen L-G, Shi Z-Y, Li J-H. Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. Ann Vasc Surg. 2012;26(4):576–90.
46. Stingele R, Berger J, Alfke K, Eckstein H-H, Fraedrich G, Allenberg J, et al. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. Lancet Neurol. 2008;7(3):216–22.
47. Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh 3rd WC, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke. 2011;42(12):3484–90.
48. Timaran CH, Mantese VA, Malas M, Brown OW, Lal BK, Moore WS, et al. Differential outcomes of carotid stenting and endarterectomy performed exclusively by vascular surgeons in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). J Vasc Surg. 2013;57(2):303–8.

Abdominal Aortic Aneurysms

8

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Abstract

Aneurysm is a permanent focal dilatation of the blood vessel greater than 50 % of its expected normal diameter. Abdominal aortic aneurysm is the most frequent extracranial aneurysm, also defined as aortic transverse diameter greater than 3 cm. There is a risk of rupture or embolization in some aneurysms. In these cases, it is necessary to perform a prophylactic surgical repair in order to avoid severe complications, including death. If rupture or embolization occurs, surgical treatment can be made urgently. Abdominal aortic aneurysm is a major public health issue and is considered as a "silent killer." It is the third cause of sudden death, the 15th general cause of death in general population and the tenth cause of death in men older than 55 years old in the United States. It is more frequent than breast, uterus, and prostate cancers. Aneurysms have a strong association with smoking. It also shares some others risk factors for atherosclerosis like male gender, systemic hypertension, and old age but not diabetes and hypercholesterolemia. The treatment approach for abdominal aortic aneurysms is based on the natural history of the disease, balancing the risk of rupture and the risk of the

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intervention and the patient's life expectancy. Special attention should be given to patients presenting with signs and symptoms of a ruptured abdominal aortic aneurysm. This situation is a medical emergency.

Concept

Aneurysm is a permanent focal dilatation of the blood vessel greater than 50 % of its expected normal diameter. Abdominal aortic aneurysm is the most frequent extracranial aneurysm (65–80 % of the aneurysms), also defined as aortic transverse diameter greater than 3 cm [1].

Aneurysms can be classified as true or false, the latter named pseudoaneurysm. The pseudoaneurysm is a vessel wall disruption with blood extravasation to neighboring tissues that contains the blood flow forming a capsule. On the other hand, the true aneurysm is a focal dilation of all layers of the vessel wall.

Aneurysms can be fusiform or saccular. Fusiform aneurysm is a dilation of the entire vessel circumference. Saccular aneurysm is an expansion of a part of the vessel wall, like a diverticulum [2, 3].

Ectasia is an intermediate state in which the focal arterial dilation is lesser than 50 % of the normal expected vessel diameter. Arteriomegaly refers to a diffuse (not focal) vessel dilatation greater than 50 % of the normal expected diameter [4].

There is a risk of rupture or embolization in some aneurysms. In these cases, it is necessary to perform a prophylactic surgical repair in order to avoid severe complications, including death. If rupture or embolization occurs, surgical treatment can be made urgently.

Epidemiology

The prevalence of abdominal aortic aneurysms in individuals older than 65 years old is three to fourfold higher in men: estimates range between 1.7–4.5 % in men vs. 0.5–1.3 % in women. According to the Centers for Disease Control and Prevention (CDC), in 2013, 0.07 % of the deaths in women and 0.13 % of the deaths in men were attributable to ruptured abdominal aortic aneurysms [5]. Abdominal aortic aneurysm is a major public health issue and is considered as a "silent killer." It is the third cause of sudden death, the 15th general cause of death in the general population and the tenth cause of death in men older than 55 years old in the United States. It is more frequent than breast, uterus, and prostate cancers [6, 7]. Famous people like the scientist Albert Einstein in 1950s and the actress Lucille Ball in the final of 1980s died in consequence of abdominal aortic aneurysm rupture.

Aneurysms have a strong association with smoking. It also shares some other risk factors for atherosclerosis like male gender, systemic hypertension, and old age but not diabetes and hypercholesterolemia. About 1.7 % of women and 5 % of men over 65 years old have infrarenal aortic diameter greater than 3 cm and the

incidence of aortic aneurysms increases 6 % for every decade after this age [8]. Another important risk factor is family history for abdominal aortic aneurysm, increasing by 30 % the risk for the subject to develop an aneurysm [9].

Clinical Presentation

Abdominal aortic aneurysm rarely causes symptoms since it is considered the "silent killer." Most of the abdominal aortic aneurysms is detected incidentally through imaging tests for the diagnosis of other diseases, especially in men seeking urologic attention for prostatic issues and is completely asymptomatic [10].

Few patients report pulsatility in the abdomen, like a heart in the belly.

Physical examination is not very accurate to detect abdominal aortic aneurysm. However, if suspected and targeted, approximately 50 % of abdominal aortic aneurysms with diameter greater than 4 cm can be found, but its diameter is generally underestimated due to the presence of intestinal loops and factors related to the abdominal wall. Only 29 % of the abdominal aortic aneurysm with diameter lesser than 4 cm can be detected through physical examination [1, 4, 11]. On the other hand, it can be falsely suspected in thin patients with aortic pulse prominence. Abdominal aortic aneurysm in young patients tends to be larger, symptomatic, and is associated to family history [12].

The physical exam accuracy depends on the Body Mass Index (BMI). Higher BMI values are associated with false-negative results [13]. Rarely, it may cause local duodenal compression symptoms such as early satiety, nausea, and vomiting. It can also cause hydronephrosis by extrinsic ureter compression or deep venous thrombosis by extrinsic compression of iliac veins or inferior cava vein. A few patients can complain of low back pain or nonspecific abdominal pain. Acute limb ischemia can result from distal embolization by aneurysm wall thrombus fragmentation. Erosion of the vertebral body by the aneurysm wall can lead to back pain or other neurological manifestations. However, when abdominal aortic aneurysms become symptomatic, the patient typically refers recent onset of abdominal or lumbar pain, and it is probably due to acute wall expansion or rupture [1, 10].

The classical clinical triad of a ruptured abdominal aortic aneurysm is acute abdominal or lumbar pain, shock and pulsatile abdominal mass, particularly, but not exclusively, in a male patient older than 60 years old. Patients may describe the pain as radiating to the scrotum, anus, or inguinal region. Some patients report pain in the thigh due to irritation of the muscle psoas by the retroperitoneal blood. Sudden hematemesis can also occur as a result of erosion of the aneurysm to duodenum. Rarely bruising on the flank is seen [1, 10].

The mortality rate for ruptured abdominal aortic aneurysm may be greater than 90 %. About 75 % of the patients die in place, another 10 % die during hospital transportation, and those few who reach the operating room have a mortality rate higher than 50 %[14].

Table 8.1 Risk of rupture for fusiform aneurysms according to the transverse abdominal aorta diameter [1, 4, 17]

Abdominal aortic aneurysm diameter (cm)	Risk of rupture in 12 months (%)
<4.0	0
4–4.9	0.5–5
5–5.9	1–13
6–6.9	10–20
7–7.9	20–40
>8	30–50

Adapted from: *"Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: A comprehensive review. Exp Clin Cardiol. 2011;16(1):11–5."* **and** *"Belardi P, Lucertini G, De Caro G. Type I aneurysmosis: complementary index for diagnosis. Vascular. 2005;13(1):11–5."* **and** *"Zankl AR, Schumacher H, Krumsdorf U, Katus HA, Jahn L, Tiefenbacher CP. Pathology, natural history and treatment of abdominal aortic aneurysms. Clin Res Cardiol. 2007;96(3):140–51"*

The natural history of the disease is a slow but continuous increasing of the aneurysm diameter overtime and eventually rupture and death. However, not all abdominal aortic aneurysm patients will die due to aneurysm rupture, which occurs in about 50–60 %, the remaining dying from other causes, particularly due to coronary artery disease or stroke [1, 12].

Therefore, the most widespread estimation of rupture risk remains aneurysm diameter, which is taken in consideration with aneurysm morphology and aneurysm growth rate. Initial aneurysm diameter predicted subsequent surgical repair: 27 % of patients with diameter initially 4–4.4 cm underwent repair during follow-up compared with 53 % of patient with diameter of 4.5–4.9 cm and 81 % of patient with 5–5.4 cm [15]. There were a number of independent factors that affected aneurysm growth rate, most notably current smoking. The presence of diabetes reduced the growth rate [16].

There are four risk factors for aneurysm rupture [1, 4, 17]. The first and main factor is the transverse aortic diameter, which is linearly correlated to the risk of rupture for fusiform aneurysms (Table 8.1).

The second factor is the growth rate of the transverse aortic diameter. An increase of 1 cm or more in 12 months is a marker for aneurysm rupture, regardless of the previous diameter [1, 4, 17].

The third factor is the shape of the aneurysm. Saccular aneurysms have a more erratic and unpredictable behavior, with rupture not associated to its diameter. Therefore, if clinical conditions are favorable, it is an indication for intervention [1, 4, 17].

The fourth and last risk factor for rupture is the presence of symptoms. As seen above, recent onset of abdominal or lumbar pain is probably due to acute wall expansion or rupture [1, 4, 17].

Some small aneurysm rupture and some large don't. These first three "risk factors," diameter, growth rate, and morphology, are simply clinical surrogate markers for some as of yet unknown process, likely a defect of some sort in extracellular matrix or connective tissue. This fact is still poorly understood.

Image Exams

Abdominal Ultrasonography

Once physical exam has low accuracy, an image test should be indicated to confirm the presence of the abdominal aortic aneurysm. Abdominal ultrasound is cheaper, most commonly used for surveillance, well accepted by patients, does not have radiation, and is relatively accurate over serial measurements. It is also very suitable to follow up aortic diameters of initially nonsurgical patients overtime [18].

In emergency department is frequently a test of choice. An association of free abdominal fluid and large aortic diameter reveals ruptured aneurysm in many cases.

It is also useful as screening method for patients with risk factors for abdominal aortic aneurysm (see below). However, if the patient has a surgical indication for the abdominal aortic aneurysm (see below), other imaging tests should be used for a precise preoperative planning [18, 19].

Angiotomography

Angiotomography is more expensive than ultrasound and its use involves radiation exposure and intravenous hyperosmolar contrast medium injection that can lead to allergic reactions and nefrotoxicity. However, this method offers more accurate measurements possibilities. Thus, it is the method of choice in preoperative planning for abdominal aortic aneurysms repair [19].

Magnetic Resonance Imaging

This method is distinguished by the absence of ionizing radiation. However, the high cost, the difficulty of analyzing calcified plaques, the low resolution when compared to angiotomography, the complexity of standardization, and intolerance in claustrophobic patients are limiting factors. Magnetic resonance imaging has its use established in patients allergic to iodine medium contrast.

Historically, the use of this technique in patients with chronic renal failure and contraindication to use of iodine contrast medium has been observed. However, recent studies have shown an increased risk of fatal nephrogenic sclerosing fibrosis in patients with chronic renal failure after intravenous injection of gadolinium. It is a second-line method in the preoperative planning for abdominal aortic aneurysms surgical repair [19].

Screening Program

As previously seen, abdominal aortic aneurysms are mostly asymptomatic. However, its first symptom can be rupture. The mortality rate after abdominal aortic aneurysm rupture may be greater than 90 %. Once the mortality rate for the elective repair is around 5 %, it is advisable to actively screen for patients with

asymptomatic abdominal aortic aneurysm in order to avoid death [20, 21]. Screening with abdominal ultrasound an asymptomatic and selected group of patients was able to reduce the overall mortality and aneurysm-related mortality in several studies. The recommendations of the U.S. Preventive Services Task Force are summarized below:

- 65–75 years old smoker men—Screening with ultrasonography
- 65–75 years old non-smoker men—Selectively screening rather than routinely screening all men in this group
- 65–75 years old smoker women—Current evidence is insufficient to assess the balance of benefits and harms of screening
- 65–75 year old non-smoker women—Recommends against routine screening [20, 21]

Treatment

The treatment approach for abdominal aortic aneurysms is based on the natural history of the disease, balancing the risk of rupture and the risk of the intervention and the patient's life expectancy [1, 4, 17].

As shown above, the risk of rupture is related to aortic diameter in fusiform aneurysms, the presence of saccular aneurysm, increase of aneurysm diameter >1 cm in 12 months, or the presence of recent symptoms, particularly abdominal or lumbar pain [1, 4, 17].

On the other hand, the risk of the intervention is associated with the presence of comorbidities such as symptomatic coronary artery disease, heart failure, renal failure, chronic obstructive pulmonary disease, and old age [1, 4, 17].

The method of interventional treatment also is related to postoperative mortality. Open repair for abdominal aortic aneurysm is performed under general anesthesia and through a large midline or retroperitoneal incision. After clamping the infrarenal aorta and iliac arteries to achieve hemostasis, the surgeon opens the aneurysm sac, removing thrombus and debris from within the aorta, suturing a graft into the aorta proximally and distally at the iliac or femoral vessels, whichever is deemed appropriate. Short-term mortality for elective series ranges from 1 to 5 % [22]. Perioperative complications related to the procedure include lower extremity ischemia, bowel ischemia, pelvic ischemia, renal dysfunction, and late complications include incisional hernia, anastomotic aneurysm, graft infection, and aortoenteric fistulae. Late complications were indentified in 9.5 % of patients [23].

Endovascular surgery is performed by inserting graft components folded and compressed within a delivery sheath through the lumen of an access vessel, usually the common femoral artery. Upon deployment, the endograft expands, attaching to the aorta wall and excluding the aneurysm. Endovascular repair is associated with lower perioperative morbidity and mortality compared with open surgical repair. The short-term mortality is 1.6 %. Endograft-related complications are common and occur in 11–30 % of the cases [24]. Technical complications include vascular injury, endoleak, breakdown, fracture, or endograft collapse. Endoleak is defined as

Table 8.2 Comparative early mortality in EVAR versus open abdominal aortic repair [24, 26, 27]

	EVAR (%)	Open repair (%)
EVAR trial	1.8	4.3
DREAM trial	1.2	4.6
OVER trial	0.5	3.0

Adapted from: "*Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607–18.*" **and** *"Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863–71."* **and** *"Lederle FA, Freischlag JA, Kyriakides TC, Padberg FT, Jr., Matsumura JS, Kohler TR, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA. 2009;302(14):1535–42"*

Table 8.3 Indications for abdominal aortic aneurysms surgical approach [1, 4, 17, 28]

Transverse diameter greater than 5.0–5.5 cm for fusiform abdominal aortic aneurysm
Greater aortic expansion rate (>1 cm/year) for fusiform abdominal aortic aneurysm
Transverse diameter greater than 4.5 cm for saccular abdominal aortic aneurysms
Characteristic abdominal pain or rupture signs in any diameter
Distal embolization (mural thrombus)

Adapted from: *"Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: A comprehensive review. Exp Clin Cardiol. 2011;16(1):11–5."* **and** *"Belardi P, Lucertini G, De Caro G. Type I aneurysmosis: complementary index for diagnosis. Vascular. 2005;13(1):11–5."* **and** *"Zankl AR, Schumacher H, Krumsdorf U, Katus HA, Jahn L, Tiefenbacher CP. Pathology, natural history and treatment of abdominal aortic aneurysms. Clin Res Cardiol. 2007;96(3):140–51"* **and** *"Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1–s58"*

persistent flow blood into the aneurysm sac after the device placement and indicates failure to completely exclude the aneurysm. This complication is the most prevalent, occurring with all device types in an incidence of 10–45 % [25] (Table 8.2).

Therefore, intervention should be indicated when the risk of rupture is higher than the risk of the intervention and that the patient has a life expectation >1 year [28]. Indications for surgical abdominal aortic aneurysms repair are summarized in Table 8.3.

Special attention should be given to patients presenting with signs and symptoms of a ruptured abdominal aortic aneurysm. This situation is a medical emergency. These patients should receive advanced life support, airway protection, but moderate intravascular volume replacement (hypotensive protection) and should be referred and safely transported to the closest vascular unit [1, 4, 17, 28].

Medical Approach

Smoking Cessation

About 18–52 % of patients with aneurysms are smokers. Smoking cessation can improve lung function and benefit postoperative outcomes and reduce short- and long-term cardiovascular events [29].

Exercise

There is evidence suggesting that exercise may be beneficial in patients with small aneurysms [30].

Pharmacotherapy

The majority of the recognized aneurysms is small (<4 cm) and does not need surgical intervention. Pharmacological treatment is aimed at reducing cardiovascular associated risk and aortic expansion rate. Although historical series have shown reduction in the aortic expansion rate, large meta-analyses studies have not been able to confirm these results. Based on smaller studies, beta-blockers and statins are most suitable for this purpose [15].

Doxycycline and Roxithromycin

Doxycycline and roxithromycin antibiotics have demonstrated aortic expansion rate reduction in small prospective randomized trials. The mechanism of action may be to inhibit metalloproteinases, not as an antibiotic. The low side effects incidence has encouraged its use in patients with small aneurysms and large aneurysms with high operative risk for surgery [31].

Beta-Blockers

Recent evidence has discredited previous work on beta-blockers in terms of growth and they are quite in favor now. The use is associated with a significant reduction in perioperative and long-term mortality. It is recommended long-term use, preferably over 30 days before the surgery. The target heart rate should be between 60 and 70 beats per minute [32].

Antiplatelet Therapy

Antiplatelet therapy also demonstrated reduced mortality and frequency of cardiovascular events of any kind [33].

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be used for blood pressure control and improve cardiac function. These medicines are able to reduce cardiovascular mortality and morbidity [34].

What the Generalist Practioner Can Do for This Patient?

Screening with abdominal ultrasound should be performed in 65–75 years old smoker men. Most of the recognized abdominal aortic aneurysms are small and do not need surgical intervention. So the patient must be informed about the condition and the need for surveillance, avoiding panic due to misinformation.

Comorbidities and risk factors such as systemic hypertension, smoking, coronary artery disease, heart failure, renal failure, and chronic obstructive pulmonary disease should be approached properly.

Use of antiplatelet drugs, statins, and beta-blockers has been shown to reduce cardiovascular events. If the patient have systemic hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and/or beta-blockers should be preferred.

Patients should be advised to practicing supervised physical exercises if there is no contraindication.

When to Refer to Vascular Surgery?

Basically, small aneurysms should be treated conservatively with surveillance at regular periods of 6–12 months with ultrasound or other image exam. However, it is advisable to refer to a vascular unit just for knowledge.

Electively, the patient should be referred to a vascular unit in cases of transverse diameter greater than 5.0–5.5 cm for fusiform abdominal aortic aneurysm, aortic expansion rate >1 cm/year for fusiform abdominal aortic aneurysm, or saccular abdominal aortic aneurysms regardless of the diameter.

Urgently the patient should be referred to a vascular unit in cases of recent symptoms of abdominal or lumbar pain (excluding other possible causes) and distal embolization.

References

1. Aggarwal S, Qamar A, Sharma V, Sharma A. Abdominal aortic aneurysm: a comprehensive review. Exp Clin Cardiol. 2011;16(1):11–5.
2. Batt M, Haudebourg P, Planchard PF, Ferrari E, Hassen-Khodja R, Bouillanne PJ. Penetrating atherosclerotic ulcers of the infrarenal aorta: life-threatening lesions. Eur J Vasc Endovasc Surg. 2005;29(1):35–42.
3. Eggebrecht H, Plicht B, Kahlert P, Erbel R. Intramural hematoma and penetrating ulcers: indications to endovascular treatment. Eur J Vasc Endovasc Surg. 2009;38(6):659–65.
4. Belardi P, Lucertini G, De Caro G. Type I aneurysmosis: complementary index for diagnosis. Vascular. 2005;13(1):11–5.
5. Lo RC, Schermerhorn ML. Abdominal aortic aneurysms in women. J Vasc Surg. 2016;63(3):839–44.
6. WISQARS Leading Causes of Death Reports. 2016. http://webappa.cdc.gov/sasweb/ncipc/leadcaus10.html.
7. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
8. Scott RA, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. Br J Surg. 1991;78(9):1122–5.
9. Frydman G, Walker PJ, Summers K, West M, Xu D, Lightfoot T, et al. The value of screening in siblings of patients with abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2003;26(4):396–400.
10. Metcalfe D, Holt PJ, Thompson MM. The management of abdominal aortic aneurysms. BMJ. 2011;342:d1384.
11. Lederle FA, Walker JM, Reinke DB. Selective screening for abdominal aortic aneurysms with physical examination and ultrasound. Arch Intern Med. 1988;148(8):1753–6.

12. Muluk SC, Gertler JP, Brewster DC, Cambria RP, LaMuraglia GM, Moncure AC, et al. Presentation and patterns of aortic aneurysms in young patients. J Vasc Surg. 1994;20(6):880–6; discussion 7–8.
13. Venkatasubramaniam AK, Mehta T, Chetter IC, Bryce J, Renwick P, Johnson B, et al. The value of abdominal examination in the diagnosis of abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2004;27(1):56–60.
14. Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, Acher CW, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med. 2002;346(19):1437–44.
15. Sweeting MJ, Thompson SG, Brown LC, Powell JT. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. Br J Surg. 2012;99(5):655–65.
16. Thompson SG, Ashton HA, Gao L, Buxton MJ, Scott RA. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. Br J Surg. 2012;99(12):1649–56.
17. Zankl AR, Schumacher H, Krumsdorf U, Katus HA, Jahn L, Tiefenbacher CP. Pathology, natural history and treatment of abdominal aortic aneurysms. Clin Res Cardiol. 2007;96(3):140–51.
18. Jaakkola P, Hippelainen M, Farin P, Rytkonen H, Kainulainen S, Partanen K. Interobserver variability in measuring the dimensions of the abdominal aorta: comparison of ultrasound and computed tomography. Eur J Vasc Endovasc Surg. 1996;12(2):230–7.
19. Pavone P, Di Cesare E, Di Renzi P, Marsili L, Ventura M, Spartera C, et al. Abdominal aortic aneurysm evaluation: comparison of US, CT, MRI, and angiography. Magn Reson Imaging. 1990;8(3):199–204.
20. Guirguis-Blake JM, Beil TL, Senger CA, Whitlock EP. Ultrasonography screening for abdominal aortic aneurysms: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med. 2014;160(5):321–9.
21. Final update summary: abdominal aortic aneurysm: screening—US Preventive Services Task Force. 2016.
22. Sarac TP, Bannazadeh M, Rowan AF, Bena J, Srivastava S, Eagleton M, et al. Comparative predictors of mortality for endovascular and open repair of ruptured infrarenal abdominal aortic aneurysms. Ann Vasc Surg. 2011;25(4):461–8.
23. Kadakol AK, Nypaver TJ, Lin JC, Weaver MR, Karam JL, Reddy DJ, et al. Frequency, risk factors, and management of perigraft seroma after open abdominal aortic aneurysm repair. J Vasc Surg. 2011;54(3):637–43.
24. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351(16):1607–18.
25. Veith FJ, Baum RA, Ohki T, Amor M, Adiseshiah M, Blankensteijn JD, et al. Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. J Vasc Surg. 2002;35(5):1029–35.
26. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362(20):1863–71.
27. Lederle FA, Freischlag JA, Kyriakides TC, Padberg Jr FT, Matsumura JS, Kohler TR, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA. 2009;302(14):1535–42.
28. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1–58.
29. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. J Vasc Surg. 2003;38(2):329–34.
30. Tew GA, Moss J, Crank H, Mitchell PA, Nawaz S. Endurance exercise training in patients with small abdominal aortic aneurysm: a randomized controlled pilot study. Arch Phys Med Rehabil. 2012;93(12):2148–53.

31. Mosorin M, Juvonen J, Biancari F, Satta J, Surcel HM, Leinonen M, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. J Vasc Surg. 2001;34(4):606–10.
32. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J Vasc Surg. 2005;41(4):602–9.
33. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849–60.
34. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. Lancet. 2006;368(9536):659–65.

Peripheral and Visceral Aneurysm

9

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Abstract

Peripheral arterial aneurysms are abnormal dilations of the peripheral arteries caused by weakening of the arterial wall, usually caused by atherosclerosis, trauma, infection, or poststenotic abnormalities. By definition, the "peripheral artery aneurysm" excludes aortic, aorto-iliac, cerebral, and coronary vessels. The exact pathogenic mechanism of aneurysm formation is as yet still unknown. Conventional risk factors, including environmental and genetic factors, may be influenced by mechanical or hemodynamic factors, (including poststenotic flow changes) with gradual expansion over time and increasing risk of rupture or thrombosis, distal embolization, and local compression symptoms. The most common peripheral arterial aneurysm is the popliteal artery aneurysm, and the main complication is thrombosis. Visceral arterial aneurysms are abnormal dilations of the visceral arteries caused by weakening of the arterial wall, usually caused by atherosclerosis, trauma, infection, or poststenotic abnormalities. The most common visceral arterial aneurysm is splenic arterial aneurysm, and the

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main complication is rupture. Greater caution is needed in patients with visceral aneurysms, especially in pregnant women. Expert opinion in a timely manner is desirable in these circumstances.

This chapter is dedicated to peripheral and visceral aneurysms. Peripheral arteries aneurysms have thrombosis and visceral arterial aneurysm have rupture as main complication.

Femoral Artery Aneurysms

The diameter of the common femoral artery increases with age during growth and also in adults; it is related to age, body size, and sex, with diameter larger in males than females. The incidence of true aneurysms of the femoral artery is low, and femoral artery aneurysms are usually associated with other aortic or peripheral aneurysms. Pseudoaneurysms or false aneurysms of the femoral artery are more common, perhaps due to the increasing number of percutaneous diagnostic and therapeutic vascular interventions being performed. Increasing number of femoral pseudoaneurysms is also due to injection by drug abusers, frequently associated with infection [1]. True and false aneurysms of the femoral artery may result in thrombosis, rupture, and embolization. Femoral artery aneurysm may be confined to the common femoral artery in 80 % or may involve the proximal superficial femoral artery in 15 % or profunda femoral artery in 5 % [2, 3]. Femoral arterial aneurysm is 20 fold more common in men than women. It is estimated that up to 60 % of patients with femoral aneurysms have associated distal occlusive disease. Femoral artery aneurysm main risk factor is smoking, and the main complication is thrombosis. Most of the patients are asymptomatic, and they may have acute ischemia in the affected limb as initial symptom. They are usually associated with popliteal artery aneurysms. Diagnosis is suspected when there is increased femoral pulses amplitude, and it can be confirmed with vascular Doppler ultrasound. Surgery is indicated when greater than 2 cm or intraluminal thrombus presence [3]. Despite rapid improvement in endovascular technology, the common femoral artery still presents major challenges for stent graft exclusion. Its short length, the need for sealing zones, its close proximity to the inguinal ligament during hip flexion, repetitive stent compression and bending with normal movement, and the need to preserve flow to the superficial femoral artery and profunda femoral artery are important considerations. Open surgery with interposition of graft or vein of bypass surgery is commonly indicated [3, 4]. There is a limited literature-based evidence to use thrombin injection to treat post-puncture pseudoaneurysms. Usual approaches consist of compression (blind or ultrasound-guided) as first-line treatment. When the compression technique fails, thrombin can be used [5]. It is feasibly endovascular treatment of true superficial artery aneurysm, but the open surgery is commonly indicated. Rupture of profunda femoral artery aneurysm is more frequently then thrombosis. There is no evidence for endovascular intervention in profunda femoral

artery aneurysm and stenting at this time, but this may be safely performed in the appropriate anatomical setting. In some cases, revascularization is recommended, but only arterial ligation can be performed [3].

Popliteal Artery Aneurysm

The most commonly occurring aneurysms in the periphery are those involving the popliteal artery. They comprise up to 85 % of all such aneurysms, occur almost exclusively in men, and are diagnosed at an average age of 65 years. The popliteal artery is said to be aneurysmal when its diameter is greater than 2 cm. These aneurysms are frequently bilateral (53 %) and are associated with abdominal aortic aneurysms 40–50 % of the time. In the past, only 1–2 % of patients with abdominal aortic aneurysms were found to harbor popliteal aneurysms. However, the incidence reported in contemporary series based on routine ultrasound scanning is higher (14 %) [6, 7]. Between 50 to 75 % of patients found to have popliteal artery aneurysms are symptomatic on presentation. Diagnosis is suspected when there is increased popliteal pulses amplitude, and it is confirmed with vascular Doppler ultrasound. It presents surgical indication when larger than 2 cm or intraluminal thrombus presence [6]. The most common acute symptoms include lower extremity ischemia (claudication or rest pain) caused by thrombosis of the aneurysm or distal embolization of intra-aneurysmal thrombus. Alternatively, chronic symptoms can develop when aneurysms thrombose or embolize in the presence of adequate collateral vessels. Compression of adjacent structures such as nerves and veins can cause leg pain and calf swelling, respectively. Uncommonly, popliteal artery aneurysms rupture leading to a limb-threatening circumstance and an amputation rate approaching 50–70 %. If the patient is young and active, early bypass graft using vein is recommended. Endovascular surgery may offer better results for the patients with severe clinical status [8]. Medium term benefits of endovascular and open surgery are similar for the treatment of popliteal arterial aneurysm. However, short-term complications like thrombosis are significantly greater in the endovascular surgery. The comparison between endovascular and open surgery is currently controversial, and the unknown long-term results [9].

Subclavian Artery Aneurysm

Subclavian aneurysm is related with repetitive trauma in the region especially in cases of shoulder girdle vascular compression syndromes (thoracic outlet syndrome). There are three forms of thoracic outlet syndrome depending on the predominating compression of the brachial plexus roots, the subclavian vein or the artery, with neurogenic the most frequent clinical expression. Despite the fact that arterial thoracic outlet syndrome is the least frequent 1–5 % of all cases, it is most severe due to damage to the arterial wall by repetitive local trauma leading to a stenosis and/or poststenotic aneurysmatic dilation, eventually causing distal embolization and limb-threatening secondary ischemia. Aneurismatic dilatation is seems

in 36 % of arterial thoracic outlet syndrome [10]. Diagnosis can be confirmed with Doppler vascular ultrasound. In some cases, it may be necessary to conduct computerized angiotomography or magnetic ressonance image [11]. Subclavian artery aneurysm should be treated when encountered; there is no size criterion, but the majority are large or symptomatic at diagnosis. It can be well treated with both open and endovascular technique in the elective situation, but mortality is high in emergency situations. The durability of endovascular techniques is as yet unproven, and there are no data to support its preferential use. Open surgery with exposure of the proximal subclavian artery aneurysm is associated with increased morbidity and mortality, but open surgery remains the only method with proven durability and, should, therefore, be the treatment of choice in the majority of patients [3].

Visceral Artery Aneurysms

Splenic Artery Aneurysms

Splenic artery aneurysms are the second most common in the abdominal cavity excluding aorto-iliac aneurysms and they respond for 60 % of visceral aneurysms. The typical age presentation is between 60 to 70 years old. It has a 4:1 female:male predominance and is frequently encountered in women with multiple pregnancies. Hormonal changes during pregnancy may be associated with structural weakening and increased arterial wall stress. A similar underlying pathophysiology is thought to be involved in the formation of splenic artery aneurysms in patients with portal hypertension. Although splenic artery aneurysm is four times more common in women, splenic artery aneurysm is approximately three times more likely to rupture in men [3]. Splenic pseudoaneurysms have a slight male predominance, probably related to pancreatitis and pancreatic pseudocyst [12]. True aneurysms of the splenic artery are usually smaller than 3 cm at diagnosis and calcification, and mural thrombus may frequently occur. However, calcification does not appear to protect against rupture and recent clinical studies suggest that the risk of rupture is low, perhaps close to 2–3 %. Rupture risk is increased with liver transplantation, portal hypertension, and pregnancy, with a high mortality to both mother and fetus [3]. There is no firm consensus on the aneurysm size for intervention in asymptomatic patients, but there is general agreement that aneurysms greater than 2.0 cm in good-risk patients should be repaired [13]. An endovascular first approach is recommended, especially in patients with pseudoaneurysms. Open surgical intervention is still the treatment of choice in cases of aneurysm rupture and hemodynamic instability, and those with unfavorable anatomy for the endovascular option [3].

Hepatic Artery Aneurysm

The true incidence of hepatic artery aneurysm is unknown, but, excluding traumatic aneurysms, patients most commonly present during their sixth decade of life and men are more frequently affected. It is thought to account for 20 % of all visceral

arteria aneurysm. Hepatic artery aneurysms are associated with atherosclerosis (32 %), acquired medial degeneration (24 %), trauma (22 %), and mycotic causes (10 %). Polyarteritis nodosa, cystic medial necrosis, and other arteriopathies have also been incriminated in the origin of these lesions. These aneurysms are typically fusiform when less than 2 cm and saccular when greater than 2 cm in diameter. Treatment is indicated for hepatic [14] arterial aneurysm at around 2.0 cm. Symptoms are unusual but, if present, characteristically include right upper quadrant and epigastric pain and biliary tract obstruction. The physical finding of pulsatile mass or abdominal bruit is not common. Abdominal pain and jaundice may occur. Hemobilia, and hematemesis may be seen, likely due to aneurysm leakage into the biliary tree. The frequency of hepatic arterial aneurysm rupture is less than 20 %, and the mortality rate occurring with rupture approximates 35 % [3, 15]. Conventional surgical intervention is still the treatment of choice in cases of aneurysm rupture and hemodynamic instability in patients with inadequate collateral circulation and anatomy unsuitable for an endovascular option. In general, the endovascular option is considered, if technically possible in a patient with appropriate anatomy and available equipment and expertise, with no contraindication to the contrast medium, and with acceptable risk of end organ ischemia [3].

Superior Mesenteric Artery Aneurysms

Superior mesenteric artery aneurysm account for 5.5 % of all visceral artery aneurysm. It affects men and women in equal proportion. They mostly occur in the proximal segment of the vessel, usually within the first 5 cm of the origin. Mycotic aneurysms have been reported to account for between one-third and two-thirds of all cases although other aetiologies such as inflammation, vasculitis, trauma, arterial dissection, fibromuscular dysplasia, and atherosclerosis have been reported. They are most often symptomatic, with abdominal pain and discomfort. A pulsatile abdominal mass can be mobilized in thin patients. Approximately half of symptomatic patients proceed to aneurysm rupture [3, 16]. These aneurysms should be operated due to high risk of thrombosis or rupture. Surgical options depend on the mode of presentation, elective or emergency, and include aneurysmectomy, aneurysmorrhaphy, and simple ligation, with or without arterial reconstruction. Need for reconstruction is dependent on the adequacy of the collateral circulation. There is limited published endovascular experience and few large case series, but procedures utilizing coil embolization, stent graft placement, flow diverting stents, and embolizing agents have all been reported [3, 17].

Celiac Artery Aneurysms

Celiac artery aneurysms are uncommon and account for 4 % of all visceral artery aneurysms; however, they are frequently associated with aortic aneurysms in 20 % of cases and with other visceral arterial aneurysm in 40 %, and also share similar

pathology. Most celiac aneurysms present during the fifth decade of life and are seen equally in males and females. Recent studies have indicated a rupture risk of 13 % with mortality rates approaching 100 % when rupture does occur, but there is clear correlation between aneurysm size, rate of growth, and tendency to rupture. The celiac artery aneurysm management may include aneurysm resection with primary reanastomosis, aneurysmorrhaphy, or ligation, with or without arterial reconstruction [3, 18].

Endovascular therapy is more likely to involve a complete occlusion of the vessel. This can be achieved by means of coils or occlusion plugs, or by distal celiac or branch vessel occlusion in association with aortic origin occlusion, but adequate and well-developed collateral circulation. The small number of published cases limits the data, but complications of celiac artery occlusion include hepatic ischemia, gangrenous cholecystitis, enteric ulceration, and hepatic cirrhosis [19].

Renal Arteries Aneurysm

The true incidence of renal arteries aneurysm is not clearly known. Almost totally are incidental finding during imaging exams. The incidence of 0.03–0.09 % in autopsy series can be underestimated. Today, using imaging series, an estimated incidence of 0.3–1 % is acceptable. Renal arterial aneurysms are bilateral in 10 % of cases [20]. Renal arterial aneurysm typically present in the sixth decade. Some authors suggest that males present up to a decade later in life than females. Women are more commonly afflicted with Renal Arteries Aneurysm, likely due to the high incidence of associated fibromuscular dysplasia. A minority of patients will present with symptoms, and clinical exam may reveal hypertension. Computed tomography is the most common contemporary diagnostic modality, followed by magnetic resonance imaging, ultrasonography, and catheter-based arteriography [21]. The current recommendation to repair all asymptomatic renal arterial aneurysms >2 cm in diameter has led to an increase in renal arterial aneurysm procedures, but there remains significant controversy surrounding these treatment criteria [22]. The natural history of Renal Arteries Aneurysm is that of slow to null growth. While historic series describe rupture rates as high as 14–30 % with associated mortality of 80 %, this is not supported by contemporary data [21]. The most recent and largest multi-institutional series of nonoperative renal artery aneurysm found successful surveillance of 88 aneurysms measuring 2–3 cm and seven aneurysms measuring >3 cm without complication or rupture during a mean of 49 months [23]. Other indications are female gender within childbearing age, symptoms like pain, hematuria, medically refractory systemic hypertension with important renal artery stenosis, thromboembolic event, dissection, and rupture [21]. Contemporary rupture rates are estimated at 3–5 % with nongestational mortality <10 % [21]. Gestational ruptures typically occur in the third trimester with only a few case reports of rupture postdelivery. Rupture during pregnancy has been described in aneurysms as small as 1 cm. Historic reports imply dismal consequences (56–92 % maternal mortality and 82–100 % fetal mortality) [24]. Contemporary outcomes for both mother and fetus may be improving, as

there are anecdotal reports of gestational rupture resulting in both maternal and fetal survival [21]. Conventional open surgery offers low morbidity, negligible mortality, and durable patency. The young age of many patients and excellent projected long-term survival (up to 91 % in 10 years) reinforces the importance of performing a technically sound procedure [25]. Traditional endovascular therapies have utilized coil embolization for distal and parenchymal aneurysms and stent graft exclusion for main renal artery lesions. Comparisons of open surgical and endovascular procedures have reported no significant difference in mortality, perioperative morbidity, freedom from reintervention, decline in renal function, or length of stay [22, 23].

What the General Practitioner Can Do for This Patient?

Most patients with peripheral and visceral arterial aneurysm are asymptomatic, and they do not have surgical indication when incidentally diagnosed. Thus, it must be done strict comorbidities control. For cardiovascular risk reduction, the patient should receive acetylsalicylic acid, statins, and beta blockers. In case of hypertension, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are better indicated. The same should be done for patients with peripheral aneurysms without surgical indication. Careful vascular clinical examination should be made in all elderly male smoker patients. If increased femoral or popliteal pulse amplitude or pulsatile abdominal mass is found in clinical examination, a vascular ultrasound with Doppler should be indicated. Greater caution is needed in patients with visceral aneurysms, especially in pregnant women. Expert opinion in a timely manner is desirable in these circumstances.

When to Refer to the Expert?

In the common femoral and popliteal artery aneurysms greater than 2 cm, in subclavian artery greater than 1.5 cm, or when there is intraluminal thrombus presence on any peripheral aneurysm. Patients with lower limb ischemia and pregnant women with visceral aneurysms should also be referred to the expert.

References

1. Corriere MA, Guzman RJ. True and false aneurysms of the femoral artery. Semin Vasc Surg. 2005;18(4):216–23.
2. Piffaretti G, Mariscalco G, Tozzi M, Rivolta N, Annoni M, Castelli P. Twenty-year experience of femoral artery aneurysms. J Vasc Surg. 2011;53(5):1230–6.
3. Posner SR, Wilensky J, Dimick J, Henke PK. A true aneurysm of the profunda femoris artery: a case report and review of the English language literature. Ann Vasc Surg. 2004;18(6):740–6.
4. Morrissey NJ. Endovascular treatment of peripheral arterial aneurysms. Mt Sinai J Med. 2004;71(1):1–3.

5. Tisi PV, Callam MJ. Treatment for femoral pseudoaneurysms. Cochrane Database Syst Rev. 2013;11:CD004981.
6. Wain RA, Hines G. A contemporary review of popliteal artery aneurysms. Cardiol Rev. 2007;15(2):102–7.
7. Diwan A, Sarkar R, Stanley JC, Zelenock GB, Wakefield TW. Incidence of femoral and popliteal artery aneurysms in patients with abdominal aortic aneurysms. J Vasc Surg. 2000;31(5):863–9.
8. Dawson J, Fitridge R. Update on aneurysm disease: current insights and controversies: peripheral aneurysms: when to intervene—is rupture really a danger? Prog Cardiovasc Dis. 2013;56(1):26–35.
9. Lovegrove RE, Javid M, Magee TR, Galland RB. Endovascular and open approaches to non-thrombosed popliteal aneurysm repair: a meta-analysis. Eur J Vasc Endovasc Surg. 2008;36(1):96–100.
10. Marine L, Valdes F, Mertens R, Kramer A, Bergoeing M, Urbina J. Arterial thoracic outlet syndrome: a 32-year experience. Ann Vasc Surg. 2013;27(8):1007–13.
11. Sanders RJ, Hammond SL, Rao NM. Diagnosis of thoracic outlet syndrome. J Vasc Surg. 2007;46(3):601–4.
12. Woods MS, Traverso LW, Kozarek RA, Brandabur J, Hauptmann E. Successful treatment of bleeding pseudoaneurysms of chronic pancreatitis. Pancreas. 1995;10(1):22–30.
13. Abbas MA, Stone WM, Fowl RJ, Gloviczki P, Oldenburg WA, Pairolero PC, et al. Splenic artery aneurysms: two decades experience at Mayo clinic. Ann Vasc Surg. 2002;16(4):442–9.
14. Arneson MA, Smith RS. Ruptured hepatic artery aneurysm: case report and review of literature. Ann Vasc Surg. 2005;19(4):540–5.
15. Grego FG, Lepidi S, Ragazzi R, Iurilli V, Stramana R, Deriu GP. Visceral artery aneurysms: a single center experience. Cardiovasc Surg. 2003;11(1):19–25.
16. Messina LM, Shanley CJ. Visceral artery aneurysms. Surg Clin North Am. 1997;77(2):425–42.
17. Stone WM, Abbas M, Cherry KJ, Fowl RJ, Gloviczki P. Superior mesenteric artery aneurysms: is presence an indication for intervention? J Vasc Surg. 2002;36(2):234–7; discussion 7.
18. Stone WM, Abbas MA, Gloviczki P, Fowl RJ, Cherry KJ. Celiac arterial aneurysms: a critical reappraisal of a rare entity. Arch Surg. 2002;137(6):670–4.
19. Leon Jr LR, Mills Sr JL, Jordan W, Morasch MM, Kovacs M, Becker GJ, et al. The risks of celiac artery coverage during endoluminal repair of thoracic and thoracoabdominal aortic aneurysms. Vasc Endovascular Surg. 2009;43(1):51–60.
20. Orion KC, Abularrage CJ. Renal artery aneurysms: movement toward endovascular repair. Semin Vasc Surg. 2013;26(4):226–32.
21. Coleman DM, Stanley JC. Renal artery aneurysms. J Vasc Surg. 2015;62(3):779–85.
22. Tsilimparis N, Reeves JG, Dayama A, Perez SD, Debus ES, Ricotta II JJ. Endovascular vs open repair of renal artery aneurysms: outcomes of repair and long-term renal function. J Am Coll Surg. 2013;217(2):263–9.
23. Klausner JQ, Lawrence PF, Harlander-Locke MP, Coleman DM, Stanley JC, Fujimura N. The contemporary management of renal artery aneurysms. J Vasc Surg. 2015;61(4):978–84.
24. Cohen JR, Shamash FS. Ruptured renal artery aneurysms during pregnancy. J Vasc Surg. 1987;6(1):51–9.
25. English WP, Pearce JD, Craven TE, Wilson DB, Edwards MS, Ayerdi J, et al. Surgical management of renal artery aneurysms. J Vasc Surg. 2004;40(1):53–60.

Thoracic, Thoracoabdominal, and Iliac Artery Aneurysms

10

Guilherme de Castro Santos, Raquel Ferreira Nogueira, and Carolina Ribeiro dos Santos

Abstract

The estimated incidence of thoracic aortic aneurysms is approximately 6/100,000 person-years, the risk of rupture for large aneurysms is up to 74 % in patients without repair, and 90 % of patients do not survive rupture. Most of them are asymptomatic and the risk factors are the same related to abdominal aortic aneurysm. The majority of the patients are asymptomatic. They manifest themselves clinically with chest pain and can cause compressive symptoms when too large. The treatment approach for descending thoracic aortic aneurysms is based on the natural history of the disease, balancing the risk of rupture and the risk of the intervention and the patient's life expectancy. Thoracic abdominal aortic aneurysms are those in which the aorta dilation encompasses the visceral vessels ostia. They are uncommon in clinical practice with prevalence estimated at between 10 to 25 new cases per 100,000 inhabitants. It is four times more common in men and has the same risk factors as abdominal aortic aneurysms. The decision to indicate intervention for a patient with a thoracic abdominal aneurysm involves assessment of the likelihood of aortic rupture versus the operative

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risk of the individual subject. The two major factors (the patient's physiologic reserve and vascular anatomy) play a significant role in determining whether a patient is best suited for open repair or an endovascular approach.

Thoracic, thoracoabdominal, and iliac artery aneurysms are most uncommon in comparison with the abdominal aortic aneurysms. High mortality rates are related with rupture, the most important complication.

Thoracic Aortic Aneurysm

The thoracic aortic aneurysms have an estimated incidence of approximately 6/100,000 person-years, the risk of rupture for large aneurysms is up to 74 % in patients without repair, and 90 % of patients do not survive rupture [1].

Most of them are asymptomatic, and the risk factors are the same related to abdominal aortic aneurysm. The majority of the patients are asymptomatic. They manifest themselves clinically with chest pain and can cause compressive symptoms when too large. There may be dyspnea, chest discomfort, and hoarseness in case of recurrent laryngeal nerve compression. Diagnosis is usually made through computerized angiotomography. There may be signs of mediastinum widening in chest x-ray. They have indication for surgical approach when larger than 6 cm in the descending aorta, when patients have characteristic pain and in every patient with symptoms or signs of rupture [2, 3].

The treatment approach for descending thoracic aortic aneurysms is based on the natural history of the disease, balancing the risk of rupture and the risk of the intervention and the patient's life expectancy. Both open and endovascular repair of descending thoracic aneurysm have been shown to have multiple and severe complications. The early mortality varies to 5.7–9.7 % in open surgery and 1.9–2.0 % in endovascular surgery [1, 4, 5]. Endovascular surgery demonstrates midterm favorable outcomes and confirms low risks for patients with thoracic aortic aneurysm. The most common complication of endovascular surgery is the endoleaks that can be observed in 15 % of patients [6, 7].

Thoracoabdominal Aortic Aneurysm

Thoracic abdominal aortic aneurysms are those in which the aorta dilation encompasses the visceral vessels ostia. They are uncommon in clinical practice with prevalence estimated at between 10 to 25 new cases per 100,000 inhabitants. It is fourfold more common in men and has the same risk factors as abdominal aortic aneurysms. The most common type surrounds the entire abdominal aorta from the celiac artery and involves the aortic portion where to originate the visceral arteries [8]. Surgical treatment is technically complex and presents many particularities regarding access, exposure, the level of aortic clamping, reconstruction of visceral arteries and preserving vital organs function. It has high mortality when untreated, especially when larger than 5 cm, and rupture risk is greater than 50 % [9]. They have indication of surgical correction when larger than 5 cm in transverse diameter, in patients with signs and

symptoms of rupture, in those with characteristic pain and those with growth rate greater than 6 mm in a year. In dedicated centers, mortality rates can vary from 3–21 %. Severe complications like renal failure, paraplegia, acute myocardial infarction, and stroke are frequently linked with this type of surgery. Endovascular repair of abdominal aortic aneurysms required a specific aortic anatomy, without dilatation in portions where the dispositive will be fixed. Complex aortic aneurysms require branched or fenestrated endoprothesis. The development of branched grafts opened the way to treat thoracoabdominal aneurysms endovascularly. Survival rates are above 90 %, with high spinal cord ischemia rates between 2.7 to 20 % [10–12]. Although promising, the fenestrated and branched endografts still carry a significant rate of mortality and complications, mostly related to the complexity of the procedure [13].

The decision to indicate intervention for a patient with a thoracic abdominal aneurysm involves assessment of the likelihood of aortic rupture versus the operative risk of the individual subject. The two major factors (the patient's physiologic reserve and vascular anatomy) play a significant role in determining whether a patient is best suited for open repair or an endovascular approach [14].

Iliac Artery Aneurysm

Common iliac arteries aneurysms are the most frequent after abdominal aortic aneurysm. Isolated iliac artery aneurysm is a relatively uncommon disease, accounting for approximately 0.4–1.9 % of all arterial aneurysms, with an estimated incidence in the general population of about 0.03 % [15]. Internal iliac aneurysms are the third most common aneurysm and may present alone. About 40 % of the internal iliac aneurysms are ruptured when diagnosed with a 31 % mortality rate. External iliac aneurysms are extremely rare [16]. Clinical presentation, risk factors, and diagnostic methods are similar to those of abdominal aortic aneurysms. They have indication for surgery when associated with surgical diameter aortic aneurysms, when larger than 3.0–3.5 mm and in patients with characteristic pain and with symptoms and signs of rupture. Iliac artery aneurysms located deep in the pelvis frequently prevent detection with physical exam, allowing them to typically grow to large diameters [16]. Surgical treatment of isolated iliac artery aneurysm includes open and endovascular repair. Endovascular repair is associated with lower perioperative mortality [17]. The treatment of internal aneurysm includes embolization and use of a branched endoprothesis [18].

What the General Practitioner Can Do for This Patient?

Most patients with thoracic and thoracoabdominal aortic aneurysm are asymptomatic and they don't have surgical indication when incidentally diagnosed. Thus, it must be done strict comorbidities control. For cardiovascular risk reduction, the patient should receive acetylsalicylic acid, statins, and beta-blockers. In case of hypertension, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are better indicated. Patients should be advised to smoking cessation and to perform supervised physical exercises if they can.

When to Refer to the Expert?

In cases of thoracic aortic aneurysm with transverse diameter greater than 6.0 cm or thoracoabdominal aortic greater than 5 cm, iliac arteries greater than 3 cm. When there is any rupture symptom or sign or characteristic pain.

References

1. Matsumura JS, Cambria RP, Dake MD, Moore RD, Svensson LG, Snyder S. International controlled clinical trial of thoracic endovascular aneurysm repair with the Zenith TX2 endovascular graft: 1-year results. J Vasc Surg. 2008;47(2):247–57; discussion 57.
2. Elefteriades JA, Ziganshin BA, Rizzo JA, Fang H, Tranquilli M, Paruchuri V, et al. Indications and imaging for aortic surgery: size and other matters. J Thorac Cardiovasc Surg. 2015;149(2 Suppl):S10–3.
3. Ziganshin BA, Elefteriades JA. Surgical management of thoracoabdominal aneurysms. Heart. 2014;100(20):1577–82.
4. Fairman RM, Criado F, Farber M, Kwolek C, Mehta M, White R, et al. Pivotal results of the Medtronic Vascular Talent Thoracic Stent Graft System: the VALOR trial. J Vasc Surg. 2008;48(3):546–54.
5. Dillavou ED, Makaroun MS. Predictors of morbidity and mortality with endovascular and open thoracic aneurysm repair. J Vasc Surg. 2008;48(5):1114–9; discussion 9–20.
6. Jordan Jr WD, Rovin J, Moainie S, Bavaria J, Cambria R, Fillinger M, et al. Results of a prospective multicenter trial of CTAG thoracic endograft. J Vasc Surg. 2015;61(3):589–95.
7. Biancari F, Mariscalco G, Mariani S, Saari P, Satta J, Juvonen T. Endovascular treatment of degenerative aneurysms involving only the descending thoracic aorta: systematic review and meta-analysis. J Endovasc Ther. 2016;23(2):387–92.
8. Crawford ES, DeNatale RW. Thoracoabdominal aortic aneurysm: observations regarding the natural course of the disease. J Vasc Surg. 1986;3(4):578–82.
9. Hansen PA, Richards JM, Tambyraja AL, Khan LR, Chalmers RT. Natural history of thoracoabdominal aneurysm in high-risk patients. Eur J Vasc Endovasc Surg. 2010;39(3):266–70.
10. Verhoeven EL, Tielliu IF, Ferreira M, Zipfel B, Adam DJ. Thoraco-abdominal aortic aneurysm branched repair. J Cardiovasc Surg (Torino). 2010;51(2):149–55.
11. Fattori R, Russo V, Lovato L, Buttazzi K, Rinaldi G. Endovascular management of thoracic aortic aneurysms. Cardiovasc Intervent Radiol. 2011;34(6):1137–42.
12. D'Elia P, Tyrrell M, Sobocinski J, Azzaoui R, Koussa M, Haulon S. Endovascular thoracoabdominal aortic aneurysm repair: a literature review of early and mid-term results. J Cardiovasc Surg (Torino). 2009;50(4):439–45.
13. Marzelle J, Presles E, Becquemin JP. Results and factors affecting early outcome of fenestrated and/or branched stent grafts for aortic aneurysms: a multicenter prospective study. Ann Surg. 2015;261(1):197–206.
14. Greenberg RK, Clair D, Srivastava S, Bhandari G, Turc A, Hampton J, et al. Should patients with challenging anatomy be offered endovascular aneurysm repair? J Vasc Surg. 2003;38(5):990–6.
15. Dorigo W, Pulli R, Troisi N, Alessi Innocenti A, Pratesi G, Azas L, et al. The treatment of isolated iliac artery aneurysm in patients with non-aneurysmal aorta. Eur J Vasc Endovasc Surg. 2008;35(5):585–9.
16. Santilli SM, Wernsing SE, Lee ES. Expansion rates and outcomes for iliac artery aneurysms. J Vasc Surg. 2000;31(1 Pt 1):114–21.
17. Buck DB, Bensley RP, Darling J, Curran T, McCallum JC, Moll FL, et al. The effect of endovascular treatment on isolated iliac artery aneurysm treatment and mortality. J Vasc Surg. 2015;62(2):331–5.
18. Noel-Lamy M, Jaskolka J, Lindsay TF, Oreopoulos GD, Tan KT. Internal iliac aneurysm repair outcomes using a modification of the iliac branch graft. Eur J Vasc Endovasc Surg. 2015;50(4):474–9.

Risk Factors and Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism

11

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Abstract

Deep venous thrombosis (DVT) is the formation of an intraluminal thrombus that occludes wholly or partially deep veins' lumen. There is no single cause for DVT, but there are medical conditions that increase the likelihood of developing thrombi. Therefore, the incidence of this condition is associated with the number of risk factors present. Although, there are several risk factor assessment and protocols available for DVT prevention in daily medical practice.

The DVT's prevention decreases the risk of pulmonary embolism. An estimated one-third of cases of pulmonary embolism progress to death if the condition remains untreated. Survivors are subject to chronic complications: about 4 % develop pulmonary hypertension, and 25–50 % have post-thrombotic syndrome in the lower limb.

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Abbreviations

BMI Body mass index
DVT Deep venous thrombosis

Introduction

Deep venous thrombosis is the intraluminal formation of thrombus (clots) in the deep veins of the limbs, mostly in the lower limbs [1]. One of its main complications is the detachment of part of the thrombus from the vessel wall, that follows the blood flow up to the pulmonary vessels, leading to pulmonary embolism. The latter is the main cause of inhospital deaths worldwide (around 15 %) and paradoxically, the most preventable [2]. The whole process, e.g., the association of deep venous thrombosis and pulmonary embolism, is named Venous Thromboembolism [3].

Therefore, to prevent venous thromboembolism, it is necessary to recognize the patient's individual risk factors and, according to the number of risk factors, to categorize him or her in low, moderate, high, or very high risk for development of venous thromboembolism, in order to take proper measures to avoid thrombus formation and death (thromboprophylaxis), particularly, but not exclusively, in the hospitalized patient.

Natural History of Venous Thromboembolism and Complications

Most treated deep venous thrombosis are recanalized. The recanalization time is variable and depends on the extent of thrombosis and early treatment. The significant reduction of thrombus occurs around 3 months. However, complete resolution can extend over several months. Ultrasonography is the main test that follows this resolution [3, 4].

The most fatal complication of deep venous thrombosis (untreated) is pulmonary embolism which mostly is often asymptomatic [3]. It is estimated that one-third of the cases of pulmonary embolism progress to death if the condition remains untreated. Survivors are subject to chronic complications: about 4 % develop pulmonary hypertension with pulmonary embolism [5], and 30–50 % of deep venous thrombosis patients develop post-thrombotic syndrome in lower limb, despite the use of anticoagulation [5].

Identification of Risk Factors for Venous Thromboembolism

There is no single cause for deep venous thrombosis, but there are medical conditions that increase the likelihood of developing a thrombus in the deep veins. Therefore, the incidence of this condition is associated with the number of risk factors presenting by the individual patient [6].

There are several risk factor assessment tools and protocols available for the prevention of deep venous thrombosis [7, 8]. The American College of Chest Physicians guidelines (2012) recommend the use of Caprini score to stratify risk of development of deep venous thrombosis and to guide the appropriate thromboprophylaxis. This protocol presents 37 risk factors, and each one is scored as shown in the Table 11.1

Table 11.1 The Caprini Risk Assessment Model—with description of risk factors and their corresponding scores, used for categorizing risk of thromboembolic event

1 Point	2 Points	3 Points
1. Age 41–60 years	12. Age 60–74 years	20. Age >75 years
2. Major surgery planned	13. Arthroscopic surgery	21. History of venous thrombosis or pulmonary embolism previously
3. Varicose veins of the lower limbs	14. Cancer (past or present)	22. Family history of thrombosis
4. History of inflammatory bowel disease	15. Major surgery (>45 min)	23. V Factor positive Leiden
5. Recurrent edema of the lower limbs	16. Laparoscopic surgery (>45 min)	24. Prothrombin 20210 A
6. Obesity (BMI > 25 kg/m^2)	17. Patient confined to bed (>72 h)	25. Positive lupus anticoagulant
7. Acute myocardial infarction	18. Member immobilization (cast)	26. Elevated serum homocysteine
8. Congestive heart failure	19. Central venous access	27. Elevated anticardiolipin antibodies
9. Sepsis (<1 month)		28. Heparin-induced thrombocytopenia
10. Severe pulmonary disease (<1 month), including pneumonia		29. Other congenital or acquired thrombophilia
11. Chronic obstructive pulmonary disease		

5 Points	1 Point (for women only)
30. Elective major lower extremity arthroplasty	35. Oral contraceptives or hormone replacement therapy
31. Hip, pelvis, or leg fracture (<1 month)	36. Pregnancy or postpartum (<1 month)
32. Stroke (<1 month)	37. History of unexplained abortion (>3), premature birth with toxemia or growth-restricted infant
33. Multiple trauma (<1 month)	
34. Acute spinal cord injury—paralysis (<1 month)	

BMI body mass index

Adapted from: *"Guyatt GH, Akl EA, Crowther M, Schünemann HJ, Gutterman DD, Zelman Lewis S, et al. Introduction to the ninth edition: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):48S–52S."* **and** *"Arcelus JIC, J.A. Acute Deep Venous Thrombosis: Prevention and Medical Treatment. In: Rutherford RB, editor. Vascular Surgery. Philadelphi a. 2014. p. 776."* **and** *"Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77S."* **and** *"Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med. 2002;162(10):1144–8"*

Table 11.2 Classification of risk groups for venous thromboembolism

Risk group	Total score
Low	0–1 point
Moderate	2 points
High	3–4 points
Very high	≥5 points

Calculated from the scores of individual risk factors
Adapted from: "*Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. Curr Opin Pulm Med. 2010;16(5):448–52*"

[1, 3, 9, 10]. Any of the risk factors 1–11 gives one point, not more than one point, and the same reasoning applies to other groups. The total risk factors score classifies patients into four levels of risk for deep venous thrombosis (Table 11.2).

Classification of Groups of Risk for Venous Thromboembolism According to the Individual Risk Factors Scoring

After identification and scoring of all individual risk factors, the patient is categorized into one of the four possible Groups of Risk for the development of venous thromboembolism.

Prophylaxis

According to the stratification described in Table 11.2, an individualized proper prophylaxis for venous thromboembolism is identified. Prophylaxis is medical measure adopted to prevent the formation of thrombus in deep veins and subsequent pulmonary embolism and depends on the correct identification of risk factors. These measures may be (1) early mobilization of patients (i.e., to avoid blood stasis), (2) use of an intermittent pneumatic compression device, (3) use of medicinal compression stockings, and (4) use of anticoagulant medications in low doses [1, 3].

The medicinal socks compression and pneumatic devices are mechanical methods. Although mechanical methods of prophylaxis have not been studied as extensively as the pharmacologic agents, they may represent the sole alternative for patients with contraindications to anticoagulants. Most physical methods may and should be combined with the pharmacologic agents in patients at very high risk to develop venous thromboembolism whenever possible, because they act on different pathogenic factors [3].

Hospitalized Nonsurgical Patients

The mechanical or medical thromboprophylaxis is not recommended for all hospitalized medical patients, with low risk for venous thromboembolism. Whether these patients have a medium to high risk of thrombosis it is indicated

Table 11.3 Recommended doses of medications in the prophylaxis of deep venous thrombosis in nonsurgical patients, according to the stratification of risk factors for thrombosis

Low risk	Moderate risk	High risk
No medications	LMWH—20 mg daily	LMWH—40 mg daily
	LDUH—5000 UI twice a day	LDUH—5000 UI three times a day
	Fondaparinux—2.5 mg daily	Fondaparinux—2.5 mg daily

LMWH low-molecular-weight heparin, *LDUH* low-dose unfractionated heparin
Adapted from: "*Arcelus JIC, J.A. Acute Deep Venous Thrombosis: Prevention and Medical Treatment. In: Rutherford RB, editor. Vascular Surgery. Philadelphia. 2014. p. 776*"

low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH), or fondaparinux [1]. The recommended doses are listed in Table 11.3 [3].

In cases of high risk for bleeding, it is advisable the use of mechanical thromboprophylaxis [1, 3]. In these cases, intermittent pneumatic compression is recommended in deep venous thrombosis prophylaxis for its known efficacy and reduced risk of bleeding [11]. The recommended doses for patients in the very high risk group are the same as recommended for the high risk group.

Hospitalized Surgical Patients

Early Mobilization

Encouraging the patient to walk should be the first prophylactic measure for deep venous thrombosis. In patients confined to bed, physical therapy may be an alternative to early mobilization in order to help the blood return to the heart. Another measure is the elevation of the lower limbs, which reduces swelling and decreases venous pressure [1, 3].

Intermittent Pneumatic Compression

Pneumatic compression is the positioning of pneumatic boots or clothing around the legs of the patient. It is considered the most effective mechanical prophylactic method and is indicated in cases of moderate or high risk for deep venous thrombosis and bleeding [1]. This method prevents venous stasis by intermittent compression of the calves. The device is inflated to a pressure of 35–55 mmHg for 10–35 s and deflated for about 1 min [1, 12].

The use of the intermittent pneumatic compression must be introduced immediately after the beginning of surgery and should be maintained until the resumption of regular patient mobility [3].

Elastic Compression Stockings

The use of elastic compression stockings prevents intraoperative strain of the calf veins. The venous distention encourages edema and intravascular blood stasis [3].

The method produces a 68 % reduction in cases of deep venous thrombosis for postoperative patients with moderate risk [13].

The stocking should not be used in patients with peripheral arterial disease (i.e., ankle arm index <0.8), patients with severe edema, and in cases of dermatitis [3].

Anticoagulant Medications

Surgical patients stratified as low risk by Caprini score don't need medication or mechanical prophylaxis (Compression Air Flashing Intermittent or Elastic Compression Stockings). In such cases, just early ambulation is indicated [1].

Patients who are at moderate, high, or very high risk should receive prophylaxis medication, according surgical procedure performed [1].

Patients undergoing abdominal-pelvic surgery without high bleeding risk and moderate or high risk for venous thromboembolism require prophylactic anticoagulation. The recommended doses are listed in Table 11.4 [1, 3, 9].

In orthopedic procedures, the recommended dose for prophylaxis is similar to abdominal-pelvic surgery. However, due to the high incidence of thrombosis in these procedures, the use of prophylactic drug should be extended for a minimum period of 10–14 days [1, 3].

Another alternative to the use of heparin for surgical prophylaxis is the administration of fondaparinux at a dose of 2.5 mg daily [3]. Fondaparinux should be given 6–8 h after surgery and serves on the selective inhibition of factor Xa [14]. Unlike heparin, fondaparinux does not induce thrombocytopenia.

Other Anticoagulants

Oral anticoagulants (i.e., rivaroxaban, apixaban) also directly inhibit factor Xa. Rivaroxaban can be used for thromboprophylaxis at a dose of 10 mg/day [15, 16]. The benefit is similar to the low-molecular-weight heparin and it can be administered safely in acutely ill medical patients [16]. It has two main advantages: (1) it is taken orally (as compared to heparin, which must be subcutaneously administered) and (2) it does not need to be controlled by laboratory tests, compared to the use of

Table 11.4 Recommended doses of medications in the prophylaxis of deep venous thrombosis in surgical patients, according to the stratification of risk factors for thrombosis

Low risk	Moderate risk	High risk
– No medications	LMWH—20 mg daily	LMWH—40 mg daily
– Early mobilization	LDUH—5000 UI twice a day	LDUH—5000 UI three times a day
	Fondaparinux—2.5 mg daily	
	High risk of bleeding—intermittent pneumatic compression (patients with ankle arm index > 0.8)	

LMWH low-molecular-weight heparin, *LDUH* low-dose unfractionated heparin

Adapted from: *"Guyatt GH, Akl EA, Crowther M, Schünemann HJ, Gutterman DD, Zelman Lewis S, et al. Introduction to the ninth edition: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):48S–52S."* **and** *"Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S–453S."* **and** *"Arcelus JIC, J.A. Acute Deep Venous Thrombosis: Prevention and Medical Treatment. In: Rutherford RB, editor. Vascular Surgery. Philadelphia. 2014. p. 776."* **and** *"Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77S"*

warfarin. These oral anticoagulants have short half-lives (i.e., 5–9 h) and require mandatory daily administration. The irregular use increases the risk of thrombosis [15, 16]. Apixaban is FDA-approved for the prophylaxis of deep venous thrombosis, in patients who have undergone total knee replacement or hip replacement (dose: 2.5 mg twice a day) [17].

Dabigatran (another oral anticoagulant) binds to thrombin with high specificity and affinity [3]. This drug inhibits thrombin and consequently stops the coagulation cascade. The prophylactic dose is 150 or 220 mg/day, and is indicated 4 h after orthopedic surgery [18].

Aspirin use in venous thromboprophylaxis has been studied as an alternative because of its low cost, acceptance, and no need for blood test control. However, the evidence is fragile and contradictory so far to support its use for primary prevention of venous thromboembolism [19].

Prophylaxis Duration

Thromboprophylaxis is limited to the period of hospitalization or in the persistence of risk factors (i.e., sepsis, immobilization, use of central venous catheters, early postoperative period).

However, in cancer patients, especially for those undergoing pelvic, abdominal, and orthopedic surgery (high and very high risk groups), thromboembolism risk persists after discharge. In such cases, patients will benefit from having prophylaxis extended to 30 days after discharge with low-molecular-weight heparin [3].

Although heparin is naturally an antithrombotic agent available for therapeutic use as unfractionated heparin and low-molecular-weight heparin, paradoxically this drug can cause thromboembolic complications because of a severe adverse reaction known as heparin-induced thrombocytopenia. This thrombocytopenia is presented as a prothrombotic disorder still misunderstood, resulting in the generation of thrombin in vivo, leading to a hypercoagulable state, and it may cause venous or arterial thrombosis [20]. It is also noted that there is a relative reduction in the number of platelets of 50 % between 5 and 14 days after initiation of therapy [21].

Thrombocytopenia is the main finding that directs the clinical suspicion, and the diagnosis is a delicate matter and requires a combination of clinical and laboratory testing. The absolute risk of heparin-induced thrombocytopenia is greater with treatment with unfractionated heparin (between 1 and 5 %) than with the use of low-molecular-weight heparin (less than 1 %) [21], and the options for use of these drugs are discussed and better explained in anticoagulation chapter.

Outpatient

There are some special situations to prevent venous thromboembolism in outpatient: patients confined to bed or with cancer, who have some risk factors. The risks in outpatients with cancer are: previous thrombosis, immobilization, or use of

thrombogenic medications (hormonal therapy, thalidomide, lenalidomide, angiogenesis inhibitors). If there is one of these factors, prophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin should be administered [1].

Other special situation is long-distance trip. Frequent ambulation and use of medicinal compression stockings are recommended in people at increased risk for thrombosis. These risks are obesity, previous venous thromboembolism, pregnancy, recent surgery or trauma, thrombophilic disorder, advanced age, and use of estrogen. Compressive stockings are indicated at pressure 15–30 mmHg and properly fitted below the knee. In these situations, the use of aspirin and anticoagulants is not recommended to prevent deep vein thrombosis [1].

References

1. Guyatt GH, Akl EA, Crowther M, Schünemann HJ, Gutterman DD, Zelman Lewis S, et al. Introduction to the ninth edition: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):48S–52.
2. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S–453.
3. Arcelus JI, Caprini JA. Acute deep venous thrombosis: prevention and medical treatment. In: Rutherford RB, editor. Vascular surgery. Philadelphia; 2014. p. 776.
4. Prandoni P, Cogo A, Bernardi E, Villalta S, Polistena P, Simioni P, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. Circulation. 1993;88(4 Pt 1):1730–5.
5. Nicolaides AN, Fareed J, Kakkar AK, Comerota AJ, Goldhaber SZ, Hull R, et al. Prevention and treatment of venous thromboembolism—International Consensus Statement. Int Angiol. 2013;32(2):111–260.
6. Caprini JA, Tapson VF, Hyers TM, Waldo AL, Wittkowsky AK, Friedman R, et al. Treatment of venous thromboembolism: adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. J Vasc Surg. 2005;42(4):726–33.
7. Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. Curr Opin Pulm Med. 2010;16(5):448–52.
8. Stinnett JM, Pendleton R, Skordos L, Wheeler M, Rodgers GM. Venous thromboembolism prophylaxis in medically ill patients and the development of strategies to improve prophylaxis rates. Am J Hematol. 2005;78(3):167–72.
9. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e227S–77.
10. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med. 2002;162(10):1144–8.
11. Sadaghianloo N, Dardik A. The efficacy of intermittent pneumatic compression in the prevention of lower extremity deep venous thrombosis. J Vasc Surg Venous Lymphat Disord. 2016;4(2):248–56.
12. Kakkos SK, Szendro G, Griffin M, Daskalopoulou SS, Nicolaides AN. The efficacy of the new SCD response compression system in the prevention of venous stasis. J Vasc Surg. 2000;32(5):932–40.
13. Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism. A meta-analysis. Arch Intern Med. 1994;154(1):67–72.

14. Turpie AG, Eriksson BI, Lassen MR, Bauer KA. A meta-analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery. J South Orthop Assoc. 2002;11(4):182–8.
15. Burness CB, Perry CM. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. Drugs. 2014;74(2):243–62.
16. Cohen AT, Spiro TE, Buller HR, Haskell L, Hu D, Hull R, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368(6):513–23.
17. Mandernach MW, Beyth RJ, Rajasekhar A. Apixaban for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism: an evidence-based review. Ther Clin Risk Manag. 2015;11:1273–82.
18. Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. J Thromb Haemost. 2005;3(1):103–11.
19. Sadaghianloo N, Jean-Baptiste E, Declemy S, Hassen-Khodja R, Dardik A. Use of aspirin for the prevention of lower extremity deep venous thrombosis. J Vasc Surg Venous Lymphat Disord. 2014;2(2):230–9.
20. Junqueira DR, Perini E, Penholati RR, Carvalho MG. Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2012;9:CD007557.
21. Junqueira DR, Carvalho M, Perini E. Heparin-induced thrombocytopenia: a review of concepts regarding a dangerous adverse drug reaction. Rev Assoc Med Bras. 2013;59(2):161–6.

Venous Thromboembolism: Diagnosis and Treatment

12

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Abstract

Venous thromboembolism includes deep venous thrombosis and pulmonary embolism. Deep venous thrombosis is the formation of thrombi (blood clots) in the deep veins of the vascular system of the members. The blood clot can break in the deep veins of the limbs and reach the pulmonary arteries, causing a pulmonary embolism. Venous thromboembolism is a common cause of death and it is associated with high intrahospital mortality and costs. However, it is also the most preventable cause of hospital deaths. Clinical presentations of deep vein thrombosis are wide, and the most common complaints are the affected limb pain, edema, erythema, or cyanosis. Clinical presentation of pulmonary embolism varies, the most common symptoms and signs are tachypnea, dyspnea or pleuritic pain and leg pain or swelling in the lower limbs are common. Diagnosis is based according to specific clinical situations with different strategies as: risk stratification using Wells preclinical score, serum levels of D-dimer, and/or an imaging method. Treatment aims to prevent progression of the thrombus; to reestablish blood flow when needed; to reduce complications, morbidity, and mortality

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associated; and also to avoid recurrence of thromboembolic events. Practitioners need to apply clinical and pharmacological interventions and, eventually, surgery to achieve these goals.

Introduction

Venous thromboembolism is a condition encompassing two events occurring together or separately: deep vein thrombosis and pulmonary embolism. Deep venous thrombosis is the formation of thrombi (blood clots) in the deep veins of the vascular system of the members. The blood clot attached to the deep veins of the limbs can fragment and reach the pulmonary arteries, leading to pulmonary embolism. Approximately 90 % of pulmonary emboli originate from a thrombus located in the deep venous system of the lower limbs [1]. The presence of a clot in the pulmonary arteries impairs the proper gas exchange, resulting in hypoxemia, and may block the blood flow from the right ventricle to the left side of the heart causing hypotension, shock, and eventually death [2].

Epidemiology

Venous thromboembolism is the leading cause of hospital deaths worldwide and, paradoxically, it is the most preventable [1]. In the United States, 900,000 cases of thromboembolism were estimated to occur in 2010, and 10–30 % of those patients would die [3]. The survivors of an episode of venous thromboembolism may develop complications, such as pulmonary hypertension and post-thrombotic syndrome in the lower limb. The latter may lead to loss of quality of life due to frequent ulcerations and loss of work capacity. Complications of venous thromboembolism may, therefore, be accompanied by significant economic burden to the patient and to the public social security system [4].

Clinical Presentation

Deep Vein Thrombosis

Clinical presentations of acute deep vein thrombosis range from the absence of signs and symptoms, to severe presentations such as *phlegmasia cerulea dolens*, which can lead to gangrene of the affected limb.

The factors that determine the severity of the symptoms are: (i) the location of the thrombus, (ii) the degree of venous obstruction, (iii) the time of onset, and (iv) the integrity and functionality of the lymphatic system. The more proximal the venous thrombosis (inferior vena cava, iliac and femoral veins), the greater the probability to develop severe signs and symptoms.

In the most common presentation, the patient may have calf pain, unilateral edema, erythema, or cyanosis of the affected limb and stiffening of the calf. If there is calf pain during dorsiflexion of the foot, it is called Homans' sign.

Table 12.1 Signs and symptoms of pulmonary embolism [8]

Signs		Symptoms	
Tachypnea (≥20/min)	54 %	Dyspnea (at rest or on exertion)	73 %
Tachycardia (>100/min)	24 %	Orthopnea	28 %
Rales (crackles)	18 %	Cough	34 %
Decreased breath sounds	17 %	Pleuritic pain	44 %
Increased P2	15 %	Leg pain	44 %
Jugular venous distension	14 %	Swelling in the lower limbs	41 %
Wheezes or Rhonchi	4 %	Wheezing	21 %

Adapted from: *"Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med. 2007;120(10):871–9"*

The most severe presentation is the venous gangrene, also know as *phlegmasia cerulea dolens*. It is a serious and rare condition that may be associated with cancer, heparin-induced thrombocytopenia, and depletion of protein C induced by warfarin [5, 6].

Pulmonary Embolism

The clinical presentation of pulmonary embolism is dependent on the number of clots that reaches the pulmonary arteries and the extent of thrombi, and also according to other cardiovascular or respiratory preconditions.

The classic triad of chest pain, dyspnea, and hemoptysis occurs in only 5 % of the cases.

The study Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) describes the frequency of the symptoms and signs of pulmonary thromboembolism, as shown in Table 12.1 [7].

Diagnosis

Deep Vein Thrombosis Diagnosis

The clinical manifestation of deep vein thrombosis of the lower limbs varies widely and is often asymptomatic. The preclinical test developed by Wells and colleagues is a clinical model to predict the probability of deep vein thrombosis. Therefore, the Wells scale is the most widely used scale for symptomatic patients with this suspicion of venous thrombosis. The risk increases as the risk factors increase. This statement is the basis for stratifying patients by combining the number of risk factors with clinical signs and symptoms. A score based on eight Wells criteria is a consistent and repeatable tool for stratifying outpatients as having a high, moderate, or low probability of presenting with deep vein thrombosis (Table 12.2) [9].

The score of all of the clinical features presented by a patient must be summed and applied in the following table to establish the classification risk (Table 12.3).

As the clinical manifestation of deep vein thrombosis is highly variable and the first clinical manifestation can be a fatal pulmonary embolism, clinical diagnosis has a low sensitivity. Thus, despite of rating deep vein thrombosis risk by the

Table 12.2 Clinical model for determining the probability of having deep vein thrombosis, as proposed by Wells et al. [10]

Clinical feature	Punctuation
Active cancer	1
Paresis, paralysis, or immobilization of the lower limbs	1
Immobilization (>3 days) or major surgery (up to 4 weeks)	1
Pain or discomfort along the deep venous veins trajectory	1
Limb edema	1
Calf swelling (>3 cm) compared to the normal leg	1
Cacifo's sign in the affected limb (unilateral)	1
Visible superficial collateral veins	1
Previously documented deep vein thrombosis	1
A more likely differential diagnosis from another condition	−2

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Table 12.3 Group of risk for deep vein thrombosis according to the score of the Wells preclinical testing [10]

Score	Deep vein thrombosis probability	Classification
0 points	3 % (95 % IC; 1.7–5.9 %)	Low risk
1 or 2 points	17 % (95 % IC; 12–23 %)	Moderate risk
3 or more points	75 % (95 % IC; 63–84 %)	High risk

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application of Wells preclinical testing, objective diagnostic methods are essential to a correct diagnosis [11].

Additional Tests That Increase Accuracy for the Diagnosis of Deep Vein Thrombosis

Serum D-dimer: Plasma D-dimer is a product of fibrin degradation and its plasma concentration is high in cases of acute venous thromboembolism. Testing for D-dimer levels has a sensitivity of 60–97 % for the diagnosis of deep vein thrombosis, but the specificity is lower than 35 % [4]. Thus, in isolation, this test is not a suitable method for diagnosing acute venous thrombosis, as there are many other medical conditions that also increase levels of D-dimer: recent surgical procedures, sepsis, hemorrhage, trauma, cancer, old age, pregnancy, and long periods of hospitalization. However, a negative result, i.e., low concentrations of D-dimer, associated with preclinical low probability (low-risk patient) may exclude the diagnosis of deep vein thrombosis, once some studies have shown that it is safe not to treat these patients because the deep vein thrombosis incidence in 3-month follow-up is too low [9, 12, 13].

Venography: Venography is an invasive method that was considered the gold standard for the diagnosis of deep vein thrombosis. It now has been replaced by the vascular Doppler ultrasound. Venography is a high-cost method that exposes the

patient to ionizing radiation and to injection of iodinated contrast middle. The latter can cause allergy, vein thrombosis, and nephrotoxicity [14]. However, venography is still reserved in cases in which the diagnosis of deep vein thrombosis remains inconclusive and during endovascular interventions [14, 15].

Vascular ultrasound (duplex scanning): This technique replaced venography and is considered the main imaging method for the diagnosis of deep vein thrombosis. Duplex scan is a validated technique due to its high sensitivity and specificity [16, 17]. Vascular ultrasound is noninvasive, radiation-free, cost-effective, and available at most institutions [16, 17]. Thus, vascular Doppler is the method of choice for the initial investigation of deep vein thrombosis, although diagnosis using this method may be examiner-dependent [18, 19].

Computed tomography (CT): CT is an excellent method for the diagnosis of pulmonary embolism. However, it has a lower accuracy for the diagnosis of deep vein thrombosis. Peterson et al. demonstrated that, although the sensitivity of CT is 93 %, with a negative predictive value of 97 %, CT's ability to accurately diagnose deep vein thrombosis has a specificity of 71 % with a positive predictive value of only 53 % [20]. CT has not been well studied for the diagnosis of acute deep vein thrombosis of the calf veins, which implies that the role of this technique as a comprehensive diagnostic modality for the lower limbs is questionable.

Magnetic resonance imaging: Magnetic resonance venography is an alternative method for the diagnosis of deep vein thrombosis. In a meta-analysis performed by Sampson et al. [21], it was found that the sensitivity was 91.5 % and the specificity was 94.8 %. However, estimates of both sensitivity and specificity were subject to significant heterogeneity. The studies for the diagnosis of acute venous thrombosis show good results for proximal venous segments, but decreased sensitivity to distal veins [21]. In the study of femoral vein thrombosis, magnetic resonance imaging showed 100 % sensitivity and 97 % specificity. The overall sensitivity for lower limb thrombus detection is 87 % and a specificity of 98 % [22].

In 27 % of patients with pulmonary embolism, the magnetic resonance imaging identified the thrombus source, which was not previously identified by vascular ultrasound [23]. Therefore, magnetic resonance venography may be an alternative method for patients in whom vascular ultrasound is not suitable, feasible, or inconclusive.

Strategies for the Diagnosis of Deep Vein Thrombosis in Specific Clinical Situations

Based on the specific clinical situation of each patient, practitioners can use different strategies for the diagnosis of deep vein thrombosis:

1. Outpatients: Nonhospitalized patient with suspected deep vein thrombosis should have three steps for the diagnostic approach including:
   (a) Risk stratification using the Wells criteria (preclinical testing)
   (b) Serum levels of D-dimer
   (c) Use of an imaging method (duplex scanning preferably)

The negative predictive value for venous thrombosis approximates to 100 % in outpatients who are considered to be low risk based on the Wells criteria in association with a negative D-dimer test. Similar results were shown in intermediate-risk patients who also had a negative D-dimer result. For these outpatients, no further testing is necessary to exclude the diagnosis of deep vein thrombosis [24, 25]. In contrast, a high probability of deep vein thrombosis in outpatients may require immediate anticoagulation with no additional test, pending the completion of vascular ultrasound [26, 27]. Anticoagulation treatment should be maintained until the diagnosis is confirmed or not by vascular ultrasound. If the result of the ultrasound is negative, the practitioner should measure D-dimer levels as a negative value excludes the diagnosis. In cases of a positive D-dimer result, vascular ultrasound should be repeated in 3–7 days.

Therefore, in nonhospitalized patients, the combination of a low clinical probability associated with a negative D-dimer result is sufficient to exclude deep vein thrombosis. A positive D-dimer result in patients who are considered to be moderate or high risk is an indication for immediate anticoagulation therapy. A vascular ultrasound could be scheduled for the next available agenda [26, 28].

2. Hospitalized patients (surgical or clinical): The sensitivity and specificity of the D-dimer test are substantially lower in hospitalized patients, even in those classified as low risk [29]. Several factors associated with such patients determine an elevated serum level of D-dimer [29]. Therefore, the diagnosis of a clinically suspected deep vein thrombosis in a hospitalized patient requires confirmation by imaging methods, particularly vascular ultrasound [29].
3. Pregnancy: The diagnosis of deep vein thrombosis in pregnant women has peculiarities. D-dimer levels are not as useful parameters once these levels are elevated during pregnancy. For such reasons, vascular ultrasound is the best method of diagnosis [30]. The anticoagulation approach should also be considered carefully due to the risk of bleeding complications.

Pulmonary Embolism

The diagnosis of pulmonary embolism is based on clinical manifestations and objective diagnostic methods.

Thorax X-ray—This test is often normal at the initial presentation. Faint infiltration can be observed, along with reduced lung parenchyma and elevation of the hemidiaphragm [31].

Electrocardiogram—The most frequent finding is tachycardia. Other changes in the electrocardiogram that indicate a diagnosis of pulmonary embolism include characteristic findings in S1, Q3, and T3 [31].

AngioCT—CT angiography allows the professional to visualize the thrombus within the vessels and to identify changes in the vascular lumen and lesions in the lung parenchyma (infarcts, atelectasis, and nodules). This test has high sensitivity and specificity [32] (Fig. 12.1).

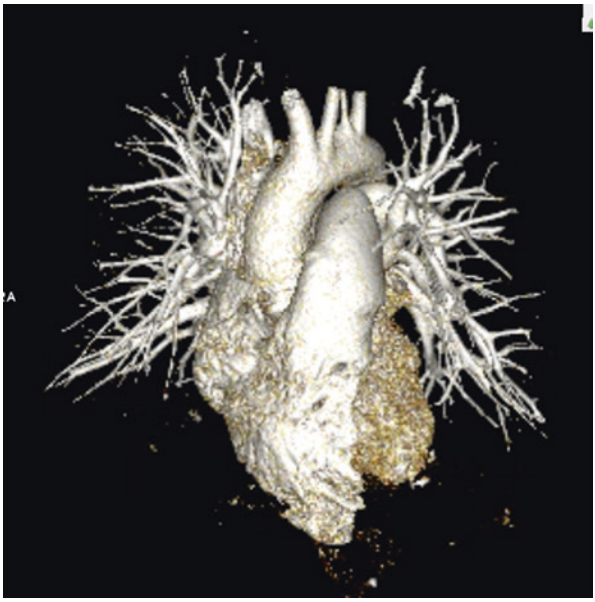

Fig. 12.1 Photograph of chest CT angiography with 3D reconstruction. Observe the rich pulmonary vasculature. The center corresponds to the main pulmonary artery alongside the aorta

Pulmonary angiography—Although invasive, pulmonary angiography is considered the gold standard for the diagnosis of pulmonary embolism. The indications for this method include patients using thrombolytic medications or candidates for embolectomy (mechanical removal of the embolus) (Fig. 12.2).

Treatment

The general objective of the treatment of deep vein thrombosis is to prevent progression of the thrombus, to reduce morbidity (pain and swelling), and reduce mortality associated with pulmonary embolism. Treatment also aims to avoid recurrence of thromboembolic events and to decrease complications related to the post-thrombotic syndrome and pulmonary hypertension [33, 34].

Clinical recommendations: Consist of recommendation for early ambulation, as this approach reduces edema and discomfort associated with the use of elastic stockings, even in the presence of a floating thrombus [30, 35].

Compression Therapy

The pathophysiology of the post-thrombotic venous disease is characterized by venous hypertension associated with valvular incompetence or luminal obstruction. As a result, venous stasis occurs in the affected leg [36, 37]. Compression therapy

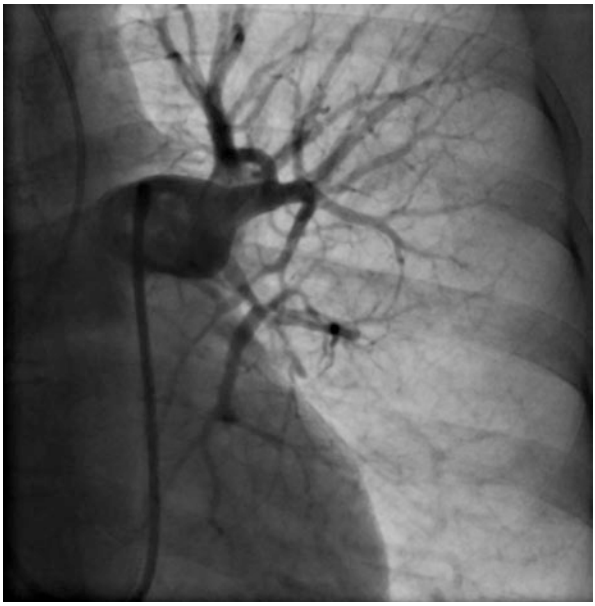

Fig. 12.2 Pulmonary angiography of the left pulmonary artery. Note the good vascularization in the upper half of the left lung. In contrast, note the poor perfusion of the lower half of the lung, where segmental and subsegmental blockage is apparent. Further note the high caliber of this pulmonary artery (pulmonary hypertension)

can be achieved through elastic stockings or nonelastic dressings. Brandjes et al. reported that the use of compression stockings with 30–40 mmHg for at least 2 years reduced the incidence of post-thrombotic syndrome by 50 % [38]. Prandoni et al. found similar results in patients with proximal vein thrombosis [4]. Partsch et al. showed that ambulation and elastic leg compression decreased pain and edema in comparison to patients at rest [37].

Pharmacological treatment: The conventional approach for the treatment of venous thromboembolism in patients with a confirmed or strongly suspected diagnosis of deep venous thrombosis is the use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) during 5–7 days followed by the oral Vitamin K antagonists (e.g., warfarin, acenocumarol) [30].

Initial treatment should start with low molecular weight heparin, unfractionated heparin, or fondaparinux for 5–7 days and suspended when the International Normalization Ratio (INR) reaches 2.0–3.0. Low molecular weight heparin has traditionally been the best choice. Warfarin should be started on the first day of treatment and continued with control based on the INR. The patients should then have anticoagulant therapy for a minimum of 3 months [30]. This combined approach is necessary once the sole use of oral vitamin K antagonists in the first days after the oral intake leads to a hypercoagulable state. Such situation could increase the extent of the thrombus and thereby lead to pulmonary embolism. Vitamin K antagonists tend to reduce the production of proteins C and S in the

first 2–4 days, which are natural anticoagulants. Only after this time there is the decrease of the production of procoagulant factors II, VII, IX, and X [39]. The updated "Chest Guidelines" recommends low molecular weight heparin over vitamin K antagonists as the treatment of option for patients with venous thromboembolism and cancer. It also suggests non-vitamin K antagonist oral anticoagulants over vitamin K antagonists for initial and long-term anticoagulant therapy for patients with venous thromboembolism and no cancer [40].

Unfractionated Heparin

Unfractionated heparin requires hospitalization and monitoring for dose adjustment. This medicine is widely available and is inexpensive. The initial dose of intravenous unfractionated heparin for the treatment of deep vein thrombosis is usually weight-adjusted, with an initial bolus of 80 U/kg of heparin, followed by continuous infusion of 18 units/kg/h [27]. The patient is typically monitored using the activated partial thromboplastin time (aPTT) every 6 h. The commercial presentation of unfractionated heparin for intravenous use is 5000 U/mL [1]. Unfractionated heparin can also be administered subcutaneously twice daily for the initial treatment of deep vein thrombosis. Treatment should start with a bolus injection followed by 5000–17,500 IU, twice daily, to achieve a therapeutic aPTT range from 1.5 to 2.5 times the control time. In most of the medical services, a weight-based nomogram to guide heparin dosing is typically recommended. The commercial presentation of unfractionated heparin for subcutaneous use is 5000 U per 0.25 mL. The subcutaneous route is not the optimal administration via for therapeutic doses due to the limited volume of medication that can be injected through this route, which impairs the achievement of the therapeutic range.

Low Molecular Weight Heparins

Low molecular weight heparin exhibits better bioavailability and more predictable pharmacokinetic and pharmacodynamics parameters than unfractionated heparin [27]. The anticoagulation effect of the low molecular weight heparins is therefore more predictable and does not require laboratory monitoring, and low molecular weight heparin can also be used without requiring hospitalization since the patient is stable. A meta-analysis of studies comparing unfractionated heparin and low molecular weight heparin for the treatment of deep vein thrombosis showed that these interventions have similar efficacy and safety [41, 42]. Subcutaneous low molecular weight heparin can be administered once or twice daily. The following doses are recommended [27, 41]: enoxaparin, 1 mg/kg every 12 h or 1.5 mg/kg every 24 h; dalteparin, 100 U/kg twice daily or 200 U/kg once per day; or tinzaparin, 175 U/kg once per day. Low molecular weight heparin is the preferred anticoagulant for pregnant patients [43].

Fondaparinux

Fondaparinux is a synthetic protein fraction that blocks factor Xa in the coagulation cascade (anti-Xa). Therefore, this drug is also an option for the initial treatment of deep vein thrombosis and pulmonary embolism. Evidence has shown that fondaparinux in combination of an initial treatment with heparins is as effective as standard treatment [44, 45]. Heparin-induced thrombocytopenia is rare during the use of fondaparinux, and this drug is thus a good alternative for cases of thrombocytopenia induced by the use of other heparins [27, 46]. Treatment is accomplished with a single daily dose of 5.0 mg for patients weighing less than 50 kg, a single daily dose of 7.5 mg for patients weighing between 50 kg and 100 kg, and a single daily dose of 10 mg for patients weighing more than 100 kg [44, 45].

Vitamin K Antagonist

Therapy with vitamin K antagonists should be initiated at a dose of 2–5 mg per day with dosage adjustment based on the results of the INR [47]. The standard warfarin dose is one 5 mg tablet per day orally, and the dose should be reduced or increased based on the INR [27]. The INR range considered suitable for anticoagulation therapy in cases of venous thromboembolism is between 2.0 and 3.0 (target 2.5). Once this range is reached, unfractionated heparin or low molecular weight heparin treatment is suspended, continuing only the oral vitamin K antagonist.

Non-vitamin K Antagonists Oral Anticoagulants

The new oral anticoagulants directly inhibit the factor Xa of the coagulation cascade or directly inhibit thrombin and have similar efficacy results for the prophylaxis and treatment of thromboembolic events in comparison to the use of heparin and warfarin [27]. Their main advantages are that they can be given orally and do not require laboratory monitoring for dose adjustment. Studies show that treatment of deep vein thrombosis and pulmonary embolism is effective when rivaroxaban is used at a dose of 15 mg 2×/day for 3 weeks, followed by 20 mg 1×/day [48, 49] and when dabigatran is used at a dose of 150 mg 2×/day [40]. Studies comparing direct oral anticoagulation drugs and standard anticoagulation show no differences in preventing recurrent pulmonary embolism and recurrent venous thromboembolism. Furthermore, there were no differences in prevention of mortality or major bleeding [50]. The updated “Chest Guidelines” suggests dabigatran, rivaroxaban, apixaban, or edoxaban as first choice drugs for treatment in patients with venous thromboembolism and no cancer [43]. For dabigatran and edoxaban, initial parenteral anticoagulation is given.

Interventional Treatment

Patients with an occlusive thrombus in the common femoral and external iliac veins often have significantly compromised venous drainage of the lower limb and are subject to high morbidity resulting from post-thrombotic syndrome. Thus, a strategy to the removal of the thrombus may be considered for these patients after an evaluation of clinical status and the risk of bleeding complications. The removal of the thrombus is performed by surgical venous thrombectomy or endovascular intervention with the use of catheters in combination with fibrinolytic drugs.

Fibrinolysis via Locoregional Intravenous Catheter in Patients with Deep Vein Thrombosis

The American College of Chest Physicians (ACCP) and the American Heart Association (AHA) recommend the removal of the venous thrombi, especially in proximal and extensive lesions, in patients presenting with clinical conditions with indication for surgical treatment and no contraindications to fibrinolytic therapy [27, 51]. In this method, a catheter is positioned within the iliac and femoral veins guided by fluoroscopy or ultrasound. Phlebography is then carried out to determine the location and extent of the thrombus, followed by the injection of fibrinolytic agents, such as streptokinase or more commonly, recombinant tissue plasminogen activator (rt-PA). These agents transform plasminogen to plasmin, which is an enzyme that performs the cleavage of fibrin (fibrinolysis) [51]. This cleavage occurs within the thrombosed vein, leading to recanalization of the vessel that was previously occluded by the thrombus. Alteplase dose is 0.01 mg/kg/h to be infused at most 96 h. This solution is prepared by diluting 20 mg of rt-PA in 500 mL of 0.9 % sodium chloride [51]. Phlebography is repeated the following day to assess if the fibrinolytic should be suspended or not. Other catheters allow drug-mechanical removal of the thrombus in a single procedure in a few minutes, but those catheters require equipment and specialized personnel and are expensive.

The best evidence shows that early elimination of the thrombus prevents or reduces post-thrombotic morbidity compared with anticoagulation alone [51]. Therefore, this procedure aims to improve long-term quality of life and reduce the morbidity of post-thrombotic venous disease [4, 51]. When the removal of thrombi is successful, the vein patency is restored, the function of the venous valve is maintained, the quality of life is improved, and the risk of thrombosis recurrence is reduced. Randomized studies have shown good clinical results for surgical removal of the thrombus in comparison to patients who received anticoagulation alone [4, 51].

Loco-regional or systemic fibrinolysis in the Pulmonary Embolism

The use of thrombolytic agents is indicated in the pulmonary embolism for severe cases. The drug can be administered through a catheter in the pulmonary artery. From this location, the drug can access the most affected artery. However, this approach requires specialized personnel and equipment [52].

Lower Vena Cava Filter Implant

A vena cava filter is a metallic endovascular device, usually in the shape of an umbrella, which is implanted into the infrarenal vena cava with the purpose of capturing thrombi that detach from the deep veins of the lower limbs and preventing those thrombi from reaching the pulmonary circulation. Therefore, the goal of this approach is to prevent pulmonary embolism, by trapping thrombi in the plunger in the vena cava within the mesh filter [30, 51].

Endovascular devices are mounted on low-profile catheters that are implanted via venous puncture, under local anesthesia in most cases. The filter ideal for the inferior vena cava should be non-thrombogenic, biocompatible, non-ferromagnetic, durable, and effective for filtering the plunger without compromising the vena cava flow [51].

The following are indications for vena cava filter placement: [27, 51]

- Patients with pulmonary embolism or proximal vein thrombosis (iliofemoral) with contraindications to anticoagulation (level of evidence: moderate)
- Patients with recurrent acute pulmonary embolism despite anticoagulant treatment (level of evidence: high)
- Patients with acute pulmonary embolism and low cardiac reserve (level of evidence: high); It is important to remove the temporary filter within the time specified in your model, if clinical conditions (level of evidence: low)

Concomitant use of a vena cava filter and anticoagulation should not be routine (level of evidence: high). If the filter was implemented due to a contraindication for anticoagulation, when the contraindication is resolved, anticoagulation should be resumed (level of evidence: low).

What Can Any General Practitioner Do for the Patient?

Venous thromboembolism is a frequent and prevalent disease. Every physician should know how to recognize the risk factors and apply anticoagulant treatment. Practitioners should begin treatment if the clinical suspicion of deep vein thrombosis or pulmonary embolism is high, even when there is no diagnostic confirmation.

In ambulatory patients with suspected deep vein thrombosis, the Wells score should be applied and a request for a D-dimer test, if available, should follow to help guide the clinical decisions.

Prophylaxis should be performed in all hospital, medical or surgical patients, and applied according to the risk group. Every hospitalized patient is at risk of venous thromboembolism.

Systemic fibrinolysis should be applied in cases of pulmonary embolism with hemodynamic instability.

When to Refer to a Specialist?

The patient should be referred to a specialist when signs of *phlegmasia* are present in a member and when vena cava filter placement or a fibrinolysis catheter is necessary.

References

1. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S–453.
2. Sanchez O, Trinquart L, Colombet I, Durieux P, Huisman MV, Chatellier G, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J. 2008;29(12):1569–77.
3. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010;38(4 Suppl):S495–501.
4. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med. 2002;162(10):1144–8.
5. Osman KA, Ahmed MH, Abdulla SA, Bucknall TE, Rogers CA. Venous gangrene and cancer: a cool look at a burning issue. Int Semin Surg Oncol. 2007;4:7.
6. Warkentin TE. Venous limb gangrene during warfarin treatment of cancer-associated deep venous thrombosis. Ann Intern Med. 2001;135(8 Pt 1):589–93.
7. Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. Curr Opin Pulm Med. 2010;16(5):448–52.
8. Stein PD, Beemath A, Matta F, Weg JG, Yusen RD, Hales CA, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med. 2007;120(10):871–9.
9. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006;10(15):1–168, iii–iv.
10. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;350(9094):1795–8.
11. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004;110(24 Suppl 1):IV4–12.
12. Bosson JL, Barro C, Satger B, Carpentier PH, Polack B, Pernod G. Quantitative high D-dimer value is predictive of pulmonary embolism occurrence independently of clinical score in a well-defined low risk factor population. J Thromb Haemost. 2005;3(1):93–9.
13. Stevens SM, Elliott CG, Chan KJ, Egger MJ, Ahmed KM. Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep venous thrombosis. Ann Intern Med. 2004;140(12):985–91.
14. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg. 1972;104(2):134–44.
15. Bettmann MA, Robbins A, Braun SD, Wetzner S, Dunnick NR, Finkelstein J. Contrast venography of the leg: diagnostic efficacy, tolerance, and complication rates with ionic and nonionic contrast media. Radiology. 1987;165(1):113–6.

16. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med. 1998;129(12):1044–9.
17. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost. 2007;5 Suppl 1:41–50.
18. Zierler BK. Ultrasonography and diagnosis of venous thromboembolism. Circulation. 2004;109(12 Suppl 1):I9–14.
19. Birdwell BG, Raskob GE, Whitsett TL, Durica SS, Comp PC, George JN, et al. The clinical validity of normal compression ultrasonography in outpatients suspected of having deep venous thrombosis. Ann Intern Med. 1998;128(1):1–7.
20. Peterson DA, Kazerooni EA, Wakefield TW, Knipp BS, Forauer AR, Bailey BJ, et al. Computed tomographic venography is specific but not sensitive for diagnosis of acute lower-extremity deep venous thrombosis in patients with suspected pulmonary embolus. J Vasc Surg. 2001;34(5):798–804.
21. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. Eur Radiol. 2007;17(1):175–81.
22. Cantwell CP, Cradock A, Bruzzi J, Fitzpatrick P, Eustace S, Murray JG. MR venography with true fast imaging with steady-state precession for suspected lower-limb deep vein thrombosis. J Vasc Interv Radiol. 2006;17(11 Pt 1):1763–9.
23. Stern JB, Abehsera M, Grenet D, Friard S, Couderc LJ, Scherrer A, et al. Detection of pelvic vein thrombosis by magnetic resonance angiography in patients with acute pulmonary embolism and normal lower limb compression ultrasonography. Chest. 2002;122(1):115–21.
24. Shields GP, Turnipseed S, Panacek EA, Melnikoff N, Gosselin R, White RH. Validation of the Canadian clinical probability model for acute venous thrombosis. Acad Emerg Med. 2002;9(6):561–6.
25. Schutgens RE, Ackermark P, Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pijlman AH, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. Circulation. 2003;107(4):593–7.
26. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e351S–418.
27. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S–94.
28. Go MR, Kiser D, Wald P, Haurani MJ, Moseley M, Satiani B. Clinical evaluation of suspected deep vein thrombosis guides the decision to anticoagulate prophylactically but does not impact the decision to perform after hours duplex venous scanning or increase its yield. J Vasc Surg. 2013;57(6):1597–602.
29. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al. Application of a diagnostic clinical model for the management of hospitalized patients with suspected deep-vein thrombosis. Thromb Haemost. 1999;81(4):493–7.
30. Cardiovascular Disease Educational and Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology, Union Internationale du Phlebologie. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). Clin Appl Thromb Hemost. 2013;19(2):116–8.
31. Bauersachs RM. Clinical presentation of deep vein thrombosis and pulmonary embolism. Best Pract Res Clin Haematol. 2012;25(3):243–51.
32. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354(22):2317–27.
33. BARRITT DW, JORDAN SC. Clinical features of pulmonary embolism. Lancet. 1961;1(7180):729–32.

34. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):401S–28.
35. Aschwanden M, Labs KH, Engel H, Schwob A, Jeanneret C, Mueller-Brand J, et al. Acute deep vein thrombosis: early mobilization does not increase the frequency of pulmonary embolism. Thromb Haemost. 2001;85(1):42–6.
36. Shull KC, Nicolaides AN, Fernandes é Fernandes J, Miles C, Horner J, Needham T, et al. Significance of popliteal reflux in relation to ambulatory venous pressure and ulceration. Arch Surg. 1979;114(11):1304–6.
37. Partsch H, Blättler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg. 2000;32(5):861–9.
38. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg. 2001;33(5):1022–7.
39. Trujillo-Santos J, Perea-Milla E, Jiménez-Puente A, Sánchez-Cantalejo E, del Toro J, Grau E, et al. Bed rest or ambulation in the initial treatment of patients with acute deep vein thrombosis or pulmonary embolism: findings from the RIETE registry. Chest. 2005;127(5):1631–6.
40. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342–52.
41. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160(2):181–8.
42. Alhenc-Gelas M, Jestin-Le Guernic C, Vitoux JF, Kher A, Aiach M, Fiessinger JN. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis. Fragmin-Study Group. Thromb Haemost. 1994;71(6):698–702.
43. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52.
44. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004;140(11):867–73.
45. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349(18):1695–702.
46. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med. 1996;334(11):677–81.
47. Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med. 1996;334(11):682–7.
48. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–510.
49. Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.
50. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev. 2015;12, CD010957.
51. Comerota AJ, Aziz F. Acute deep venous thrombosis: surgical and interventional treatment. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: Elsevier; 2014. p. 792–810.
52. Piazza G, Goldhaber SZ. Fibrinolysis for acute pulmonary embolism. Vasc Med. 2010;15(5):419–28.

Diabetic Foot

13

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Abstract

The diabetic foot is defined as the presence of ulcer, infection, or deep tissue breakdown in a foot of a person with diabetes, in association with peripheral neuropathy and/or peripheral arterial disease. Diabetic foot ulcers, the leading cause of diabetic patients' hospitalization, are among the most common, serious, and costly complications of diabetes mellitus and results in major consequences for patients, their families and society. The pathophysiologic background consists in a neuropathic foot, with the loss of protective sensation, leaving the foot vulnerable to repetitive trauma. Furthermore, the association of vascular disease and the predisposition to infection completes the triad which ultimately leads to amputation. The management of diabetic foot is complex and requires a multidisciplinary approach. Once established, it is a marker of poor limb prognosis, and, as always, the prevention is the most effective strategy.

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Introduction

Diabetic foot is one of the most serious, costly, and devastating complications of diabetes, defined as a foot affected by ulceration, associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes [1–4]. Diabetic foot complications are the leading cause of hospital admissions, lower limb amputation and mortality in patients with diabetes worldwide [5]. Early recognition of patients with feet at risk for ulcers and amputation and the appropriate management, offered by a multidisciplinary team, can reduce the rates of these outcomes [6–10].

The treatment of diabetes-related foot disease and the constant monitoring have a significant financial burden on health services [11, 12]. Moreover, they have a devastating impact on quality of life in diabetic patients and their families [13, 14].

Epidemiology

The diabetic foot ulcers are the leading cause of hospital admissions and amputations in the world, consuming 20–40 % of the available resources to care for diabetes [1, 15]. About 85 % of these amputations are preceded by infected ulcers or gangrene [2]. The annual incidence of ulcers in the general diabetic population is 2–6.8 % [1, 15], and it is estimated that 8–10 % of these people will require amputation within a year. In 5 years, reamputation rate reaches 60 % [3, 16].

The mortality rate in people with diabetic foot ulcer who underwent amputation ranges from 11 to 22 % [4, 17]. In these cases, in addition to worsening of life quality, the 5-year mortality reaches 46 % being higher than some forms of cancer [1, 15].

Natural History

The factors that lead to limb amputation are diabetic neuropathy (typically presented as sensorial and motor polyneuropathy), peripheral vascular disease, foot bone deformities, and external trauma [4]. The sensory dysfunction associated to foot deformities increases the risk of foot ulceration [3] which may be complicated by peripheral artery disease (PAD), preventing the proper healing process [6, 18]. Foot ulcers, particularly those with an ischemic component, are likely to be colonized by bacteria, which can easily complicate the clinical condition with superficial and deep infections and occasionally osteomyelitis [19]. Such components contribute to the progression of the foot at risk to complications which may result in limb amputation [3, 4].

Clinical Manifestations

The diabetic foot has a broad spectrum of clinical manifestations ranging from a "foot at risk" without macroscopic alterations, to a wide gangrene of the foot. However, the most common presentation is dry skin and bone

deformities—hammer toe or claw toe—associated with plantar callous or ulcers. All these manifestations can be grouped into three great classes: Peripheral neuropathy, peripheral arterial disease, and infection [6].

Peripheral Neuropathy

Peripheral neuropathy can be divided into three categories:

1. Sensitive neuropathy manifests as the loss of painful sensibility. It results in repetitive traumas without the perception by the patient of the tissue lesion at the foot. Burning and tingling sensations are also frequent in this type of neuropathy [6, 9, 20].
2. Motor neuropathy is responsible for foot deformities. The atrophy of intrinsic muscles and the unbalance between flexion and extension tendons induce the formation of claw toes, hammer toes, and equine foot, increasing plantar pressure and eventually ulceration [6, 20].
3. Autonomic neuropathy results in dry and fissured skin that may also lead to ulceration [6, 9, 21].

Charcot's Neuropathy

The neuroarthropathy Charcot or Charcot's foot is a serious complication in patients with diabetic neuropathy, usually unilateral. Occurs in 0.08 % up to 13 % of diabetic patients in general [22], but the prevalence is unknown due to underdiagnosis [23]. The presentation is due to exacerbated inflammatory response and increase in osteoclasts activity, leading to bone destruction and progressive displacement of bones and joints [4].

Diagnosis is based on clinical examination of the feet and radiological findings [4]. The differential diagnosis should be done with abscess or severe foot infection. In the acute phase, treatment aims to the: (1) use of anti-inflammatory drugs; (2) prolonged immobilization with a total contact cast and; (3) discharge of the foot weight with appropriate footwear [4].

Peripheral Arterial Disease

Diabetes is one of the main risk factors for the development of peripheral arterial disease. Its prevalence is estimated at 20–58 % of the diabetic population [6, 21]. The vascular history and examination associated with an objective measurement of blood flow impairment are sufficed for diagnosis. This measurement tests can be done by the ankle-brachial index, pulse volume recording, toe systolic pressure, or transcutaneous oxygen measurement. The normal value for the ankle-brachial index (measured with a hand-held Doppler) is equal or greater than 1, since the systolic pressure measured at the ankle should be the same or slightly higher as that measured in the arm in the absence of arterial obstruction of the lower limbs arteries [21, 24].

The vascular history may include symptoms of intermittent claudication or rest pain.

The Vascular examination of the ischemic foot may show some typical signs as pallor after foot elevation, reactive hyperemia after putting the foot downwards, skin atrophy, gangrene, and ulcers with poor and pale granulation [21, 24, 25].

According to the Society for Vascular Surgery (SVS) Wound, Ischemia and Foot Infection (WIfI) classification system, ischemia of the lower limb are stratified in four grades as follows [26]:

- Grade 0: No signs of limb ischemia, with an ankle-brachial index greater than 0.80;
- Grade 1: Ankle-brachial index between 0.79 and 0.60;
- Grade 2: Ankle-brachial index between 0.59 and 0.40;
- Grade 3: Ankle-brachial index lower than 0.39.

Infection

Diabetic foot infection is a feared complication for its association with high amputation and mortality rates. Usually, the infection of a chronic ulcer is the reason for the patient to seek medical attention. The infective process starts in a neuropathic ulcer, which acts as an entry port for contaminant pathogens [27].

In the examination of the wound, the presence of two or more of the following signs is diagnostic for infection: skin erythema, induration, local tenderness or pain, local warmth, and purulent discharge [26].

According to the SVS-WIfI classification system, infection is graduated in four grades, from 0 to 4 as follows [26].

- Grade 0: No signs of infection.
- Grade 1: Mild infections: superficial, and, if erythema is present, it is limited to a 2 cm halo around the ulcer.
- Grade 2: Moderate infections, where deeper tissues are involved, and erythema extend over the 2 cm halo around the wound.
- Grade 3: Severe infection: the patient presents with systemic sepsis, defined by the presence of two or more of the following signs: Temperature higher than 38 °C or lower than 36 °C, heart rate higher than 90 beats per minute, respiratory rate higher than 20 inspirations per minute or a $PaCO_2$ lower than 32 mmHg, and a white blood cell count higher than 12,000 or lower than 4000 or at least 10 % of immature forms.

Wounds

There are several classifications for diabetic foot. Wagner's classification [28] (Table 13.1) is one of the most widely used [9, 26, 29, 30].

Ischemic ulcers have flat, dry, dystrophic, and painful lesions, especially in toes. The neuropathic ulcers lesions are usually located in the plantar region of the

Table 13.1 Diabetic foot rating according to Wagner

Wagner classification	
0	Ulcer absence standing high risk
1	Shallow ulcer
2	Deep ulcer, penetrating ligaments and muscles, but without bone involvement
3	Deep ulcer with cellulitis, abscess, or osteomyelitis
4	Located gangrene restricted to the toes
5	Extensive gangrene

Adapted from: *"Wagner FW, Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle. 1981;2(2):64–122"*

midfoot, in sites of previous callus and hyperkeratosis. The neuroischemic ulcers have characteristics similar to neuropathic and ischemic ulcers together [31].

According to SVS-WIfI classification system, ulcer (or wound) is described as in four grades as follows [29]:

- Grade 0: No ulcers or gangrene;
- Grade 1: Shallow ulcer without bone exposure (except if it is limited to the distal phalanx);
- Grade 2: Deep ulcer in the forefoot/midfoot, with bone involvement, joint or tendon, superficial ulcer in calcaneus, or gangrene restricted to the toes;
- Grade 3: Extensive and deep ulcer in the forefoot/midfoot; deep ulcer on the heel; wide gangrene on forefoot/midfoot; or deep gangrene of the calcaneus.

Diagnosis

The diagnosis of diabetic foot is complex due to a variety of signs and symptoms and the broad spectrum of the clinical manifestations of the disease [32]. The diabetic foot is the result of peripheral neuropathy and peripheral arterial disease. Each one of these factors has its proper diagnosis and should be evaluated individually to identify the diabetic foot [18, 21, 25, 32].

Diabetic Neuropathy Evaluation

The neurologic exam is performed using validated instruments: the Semmes-Weinstein 10 g monofilament and the 128 Hz tuning fork for sensory evaluation and the hammer to test reflexes in the ankle [4, 9].

The patient with diabetic neuropathy is unable to perceive injuries as a result of sensory damage. It is established by an abnormal response to a 10 g monofilament test (esthesiometer) and another instrument, such as tuning fork (for vibration perception threshold) or pinprick sensation test or Achilles reflex test [9, 32]. The

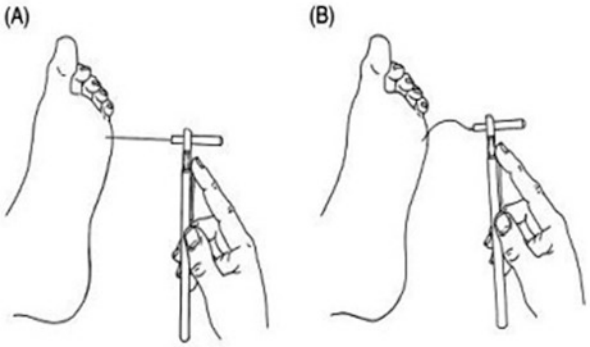

Fig. 13.1 Application of the monofilament. **Reprinted with permission from**: "*Apelqvist J, Bakker K, Van Houtum W, Nabuurs-Franssen M, Schaper N. International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes/metabolism research and reviews. 2000;16(S1):S84–S92*"

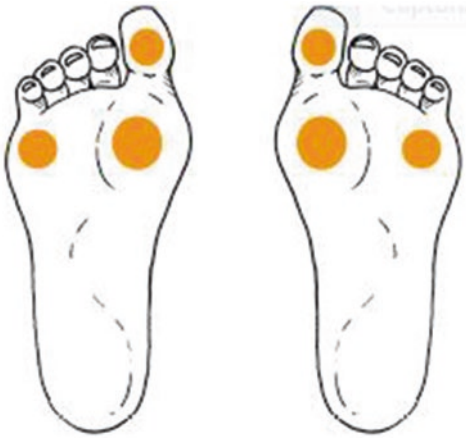

Fig. 13.2 Sites to be tested with monofilaments. **Reprinted with permission from**: "*Apelqvist J, Bakker K, Van Houtum W, Nabuurs-Franssen M, Schaper N. International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes/metabolism research and reviews. 2000;16(S1):S84–S92*"

application of monofilament and the tuning fork and tests are recommended by The International Working Group on the Diabetic Foot as shown in Figs. 13.1, 13.2, and 13.3 [7]. The protective sensation is considered absent when the patient responds to two out of three incorrect answers to the stimulus of the monofilament and the tuning fork [33].

Symptoms of neuropathy can also be registered or measured through the use of specific questionnaires such as the neuropathy disability score and the neuropathy symptom score [34].

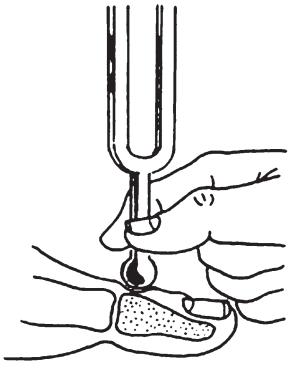

Fig. 13.3 How to use a tuning fork

The reduction in muscle strength during dorsiflexion and plantar flexion indicates motor impairment related to diabetic polyneuropathy. However, musculoskeletal foot deformities are the best evidence for muscle imbalance. The motor muscle impairment ranges from muscle weakness to paralysis, depending on the severity of the neuropathy. The joint mobility of foot and ankle must be checked; musculoskeletal deformities should be identified, and hyperkeratosis areas associated with deformities must be inspected and registered [7, 9, 14]. Gait analysis can be performed by observing the patient walking. Footprinting mat, baropodometry, and quantitative-computerized gait analysis, if available, can also be used [20].

Symptoms and signs of autonomic dysfunction include resting tachycardia, intolerance to exercise, orthostatic hypotension, sudoriferous dysfunction (manifested as anhidrosis of the extremities, which may be accompanied by hyperhidrosis in the trunk), and potentially autonomic failure in response to hypoglycemia [35].

Vascular Assessment

Vascular assessment of the diabetic foot patient should start with pulse palpation. The presence, at least, of one palpable pulse—posterior tibial or dorsallis pedis—indicates enough perfusion to heal wounds and fight infection.

In the pulseless patient, it is mandatory to evaluate limb perfusion with non-invasive tests, such as the ankle-brachial index, pulse volume recording, toe systolic pressure measurement, or transcutaneous oxygen measurement [24].

The ankle-brachial index is the most used test. It is a simple and reproducible test, which gives the physician valuable information about the limb perfusion. An index lower than 0.9 is diagnostic of arterial disease. However, an ankle-brachial index higher than 1.3 indicates that lower limb arteries are barely compressible due to wide medial calcinosis. In this scenario, another non-invasive test should be used.

Pulse volume recording uses photoplethysmography to create graphic forms of arterial pulses. Dampening of these waveforms indicates an upstream stenotic lesion. It is not affected by medial calcinosis.

Toe pressure measurement is also reliable in patients with incompressible ankle-brachial index because toe vessels are usually sparred from calcification. It also is used as a predictor of wound healing, with values lower than 30 mmHg indicating little healing potential [24].

Arterial duplex scanning does not have diagnostic value. It is a complementary test to determine which is the best treatment modality, conventional surgery or endovascular technique. Revascularization should be considered in ischemic patients [24].

Treatment

The treatment of patients with the diabetic foot is complex and requires a multidisciplinary team [10, 18]. Interventions range from preventive and basic modalities to surgical interventions such as revascularizations and limb amputations [8, 25, 32]. Patients with neuropathy or evidence of increased plantar pressure should be properly instructed on foot self-care and supplied with therapeutic footwear and devices to redistribute pressure [8]. Patients with deformities need extra wide and deep shoes, and those with severe deformity (Charcot's foot) need custom-molded shoes. The nonweight bearing will be imperative in the management of plantar ulcers [36]. Total contact cast or other casting techniques or removable devices should be prescribed for this purpose [32, 35, 37].

Table 13.2 Antibiotic according to infection severity

Infection severity	Route of administration	Environment	Antibiotic spectrum	Duration
No infection	–	–	Not necessary	–
Mild	Oral	Outpatient	Gram-positive cocci	1–2 weeks
Moderate	Oral/parenteral	Outpatient/hospitalized	Gram-positive cocci	1–3 weeks
Severe	Parenteral	Hospitalized	Broad-spectrum (including MRSA)	2–4 weeks

See text for definitions on severity [30]
MRSA Meticilin-resistant *Staphylococus aureus*
Adapted from: *"Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2012;54(12):e132–73"*

Antibiotic Treatment

All infected wounds should be treated with antibiotics and adequate wound care. Empiric antibiotic should be provided according to infection severity until antibiotic susceptibility data is available (Table 13.2) [30]. For mild to moderate infections, the regime should target gram-positive cocci. In case of severe infection, broad-spectrum antibiotics should be promptly initiated and directed according to culture results.

The suggested empiric antibiotic therapy is based on the Infectious Diseases Society of America Guideline for Diabetic Foot Infection [30].

For mild infections, oral cephalexin or amoxicillin-clavulanate showed to be effective in treating diabetic lesions. If there is a risk for methicillin-resistant *Staphylococus aureus* infection, the antibiotic should be Doxycycline or Trimethoprim/Sulfamethoxazole [30].

On the other hand, moderate and severe infections should be assessed more aggressively. Initial empiric therapy should consist of Ampicillin-sulbactam, Ertapenem, or Imipenem-cilastatin if the probable pathogen is a multi-sensible *Staphylococcus aureus*, *Streptococcus* sp., or *Enterobacteriaceae*. If meticillin-resistant *Staphylococus aureus* is suspicious, vancomycin is the choice [30].

Surgical Treatment

Debridement

Debridement is the removal of devitalized tissue of the wound bed to expose viable tissue [4]. In the presence of peripheral arterial disease, debridement can increase the wound bed due to tissue necrosis. Therefore, it is appropriate to investigate and optimize the treatment of peripheral arterial disease before and after surgical debridement, except for abscess where infection control must be immediate [38].

To prevent the formation of new wounds, debridement of sites in the foot with hyperkeratosis and calluses at intervals of 1–4 weeks is recommended [39].

The debridement may be performed by different methods: mechanical, autolytic, enzymatic, or surgical. Applying moist gauze to the wound bed performs the mechanical debridement, but it is in disuse because it is painful and is not selective to necrosis, removing viable tissues as well [4]. The autolytic method uses the body's natural action of enzymes leading to lysis of necrotic tissue, through products that keep moist the wound bed. Surgical debridement is the most effective and fast procedure through sharp, sterile blades [4]. Currently, studies have featured the use of maggot therapy from the decomposition of nonviable tissue and remove the bacteria from the wound bed [40].

Revascularization Procedures

In the presence of important peripheral arterial disease, it is necessary to improve foot perfusion if the patients' conditions are satisfactory. Revascularization can be achieved by conventional or endovascular surgery [24, 25].

The conventional surgery uses a graft to bypass the arterial obstruction, restoring the blood flow to the foot. On the other hand, the endovascular technique uses intra-arterial sheaths and guide-wires that, in combination with balloon catheters and stents, promotes the reestablishment of intra-arterial lumen [24, 25].

Limb Amputation

Diabetes is the leading cause of non-traumatic limb amputation [21]. In patients with severe involvement of the foot, amputation may be the only therapeutic choice. The indications are extensive gangrene of toes or the foot, chronic osteomyelitis, and deep tissues invasive infection.

Lower limb amputation can be divided as minor or major. Minor amputation preserves the ankle, therefore allowing the patient to walk without the use of a prosthesis. On the other hand, major amputation is performed above the ankle, with the removal of the entire foot preventing the patient to have a normal gait and consequently being able to ambulate only with a prosthesis.

Wound Care

Dressings

After the effective debridement, it is necessary to choose the dressing (described in Chap. 15) to prepare the wound bed to accelerate the process of granulation and healing [4]. The ideal dressing should keep moist the wound bed, without steep edges, must be safe, non-toxic, hypoallergenic (for health professionals and patient), and non-adherent to the wound bed. Moreover, be accepted by the patient, promote relief of pain and odor, guarantee mobility, be easy to handle, and cost-effective [39]. There is some evidence to indicate a preference for the use of hydrogel and negative pressure therapy [41, 42]. The choice between the options should consider the cost and the properties of each bandage and the characteristics wound [4, 38, 41–45]. Described below are the most used in the market:

(a) Hydrogel: Consists of insoluble polymers (carboxymethyl cellulose) and up to 96 % water [42]. It can be found as amorphous gels and sheet and may be associated with alginate (this increases the power of debridement). It is indicated to keep humidity, maintain optimal pH, promote pain relief, and assist in autolytic debridement (removal of dead tissue). The exchange period can reach up to 7 days for the sheets and 1 day for the gel [46].
(b) Alginate: It is indicated for wounds with moderate to intense exudate, so the contact of product and secretion makes up a gel, keeping the wound bed moist and retaining secretion. After applying it to the wound, it needs to be slightly humidified with saline [45].
(c) Hydrocolloid: It is indicated for wounds with moderate or little exudate. There is also another kind, the fibrous hydrocolloid, or hydrofiber, which is similar to alginate and is suitable for moderate to intense exudation. The exchange period reaches up to 5 days or saturation of the product [43].

(d) Foam: It is composed of hydrophilic polyurethane foam and is indicated for wounds with moderate to intense exudate. When combined with silver, it helps in local control of infection. Exchange period reaches up to 5 days or product's saturation [44].

(e) Negative Pressure Wound Therapy: It has not been well-established in the literature the exact way it acts yet. It is suitable for complex wounds, with moderate to intense exudation. For wounds that need greater stimulation of granulation tissue, some authors report that this therapy is indicated as adjunct therapy to other processes such as the use of grafting [41].

The negative pressure wound therapy works by applying polyurethane foam or sterile gauze sealed with polyurethane film over the wound. A tube is connected directly to a machine that performs the negative pressure (vacuum) about 60–180 mmHg, taking the secretion into a reservoir [41].

(f) Activated charcoal: Helps in removal of liquids and toxins that interfere with the cicatrization process [47]. It is indicated for wounds with low to moderate exudation and foul odor [48].

(g) Cellulose membrane: It comes in a flat sheets shape, with pores of various diameters. Acts as a temporary skin substitute, maintains humidity, and promotes the regeneration of epithelium [49]. Made from nanotechnology, after bacterial fermentation, bacterial cellulose nanofibers are set up in the three-dimensional network [50]. There are no current studies with real evidence about the use of this product.

(h) Petrolatum Gauze Non-Adhering Dressing: This product is formed by a thin pad impregnated with a mix of petrolatum (vaseline) and 3 % tribromophenate bismuth [51]. It is suitable for wounds with granulation tissues, for dry wounds with little exudate, and as an adjunct to other treatments.

Adjuvant Treatments

A recent study by the International Working Group on the Diabetic Foot recommends caution with the use of such therapies because there are not enough studies with strong evidence to justify its use [29].

The use of adjuvant therapy is recommended if the wound does not heal after the use of conventional therapies for a period greater than 4 weeks. These treatments are organic (platelet-derived growth, extracellular matrix products, among others) and hyperbaric oxygen therapy. The choice between these types of treatments depends on availability, cost-effective, wound characteristics, and the patient's clinical status associated with the standard treatment [39].

Cell and platelet system activation, after the use of plasma and platelet growth factors, stimulate and regulate the wound healing process by deploying factors that activate macrophages and epithelial cells, inducing the formation of new capillaries [39]. Hyperbaric oxygen therapy is recommended to use with caution, requiring an evaluation of transcutaneous oximetry to indicate patients with better responses to this therapy [39].

Bioengineered skin grafts reports describe good results when coupled with the negative pressure therapy, with cure rates up to 93 % [4, 39, 52–54].

Table 13.3 Risk classification based on foot examination

Risk category	Definition	Recommended treatment	Follow-up
0	Absence of neuropathy Absence of PAD No deformities	Therapeutic education and advice on footwear	Annually (with the basic care team)
1	Loss of protective sensibility and deformities	Therapeutic education, and footwear prescription for protection and accommodation of deformities	Every 3–6 months (with the specialist team)
2	Loss of protective sensibility and PAD and/or foot deformities	Therapeutic education and footwear prescription, examination, and follow-up with Vascular Surgeon	Every 2–3 months (with the specialist team)
3	History of ulcer amputation	Therapeutic education, advice on footwear and/or orthotics and follow-up with Vascular Surgeon	Every 1–2 months (with the specialist team)

PAD peripheral artery disease
Adapted from: *"Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment. A report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Phys Ther. 2008;88(11):1436–43"*

What Can the Primary Care Physician Do for This Patient?

The general physician is usually the first to handle the patient with diabetic foot. A lot can be done in an outpatient environment. All patients with diabetes must be examined at least once a year for potential foot problems [7, 32]. Initial signs and symptoms of neuropathy and peripheral vascular disease, previous ulcerations, and its healing time, infection, amputation, and interventions should be investigated. The assessment of the risk of ulceration and amputation and a proper follow-up strategy is depicted in Table 13.3 [4, 37].

The essential elements of the diabetic foot evaluation include the search for wounds and infection in the feet on a frequent basis. The physical examination should be performed on all surfaces of the foot, including the spaces between all the toes [9]. Shoes must be inspected for suitability in shape, size, and fabrication material, as well as any gait-assistive device [7, 8, 32].

When to Refer the Diabetic Foot Patient for an Expert?

A follow-up plan should be part of the treatment, focusing on the need for referral to a specialist. The priority, indication, and timelines for referral should be as follows, based on the risk category (Table 13.3) [9].

- Very low risk: Diabetic patients with protective sensation, without peripheral arterial disease, seeking for therapeutic education such as foot care, athletic training, appropriate footwear, preventing injury, etc. (category 0) should be referred within 1–3 months, and with a suggested follow-up annually.

- Low risk: Diabetic patients with loss of protective sensation, nonchanging deformity, requiring prescriptive or accommodative footwear (risk category 1) should be referral within 1 month.
- Moderate risk: Diabetic patients with peripheral arterial disease and loss of protective sensation, dorsalis pedis/posterior tibial pulses diminished or absent, swelling, or edema (risk category 2) must be referral within 1–3 weeks (if the patient is not already receiving regular vascular care).
- High risk: Diabetic patients with a previous history of ulcer or lower extremity amputation (risk category 3) are immediate outpatient referral.
- Urgent (active pathology): Diabetic patients with ulcerative wounds, with signs of infection or not, neuropathic pain or pain at rest, absence of distal pulses or gangrene, and signs of neuroarthropathy at midfoot or ankle (local redness, hyperthermia, and swollen) must be immediately referred to a hospital.

References

1. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005;366(9498):1725–35.
2. Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes Ther. 2012;3(1):1–15.
3. Boulton AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. Diabetes Metab Res Rev. 2008;24(S1):S3–6.
4. Nouvong A, Armstrong DG. Diabetic foot ulcers. In: Cronenwett JL, Johnston KW, editors. Rutherford's vascular surgery. 8th ed. Philadelphia: Elsevier Saunders; 2014. p. 1816–35.
5. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719–24.
6. Hinchliffe RJ, Brownrigg JR, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, et al. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. Diabetes Metab Res Rev. 2016;32 Suppl 1:37–44.
7. Apelqvist J, Bakker K, Van Houtum W, Nabuurs-Franssen M, Schaper N. International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes Metab Res Rev. 2000;16(S1):S84–92.
8. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. 2016;63(2):3S–21.
9. Miller JD, Carter E, Shih J, Giovinco NA, Boulton AJ, Mills JL, et al. How to do a 3-minute diabetic foot exam. J Fam Pract. 2014;63(11):646–56.
10. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev. 2000;16(S1):S75–83.
11. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Vasc Surg. 2010;52(3):17S–22.
12. Júnior A, do Amaral LAH, Bastos MG, do Nascimento LC, Alves MJM, de Andrade MAP. Prevention of lower-limb lesions and reduction of morbidity in diabetic patients. Rev Bras Ortop. 2014;49(5):482–7.
13. Mazlina M, Shamsul A, Jeffery FS. Health-related quality of life in patients with diabetic foot problems in Malaysia. Med J Malaysia. 2011;66(3):234–8.
14. Gerrits EG, Landman GW, Nijenhuis-Rosien L, Bilo HJ. Limited joint mobility syndrome in diabetes mellitus: a minireview. World J Diabetes. 2015;6(9):1108.

15. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J. 2007;4(4):286–7.
16. Izumi Y, Satterfield K, Lee S, Harkless LB. Risk of reamputation in diabetic patients stratified by limb and level of amputation: a 10-year observation. Diabetes Care. 2006;29(3):566–70.
17. Margolis D, Malay D, Hoffstad O, Leonard C, MaCurdy T, de Nava K, et al. Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. In: Rockville M, editor. Data points publication series, 10. Pennsylvania; 2011.
18. Markakis K, Bowling F, Boulton A. The diabetic foot in 2015: an overview. Diabetes Metab Res Rev. 2016;32 Suppl 1:169–78.
19. Hobizal KB, Wukich DK. Diabetic foot infections: current concept review. Diabet Foot Ankle. 2012;3.
20. Fernando M, Crowther R, Lazzarini P, Sangla K, Cunningham M, Buttner P, et al. Biomechanical characteristics of peripheral diabetic neuropathy: a systematic review and meta-analysis of findings from the gait cycle, muscle activity and dynamic barefoot plantar pressure. Clin Biomech. 2013;28(8):831–45.
21. Hinchliffe R, Brownrigg J, Andros G, Apelqvist J, Boyko E, Fitridge R, et al. Effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes Metab Res Rev. 2016;32 Suppl 1:136–44.
22. Frykberg RG, Belczyk R. Epidemiology of the Charcot foot. Clin Podiatr Med Surg. 2008;25(1):17–28. v.
23. Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S. Charcot neuroarthropathy in diabetes mellitus. Diabetologia. 2002;45(8):1085–96.
24. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(1):S1–75.
25. Mills Sr J. Lower limb ischemia in patients with diabetic foot ulcers and gangrene: recognition, anatomic patterns and revascularization strategies. Diabetes Metab Res Rev. 2016;S1:239–45.
26. Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220–34.e1–2.
27. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. Diabetes Care. 2006;29(6):1288–93.
28. Wagner Jr FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle. 1981;2(2):64–122.
29. Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Londahl M, et al. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes Metab Res Rev. 2016;32 Suppl 1:154–68.
30. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132–73.
31. Yotsu RR, Pham NM, Oe M, Nagase T, Sanada H, Hara H, et al. Comparison of characteristics and healing course of diabetic foot ulcers by etiological classification: neuropathic, ischemic, and neuro-ischemic type. J Diabetes Complications. 2014;28(4):528–35.
32. Bakker K, Apelqvist J, Lipsky B, Van Netten J, Schaper N. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev. 2016; 32:2–6.
33. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care. 2000;23(5):606–11.
34. Young M, Boulton A, MacLeod A, Williams D, Sonksen P. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36(2):150–4.

35. American Diabetes Association. (9) Microvascular complications and foot care. Diabetes Care. 2015;38 Suppl 1:S58–66.
36. Bus S, Deursen R, Armstrong D, Lewis J, Caravaggi C, Cavanagh P. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. Diabetes Metab Res Rev. 2016;32:99–118.
37. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, et al. Comprehensive foot examination and risk assessment. A report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Phys Ther. 2008;88(11):1436–43.
38. Bergin S, Gurr J, Allard B, Holland E, Horsley M, Kamp M, et al. Australian Diabetes FootNetwork: management of diabetes-related foot ulceration—a clinical update. Med J Aust. 2012;197(4):226–9.
39. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. 2016;63(2 Suppl):3S–21.
40. Federman DG, Ladiiznski B, Dardik A, Kelly M, Shapshak D, Ueno CM, et al. Wound healing society 2014 update on guidelines for arterial ulcers. Wound Repair Regen. 2016;24(1):127–35.
41. Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2013;10:CD010318.
42. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;7:CD009101.
43. Dumville JC, Deshpande S, O'Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;8:CD009099.
44. Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;6:CD009111.
45. Dumville JC, O'Meara S, Deshpande S, Speak K. Alginate dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;6:CD009110.
46. Ribeiro C, Dias F, Fregonezi G. Hydrogel dressings for venous leg ulcers. Cochrane Database Syst Rev. 2013;CD010738.
47. Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010;19(5):208. 210–2, 214–5.
48. Vaneau M, Chaby G, Guillot B, Martel P, Senet P, Téot L, et al. Consensus panel recommendations for chronic and acute wound dressings. Arch Dermatol. 2007;143(10):1291–4.
49. Qiu Y, Qiu L, Cui J, Wei Q. Bacterial cellulose and bacterial cellulose-vaccarin membranes for wound healing. Mater Sci Eng C Mater Biol Appl. 2016;59:303–9.
50. Bottan S, Robotti F, Jayathissa P, Hegglin A, Bahamonde N, Heredia-Guerrero JA, et al. Surface-structured bacterial cellulose with guided assembly-based biolithography (GAB). ACS Nano. 2015;9(1):206–19.
51. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SE. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010471.
52. Armstrong DG, Marston WA, Reyzelman AM, Kirsner RS. Comparative effectiveness of mechanically and electrically powered negative pressure wound therapy devices: a multicenter randomized controlled trial. Wound Repair Regen. 2012;20(3):332–41.
53. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2015;6:CD004123.
54. Buchberger B, Follmann M, Freyer D, Huppertz H, Ehm A, Wasem J. The importance of growth factors for the treatment of chronic wounds in the case of diabetic foot ulcers. GMS Health Technol Assess. 2010;6:Doc12.

Chronic Venous Disease and Varicose Veins

14

Maíra Faria Braga Pires, Raquel Ferreira Nogueira, and Tulio Pinho Navarro

Abstract

The lower limb venous system is responsible for the return of the blood from the leg toward the heart. Chronic venous disease occurs by a deficiency in the blood return due to structural or functional abnormalities of the veins of the lower limbs. Insufficient venous return leads to the accumulation of blood in the lower limbs and to varying degrees of venous hypertension, presenting a wide spectrum of clinical manifestations, ranging from simple telangiectasies and varicose veins to advanced forms. Chronic venous disease has a large prevalence in the world population and has significant impact on health services for high demand due to disease symptoms, activity limitation and aesthetic concern. Common symptoms are pain, cramps, heaviness, edema, and lower limb ulcer. The presence of tortuous and dilated veins must be noted, as well as telangiectasies, angiomatous formation, edema, and trophic skin alterations. CEAP classification has been proposed in order to standardize the scientific publications about varicose veins and therapeutic indications. Chronic venous disease treatment involves no interventionist actions to control symptoms and improve the quality of life with physical activity, compression therapy, phlebotropic agents, and interventional

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treatment such as sclerotherapy, transdermal laser, or surgery. Today, we have the minimally invasive methods as an alternative of surgery: endovenous ablation with laser or radiofrequency and foam sclerotherapy.

Introduction

The lower limb venous system is responsible for the return of the blood from foot, leg, and thigh toward the heart. There are three types of limb veins: superficial, deep, and perforating, which communicate the superficial veins to the deep veins [1]. They are all interconnected and the disorder present in one affects the others.

Chronic venous disease occurs by a deficiency in the blood return due to structural or functional abnormalities of the veins of the lower limbs. This is by: (1) obstruction of the venous flow (thrombosis or extrinsic compression), (2) reflux due to venous valvular incompetence that can be primary or secondary, or (3) deficiency in the calf muscle pump [2].

Insufficient venous return leads to the accumulation of blood in the lower limb and to several degrees of venous hypertension. Therefore, the chronic venous disease presents a wide spectrum of clinical manifestations, ranging from simple telangectasias (spider veins), reticular veins (subdermal), varicose veins (subdermal and subcutaneous), and leg edema to advanced forms with hyperpigmentation of the skin, dermal sclerosis, and venous ulcers [3].

Varicose veins are tortuous, dilated, and elongated veins, with loss of valvular function and wall changes related to venous hypertension. They are subdermal and subcutaneous, most commonly in lower limbs [4]. There are no classical varicose veins in the deep system due to muscle fascial sheath that prevents the dilation and stretching of the veins. The varicose veins may be (1) primary, of unknown etiology that corresponds to most cases or (2) secondary, resulting from deep vein thrombosis, vascular malformation (like vein or valve agenesis), and congenital or acquired arteriovenous fistulas.

Epidemiology

Chronic venous disease has a large prevalence in the world population, with involvement of 25–33 % of women and 10–20 % of men in the adult population, with proportional increase related to age [5–7]. The prevalence is approximately 37.9 % in the general population. According to the Framingham study, the annual incidence of varicose veins is 2.6 % in women and 1.9 % in men, with a ratio of 2 women to 1 man affected [8]. Chronic venous disease has significant high demand on health services due to the symptoms, activity limitation, and aesthetic concern.

Pathophysiology

Chronic venous hypertension is responsible for the alterations found in chronic venous disease. When the patient lies down, the foot is at the same level as the heart so the blood flows without difficulties. However, it is necessary for the blood to

overcome gravity when the patient is standing. During physical activity, contractility of the calf muscles acts as a pump that ejects the blood back to the heart (calf pump). The venous valves close after the passage of the blood avoiding blood reflux directing the blood stream to the right side of the heart [9].

During standing or sitting, especially after long periods of time, there is no calf muscles action. Then, venous stasis occurs leading to increased intravenous pressure, which may damage the venous walls and valves [9].

Venous hypertension leads to extravasation of plasma and blood elements to the surrounding tissues, mainly for skin and subcutaneous tissue. Red blood cell is degraded in the interstitial space forming hemosiderin and causing skin hyperpigmentation. Considering the microcirculation, the hypertension generates inflammation of the subcutaneous tissue, lipodermatosclerosis, and leukocyte sequestration leading to cellular damage. Fibrin increase in the interstitial tissue hinders the diffusion of metabolites leading to less availability of essentials elements to healing and ulceration eventually [10]. Hemodynamic worsening translates into clinical worsening [11].

Natural History

Varicose veins of the lower limbs are the most frequent presentation of chronic venous insufficiency, affecting 75 % of the patients. Of these, 71 % have varicosities derived from the reflux of the great saphenous vein, making it the most affected vessel in the wide clinical spectrum of chronic venous insufficiency [12]. Primary varicose veins are associated with a normal deep venous system and progress less frequent to more advanced venous disease, when compared to secondary [13]. Some risk factors for its development are: family history for varicose veins, advanced age, obesity, high number of pregnancies, phlebitis, professional prolonged orthostatic position, smoking, physical inactivity, and poor fiber diet [2].

Advanced forms of chronic venous disease with venous dilatation, edema, and ulcers are associated with low mortality rates. However, they present with severe loss of quality of life due to discomfort, high rates of recurrence, and the long evolution, having bad prognosis: 50 % of the ulcers heal in 4 months, 20 % in 2 years, 8 % in 5 years and they have annual recurrence of 6–15 % [14–17].

Lower limbs varicose veins are estimated to affect about one-third of the world population [4]. However, only about 3–6 % of the people with varicose veins will develop stasis ulcers [18]. Therefore, usually the evolution of the majority of the chronic venous diseases are benign and most patients present purely aesthetic discomfort without major problems for health in general.

Varicose veins are a small risk factor for deep vein thrombosis. So, when it occurs, other risk factors of more importance such as venous stasis, malignancy, thrombophilia, trauma, or hormonal replacement should be considered [19].

Superficial thrombophlebitis is often linked to varicose veins complications. It leads to pain and local inflammation. It can occasionally cause deep vein thrombosis if it reaches to the deep venous system through a communicating vein [20].

Clinical Manifestations

The clinical manifestations of chronic venous disease encompass a large spectrum of venous disorder from simple telangiectasies and reticular veins to venous ulcers.

Patients refer symptoms such as lower limbs pain, heaviness, edema, cramps, burning, itching, or tingling in different intensity degrees [4]. Symptoms are more pronounced at the end of the day (after long periods of orthostatic position) and in hot weather, worsening in summertime. It gets better with horizontal decubitus and lower limb elevation.

Hormonal action also influences the manifestations, with larger number of complaints during the premenstrual period and in the presence of hormone replacement or oral contraceptives use.

In advanced cases occur skin alterations such as eczema, dermatitis, hyperpigmentation (secondary to hemosiderin deposition), lipodermatosclerosis, and blanche atrophie. It can also occur wounds (stasis ulcer) mainly in malleolar region, phlebitis, and occasional bleeding [21].

Classification

CEAP classification has been proposed in order to standardize the scientific publications regarding varicose veins and therapeutic indications and takes into account the knowledge about the pathophysiology of venous disease, diagnostic methods, and the different concepts of the meaning of chronic venous insufficiency. This classification is related to four criteria: clinical (C), etiological (E), anatomical (A), and pathophysiological (P) and was adopted worldwide, being the most used currently.

CEAP classification is shown in Table 14.1 [22]:

Table 14.1 Basic CEAP classification [22]

Clinical classification (C): from 0 to 6
C0 No visible sign of venous disease
C1 Telangiectasies or reticular veins
C2 Varicose veins
C3 Edema
C4 Changes in skin and subcutaneous tissue
4a Pigmentation or eczema
4b Lipodermatosclerosis or atrophie blanche
C5 Healed ulcer
C6 Active ulcer
S: symptomatic
A: asymptomatic
Etiological classification (E)
Ec Congenital
Ep Primary
Es Secondary (post-thrombotic syndrome, trauma)
En No venous cause identified

(continued)

Table 14.1 (continued)

Anatomical classification (A)
As Superficial veins
Ad Deep veins
Ap Perforator
An No venous location identified
Pathophysiological classification (P)
Pr Reflux
Po Obstruction, thrombosis
Pr,o Reflux and obstruction
Pn No venous pathophysiology identified

Excerpted with permission from: *"Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004; 40: 1248–52"*

Table 14.2 Definitions about CEAP clinical (C) classification [22]

Corona phlebectatica	Fan-shaped pattern of numerous small intradermal veins on medial or lateral aspects of ankle foot
Telangiectasia	Confluence of dilated intradermal venules less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins
Reticular vein	Dilated bluish subdermal vein, usually 1 mm to less than 3 mm. Usually tortuous. Excludes normal visible veins in persons with thin, transparent skin. Synonyms include blue veins, subdermal varices, and venulectasies
Varicose vein	Subcutaneous dilated vein 3 mm in diameter or larger, measured in upright position. May involve saphenous veins, saphenous tributaries, or no saphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. Synonyms include varix, varices, and varicosities
Edema	Perceptible increase in volume of fluid in skin and subcutaneous tissue, characteristically indented with pressure. Venous edema usually occurs in ankle region, but may extend to leg and foot
Eczema	Erythematous dermatitis, which may progress to blistering, weeping, or scaling eruption of skin of leg. Usually seen in uncontrolled chronic venous disorder, but may reflect sensitization to local therapy
Pigmentation	Brownish darkening of skin, resulting from extravasated blood. Usually occurs in ankle region, but may extend to leg and foot
Atrophie Blanche (White atrophy)	Localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Should not to be confused with healed ulcer scars
Venous ulcer	Full-thickness defect of skin, most frequently in ankle region, that fails to heal spontaneously and is sustained by chronic venous disorder

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For a better understanding of the various CEAP clinical classes (C), precise definitions of each were described as shown below in Table 14.2 [22].

The Figs. 14.1, 14.2, 14.3, 14.4, 14.5, and 14.6 represent CEAP clinical classification from C1 to C6 respectively.

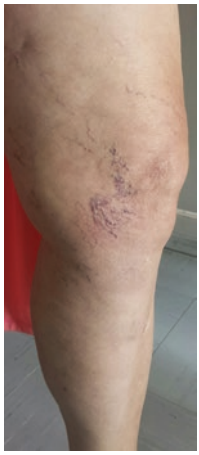

Fig. 14.1 CEAP C1: Telangiectases and diffuse reticular veins

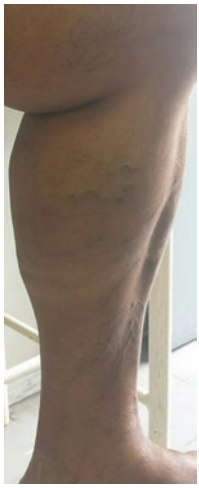

Fig. 14.2 CEAP C2: Varicose veins

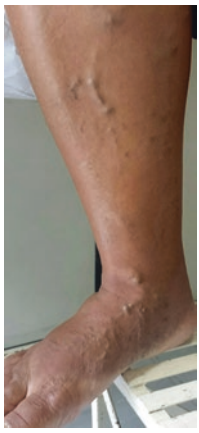

Fig. 14.3 CEAP C3: Right lower limb edema associated with varicose veins

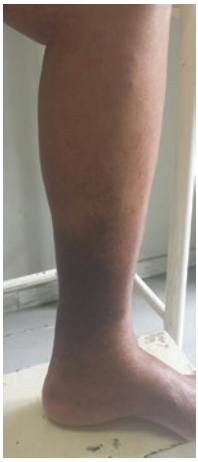

Fig. 14.4 CEAP C4: Hyperpigmentation and eczema

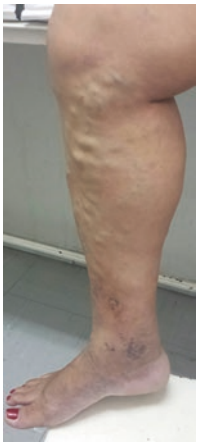

Fig. 14.5 CEAP C5: Healed ulcer in right medial malleolus

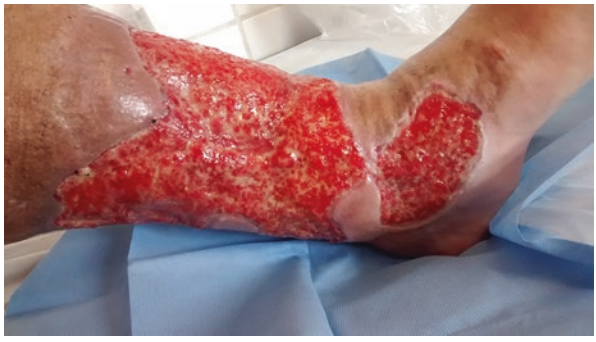

Fig. 14.6 CEAP C6: Granulated circumferential venous ulcer

Diagnosis

Chronic venous disease diagnosis is made by medical history and physical examination.

Common symptom is pain, reported by the patient as heaviness or cramps, being exacerbated by prolonged orthostatic position and relieved by lower limb elevation and bed rest [21].

The physician should also inquire about the period of evolution of the disease, the manner and intensity of progression, the influence of the weather, particularly in hot seasons, the use of estrogens and worsening in menstrual period, the number of pregnancies and the variations observed during this period and in puerperium, the occupation, as well as the posture at work, daily activities in general, with the estimated period of orthostatic, the frequency and type of physical exercises, the existence of varicose veins in the family.

At physical examination, the presence of tortuous and dilated veins must be noted, as well as telangiectasies, angiomatous formation, edema, and trophic skin alterations [21]. Lower limb pulses examination in patients with varicose veins is essential to exclude concomitant peripheral artery disease, which could change the treatment approach. Noninvasive tests like the lower limb venous duplex scan may be requested after the decision to make an intervention. They confirm the diagnosis and evaluate the etiology, whether primary or secondary, and the anatomy of the affected vessels. These tests will be better discussed in another chapter of this book.

Differential Diagnosis

Chronic venous disease manifestations can be confounded with other diseases.

Pain in the morning or just when the person takes the orthostatic position are probably not of venous origin; as well as pain at the lateral part of the thigh, which suggests nerve irritation. Pain at the knee joint, worsening after effort is typical of osteoarthritis and when located in inguinal region could be hip osteoarthritis, tendinitis, or nerve injury.

There are several systemic diseases that manifest with lower limb edema such as cardiac failure, nephrotic syndrome, liver disease, endocrine dysfunction, kidney failure, metastatic cancer, and autoimmune and inflammatory diseases. In addition, it could be considered as side effect of some medications such as calcium channel blockers, oral hypoglycemic agents, anti-inflammatory drugs, among others [21].

Deep vein thrombosis should be kept in mind if there is previous history of trauma, prolonged immobilization or major surgery. However, it should also be differentiate with: rupture of Baker's cyst, hematoma due to gastrocnemius muscle rupture, lymphedema, and erysipelas. In manifestations such as pigmentation and dermatosclerosis, the differential diagnosis should be made with dermatitis, myxedema, skin necrosis, and purpura [21].

Treatment

Clinical Treatment

Chronic venous disease initial treatment involves no interventionist action to control symptoms and improve the quality of life, as well as to prevent the development of secondary complications and disease progression. Lifestyle modifications, such as the practice of regular physical activity, intermittent elevation of the limb and weight loss should be encouraged. Compression therapy and occasionally pharmacotherapy could also be added as part of the clinical treatment.

If clinical treatment is insufficient, invasive treatment should be considered according to the anatomy and pathophysiology of the patient. Specific treatment is based on the disease's severity. Patients classified as CEAP C4 to C6 often require invasive treatment and early treatment of patients CEAP C3 could prevent disease progression to more advanced classes [23].

Compression Therapy

Compression therapy is an essential component in the treatment of patients with chronic venous disease. It promotes a graduated external compression of the leg to oppose the hydrostatic force of venous pressure that is main pathogenic factor of the disease. It also improves calf pump function, increasing the velocity of venous flow, with good effects on the microcirculation, improving the oxygenation of the skin and lymphatic circulation [23]. However, it is not efficient to prevent the disease progression [24].

External compression above 60 mmHg in patients in standing position causes the occlusion of limb vessels, which could harm the skin circulation. Therefore, this value is considered to be the safe upper limit for compression therapy [23].

Several compression methods are available: graduated compression stockings, Unna boot, elastic and nonelastic bandages, and intermittent pneumatic compression.

Graduated Compressive Stockings

Compressive stockings are designed to have the highest compressive pressure at the ankle. The compression progressively reduces from the ankle to one-third at the upper leg and a half at the thigh.

The socks are available in four scales: 15–20 mmHg, 20–30 mmHg (gentle compression), 30–40 mmHg (medium compression), 40–50 mmHg (high compression), and three lengths: 3/4 (below the knee), 7/8 (thigh), and pantyhose. Usually, the 3/4 stocking is sufficient to control the symptoms.

The appropriate stocking size is provided according to the patient's measures (thigh, calf, and ankle). Some obese patients or those with advanced chronic venous disease may require special size, and therefore it should be customized. The durability of the elastic stocking is 6–9 months, once the elasticity expires after that period [24].

Unna Boot

Unna boot is an artisanal preparation of a multilayer inelastic bandage for the lower limbs. The strips are impregnated with a paste consisting of zinc oxide,

glycerin, and gelatin. This bandaging allows movement of the ankle joint and the normal gait, helping the functioning of the calf muscle pump, preventing the occurrence of edema, improving the skin and subcutaneous microcirculation, which accelerates the healing of stasis ulcer [25]. Not every patient is well adapted to the Unna boot, and it has to be changed weekly by a health professional, which makes its use difficult for many patients. Furthermore, the Unna boot cannot be used in the presence of infection.

Elastic and Nonelastic Bandages

Compressive bandages are used in single or multiple layers for patients with advanced chronic venous disease. When applied, the pressure, the number of layers, the components, and the elastic properties of the material to be used should be considered. The bandage can be elastic and nonelastic. The main disadvantage of the nonelastic bandage is the loss of pressure when the limb loses its volume. Training in the bandage application is important once incorrect preparation can cause additional ulcers. The elastic bandage is easier to apply. It should be applied in order to have a higher pressure than the resting pressure. Drawbacks are some possible discomfort when using it and the possibility of ulcers, especially in bony prominences when adequate coverage is not applied [24].

Intermittent Pneumatic Compression

Pneumatic compression is a mechanical compression where an external force is applied by intermittent insufflation pneumatic boots. It can be used in the treatment of venous leg ulcers and lymphedema. The device is somewhat expensive, and therefore it may be a less accessible treatment for the general population [26].

Pharmacotherapy

Phlebotropic agents are drugs with venoactive properties, increasing venous tone and reducing capillary permeability. They have an anti-edema action by decreased capillary permeability, improved lymphatic drainage, venoconstriction, and anti-inflammatory action [27]. There are several classes of such drugs: flavonoids (ɣ-benzopyrones), coumarins (α-benzopyrones), saponosides (horse chestnut and extracts), among others. However, there is insufficient scientific evidence to prove their effectiveness in the treatment of chronic venous disease and stasis ulcer. It is suggested in present trials some efficacy in controlling edema and healing of venous ulcers, but further studies are still needed [28, 29]. Available trials in current literature must be interpreted cautiously since they are poorly reported and have an unclear risk of bias favoring the drugs [29].

Interventional Treatment

Sclerotherapy

Sclerotherapy is the injection of a chemical substance in the vein lumen, causing endothelial damage and consequently vein thrombosis and eventually fibrosis of the

vessel [30]. It can be used to treat veins with different calibers although it is normally used for telangiectasies and reticular veins treatment. There are several types of sclerosing agents, and they may be used in liquid form for the smaller veins and as foam for the larger ones. Sclerotherapy is used as a primary treatment or in conjunction with surgery to correct chronic venous disease [31].

Relative contraindications to sclerotherapy are: asthma, advanced diabetes complications, hypercoagulable state, leg edema, peripheral occlusive arterial disease, chronic renal failure. Absolute contraindications are: medicine allergy, cellulitis or other acute skin disease, acute respiratory disease, severe systemic disease, migratory phlebitis, acute superficial thrombophlebitis, pregnancy, hyperthyroidism, bedridden patients [32].

A common complication of sclerotherapy is skin hyperpigmentation by hemosiderin deposit. Such hyperpigmentation may be avoided by microthrombectomy in the thrombosed varicose vein to drain the clot causing less pain and inflammation by mini punctures [33]. Other complications are neoangiogenesis, injection pain, and itching after the procedure. Some rare complications include skin necrosis, thrombophlebitis, anaphylaxis, deep vein thrombosis, and pulmonary embolism.

Transdermal Laser and Intense Pulsed Light

Transdermal laser and intense pulsed light (IPL) are therapies that have arisen as a treatment option for spider veins and telangiectasies, in addition to sclerotherapy. They penetrate the skin to reach the vein to be treated without causing damage to it or to the surrounding tissues [34]. They are used for telangiectasies and reticular veins smaller than 3 mm [35, 36]. For each type of vein to be treated, it should be selected the wavelength, pulse duration, and beam diameter [37]. The action mechanism of these lasers is the light absorption by the hemoglobin. The absorbed light is converted into thermal energy which causes coagulation of the targeted vessel [38].

Indications for transdermal laser and intense pulsed light include smaller veins than a 30G needle, "matting" (vascular neoformation), sclerosing resistant veins, and patients with needle phobia [39]. Contraindications are: pregnancy, hypertrophic scars or keloids, use of anticoagulants, tanned skin, and photosensitive diseases [38].

Complications are: transient rash, hyperpigmentation, hypopigmentation, "matting," thrombosis, damage to the skin, skin burning, purpura, and local pain [38].

Surgical Treatment

Surgical treatment of lower limbs varicose veins is indicated in the presence of pain, aesthetic discomfort, or in the presence of disease complications such as superficial phlebitis, bleeding, lipodermatosclerosis, and ulcers (active or healed).

Traditional phlebectomy is invasive and painful. Today, we have the minimally invasive methods as an alternative: endovenous ablation with laser or radiofrequency and foam sclerotherapy. They offer the benefits of a faster recovery with less physical limitation, reduction of complications, and increased quality of life [40].

Surgical complications are: lesions in the femoral artery or vein, motor nerve and sensory nerve injury, deep vein thrombosis, infections, superficial phlebitis, and lymphedema.

Endovenous Ablation

Endovenous ablation uses thermal energy to obliterate the vein by laser or radiofrequency, leading to vessel thrombosis and eventually fibrosis. This technique is commonly used to the incompetent saphenous vein as an alternative to conventional stripping and to the tributaries as an alternative to conventional surgical phlebectomy [2]. The procedure is done guided by ultrasound under local or regional anesthesia in a procedure suite.

Complications such as paresthesia, rupture of the vein, superficial thrombophlebitis, deep venous thrombosis and pulmonary embolism, skin burn, infection, pigmentation, bruising, neovascularization, hemorrhage, and necrosis may occur although it is considered less invasive than conventional surgery [2].

Contraindications for the procedure includes: superficial or deep vein thrombosis, aneurysm, and ankle-brachial systolic pressure index lower than 0.9.

Radiofrequency Ablation

Radiofrequency ablation is a minimally invasive procedure that effectively treats venous reflux, with minimal discomfort to the patient and shorter recovery time, providing less time of work.

For its realization, it is used as catheter ("ClosureFAST") [41] which has a bipolar 7 cm electrode at the tip, where the heat energy is dissipated. The catheter contact with the vein wall produces endothelium destruction and vein wall occlusion by collagen contraction and thrombus formation.

Endovenous Laser Ablation

Endovenous laser ablation has many similarities with radiofrequency, but there are some differences in the catheter and the ablation mechanism. The laser uses a fiber that dissipates thermal energy, generating heat and vapor bubbles that destroy the target vein endothelium. This creates an inflammatory reaction resulting in an effective thrombotic occlusion and eventually fibrosis.

Several wavelengths are used for endovenous laser: 810, 940, 980, 1064, 1319, 1320, and 1470 nm [42]. These wavelengths differ in the ability to absorb water and hemoglobin. Recent researches suggest that the various wavelengths are equally effective, but the greater length present with lower levels of pain and bruising.

Comparison Between the Methods

Ablation is compared to conventional surgery in effectiveness. However, in the conventional surgery group, more postoperative pain and bruising were observed. On the other hand, phlebitis and hyperpigmentation was higher in the thermal ablation

group [43]. Comparing laser and radiofrequency ablation, foam sclerotherapy and stripping for saphenous vein reflux treatment, the methods were similar in efficacy. However, the late results of foam sclerotherapy were more unfavorable, with higher rates of recanalization. Either in radiofrequency or in foam sclerotherapy method, the patient's recovery was faster compared to conventional surgery and laser [44].

Primary failure and disease recurrence comparing endovenous or radiofrequency laser ablation and conventional surgery had no significant statistical difference. However, intravenous ablation showed less bruising, lower rates of wound infection, less pain, and faster return to daily activities [45].

Patients with advanced CEAP class (C5 and C6) appear to have benefit from use of endovenous ablation. Radiofrequency and endolaser are preferably recommended to open surgery because they reduce convalescence and decrease morbidity and postoperative pain [2].

What the Generalist Can Do?

Inform the patient that the disease is benign. The practitioner should also recommend some physical activity, the use of gradient elastic stockings, and stimulate lifestyle modification and weight loss. Interventional treatment should be indicated in cases of pain or complications such as edema, lipodermatoesclerosis, phlebitis, or ulcers.

When to Refer to the Expert?

The patient must be referred in cases of complications such as pain, edema, lipodermatoesclerosis, phlebitis, and ulcers or if he wishes to be operated.

References

1. Rutherford RB. Venous physiology. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: WB Saunders; 2014. p. 150–3.
2. Rutherford RB. Chronic venous disorders: general considerations. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: WB Saunders; 2014. p. 843–56.
3. Nicolaides AN, et al. Investigation of chronic venous insufficiency: a consensus statement. Circulation. 2000;102:126–63.
4. National Institute for Health and Care Excellence: Clinical Guidelines. Varicose veins in the legs: the diagnosis and management of varicose veins. Copyright National clinical Guideline Centre; July 2013.
5. Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. J Epidemiol Community Health. 1981;35(3):213–7.
6. Beaglehold R, Salmond CE, Prior IA. Varicose veins in New Zealand: prevalence and severity. N Z Med J. 1976;84(576):396–9.
7. Coon WW, Willis 3rd PW, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. Circulation. 1973;48(4):839–46.

8. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham Study. Am J Prev Med. 1988;4(2):96–101.
9. Burnand KG. The physiology and hemodynamics of chronic venous insufficiency of the lower limb. In: Gloviczki P et al., editors. Handbook of venous disorders. 2nd ed. New York: Arnold Publisher; 2001. p. 49–57.
10. Rutherford RB. Venous pathology. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: WB Saunders; 2014. p. 170–3.
11. Navarro TP, Delis KT, Ribeiro AP. Clinical and hemodynamic significance of the greater saphenous vein diameter in chronic venous insufficiency. Arch Surg. 2002;137:1233–7.
12. Goren G, Yellin AE. Primary varicose veins: topographic and hemodynamic correlations. J Cardiovasc Surg (Torino). 1990;31:672–7.
13. Nicolaides AN, et al. The value of dynamic venous pressure measurements. World J Surg. 1986;10:919–24.
14. Skene AI, Smith JM, Dore CJ, Charlett A, Lewis JD. Venous leg ulcer: a prognostic index to predict time to healing. BMJ. 1992;305:1119–21.
15. Callum MJ, Harper DR, Dale JJ. Chronic ulcer of the leg: clinical history. Br Med J. 1987;294:1389–91.
16. Mayberry JC, Moneta GL, De Frang RD, Porter JM. The influence of elastic compression stockings on deep venous hemodynamics. J Vasc Surg. 1991;13:91–100.
17. Dinn E, Henry M. Treatment of venous ulceration by injection sclerotherapy and compression hosiery: a 5 year study. Phlebology. 1992;7:23–6.
18. Nelzen O. Prevalence of venous leg ulcer: the importance of the data collection method. Phlebolymphology. 2008;15(4):143–50.
19. Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. Curr Opin Pulm Med. 2010;16(5):448–52.
20. Decousus H, Quéré I, Presles E, et al. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med. 2010;152:218–24.
21. Eberhardt RT, et al. Contemporary review in cardiovascular medicine. Chronic venous insufficiency. Circulation. 2005;111:2398–409.
22. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg. 2004;40:1248–52.
23. Partsch B, et al. Calf compression pressure required to achieve venous closure from supine to standing positions. J Vasc Surg. 2005;42:734–8.
24. Rutherford RB. Chronic venous disorders: nonoperative treatment. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: WB Saunders; 2014. p. 858–67.
25. Bergan JJ, Sparks SR. Non-elastic compression: an alternative in management of chronic venous insufficiency. J Wound Ostomy Continence Nurs. 2000;27(2):83–9.
26. Feldman JL, et al. Intermittent pneumatic compression therapy: a systematic review. Lymphology. 2012;45:13–25.
27. Ramlet AA. Pharmacologic aspects of a phlebotropic drug in CVI associated edema. Angiology. 2000;51:19–23.
28. Martinez MJ, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2005;3:CD003229.
29. Scallon C, Bell-Syer SE, Aziz Z. Flavonoids for treating venous leg ulcers. Cochrane Database Syst Rev. 2013;5:CD006477.
30. Thibault P. Sclerotherapy and ultrasound-guided sclerotherapy. In: Bergan J, editor. The vein book. Boston: Elsevier; 2007.
31. Gloviczki P, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53(5):2–48.
32. Rutherford RB. Varicose veins: endovenous ablation and sclerotherapy. In: Rutherford RB, editor. Vascular surgery. 8th ed. Philadelphia: WB Saunders; 2014. p. 885–901.
33. Scultetus AH, et al. Microthrombectomy reduces postsclerotherapy pigmentation: multicenter randomized trial. J Vasc Surg. 2003;38:896–903.

34. Sadick NS. Laser treatment of leg veins. Skin Ther Lett. 2004;9.
35. Passeron T, et al. The new 940 nanometer diode laser: an effective treatment for leg venulectasia. J Am Acad Dermatol. 2003;48:768–74.
36. Fournier N, et al. Treatment of leg telangiectasias with a 532 nm KTP laser in multi-pulse model. Dermatol Surg. 2002;28:564–71.
37. Anderson RR, et al. Mechanisms of selective vascular changes caused by dye lasers. Lasers Surg Med. 1983;3:211–5.
38. Sadick N, et al. Laser treatment of telangiectasias and reticular veins. In: Bergan J, editor. The vein book. Boston: Elsevier; 2007.
39. Lupton J, et al. Clinical comparison of sclerotherapy versus long-pulsed Nd: YAG laser treatment for lower extremity telangiectasias. Dermatol Surg. 2002;28:694–7.
40. Carroll C, Hummel S, Leaviss J, Ren S, Stevens JW, Everson-Hock E, Cantrell A, Stevenson M, Michaels J. Clinical effectiveness and cost-effectiveness of minimally invasive techniques to manage varicose veins: a systematic review and economic evaluation. Health Technol Assess. 2013;17(48):i–xvi, 1–141.
41. VNUS Medical Technologies, Inc. VNUS Closure FAST Radiofrequency brochure. San Jose: VNUS Medical Technologies Inc [VN25-91-A]; 2006.
42. Goldman MP. Intravascular lasers in the treatment of varicose veins. J Cosmet Dermatol. 2004;3:162–6.
43. Rasmussen LH, et al. Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short-term results. J Vasc Surg. 2007;46:308–15.
44. Rasmussen LH, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg. 2011;98:1079–87.
45. Siribumrungwong B, Noorit P, Wilasrusmee C, Attia J, Thakkinstian A. A systematic review and meta-analysis of randomized controlled trials comparing endovenous ablation and surgical intervention in patients with varicose vein. Eur J Vasc Endovasc Surg. 2012;44(2):214–23.

Vascular Anomalies

15

Alexandre de Tarso Machado

Abstract

This chapter is about tumors and malformations affecting the arterial, venous, and/or lymphatic system in a wide clinical manifestation and may compromise any anatomical site, within the cranium, neck, chest, abdomen, pelvis, and limbs. Symptomatic patients with hemorrhage, muscular pain, movement limitation, coagulopathy, aesthetic discomfort, or deformity have indications to be treated based on Mulliken and Glowacki's classification (modified by the International Society for the Study of Vascular Anomalies) in which vascular anomalies were divided according to cellular features, clinical presentation, natural history, and treatment into hemangiomas and vascular malformations. Besides, that contains tips dedicated to non-specialists and also objective topics for students in formation.

Vascular anomalies are tumors and malformations affecting the arterial, venous, and/or lymphatic system [1]. They may present in different clinical forms: without symptoms, as internal or external hemorrhage or tumors, causing extrinsic compression of structures (for example, the airway), or leading to muscular and articular pain, movement limitation, coagulopathy due to trapping of coagulation factors, aesthetic discomfort, deformity, and even death [1]. Any anatomical site may be affected, within the head, neck, chest, abdomen, pelvis, and limbs.

In 1982, Mulliken and Glowacki proposed a classification in which vascular anomalies were divided according to cellular features, clinical presentation, natural history, and treatment into hemangiomas and vascular malformations [3].

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In 1996, this classification was modified and adopted by the International Society for the Study of Vascular Anomalies [1, 3] that divided the lesions into vascular tumors (hemangiomas and other proliferative tumors) and vascular malformations (capillary, venous, lymphatic, arterial, and combined malformations). While tumors are caused by endothelial proliferation, malformations occur due to abnormal vessel morphogenesis [1, 4]. However, tumors and malformations may coexist [4].

Epidemiology

Vascular Tumors

Vascular tumors may be comprehensively divided into congenital or acquired, with infantile hemangioma being the most common type [3]. From a clinical standpoint, it is important to distinguish congenital vascular tumors from vascular malformations (Table 15.1) [4–6].

Vascular tumors are characterized by: (a) proliferation of endothelial cells; (b) become evident at birth in approximately 40 % of the cases (generally as precursor lesions); (c) grow rapidly after birth; and (d) show spontaneous involution after the first year of life, in a process that may span the first decade of life. The frequency ratio between women and men is 5:1 [5, 6].

Vascular Malformations

In vascular malformations, the endothelial cells follow a normal cycle. These lesions are characterized by manifesting at birth in 90 % of the cases, not regressing

Table 15.1 Classification of vascular anomalies according to the nomenclature and classification adopted by the International Society for the Study of Vascular Anomalies with correct terminologies and out-of-use equivalents to be avoided [6]

Recommended correct terminology	Correlative terminology to be avoided
Congenital vascular tumors	
Infantile hemangioma	Capillary hemangioma
Congenital hemangioma	Strawberry hemangioma
Hemangioendothelioma	
Low-flow malformations	
Capillary malformation	Port wine hemangioma
Venous malformation	Cavernous hemangioma
Lymphatic malformation	Cystic hygroma/lymphangioma
Combined malformation (without an arterial component)	
High-flow malformation	
Arteriovenous malformation	
Arteriovenous fistula	
Arterial malformation	
Combined malformation (with an arterial component)	

Adapted From: "*Gontijo B, Pereira LB, Silva CMR. Vascular malformations. An Bras Dermatol. 2004; 79(1):7–25*"

spontaneously and growing proportionally to the child's growth, triggered by physiological, endocrine, traumatic, or infectious stimuli. The female-to-male ratio is 1:1 [5, 6].

According to the nature of the vascular channels, vascular malformations are categorized into capillary, arterial, venous, lymphatic, or combined. They may be additionally classified as high-flow or low-flow malformations [1, 2]. High-flow malformations include arterial and arteriovenous malformations and arteriovenous fistulas, whereas low-flow malformations include venous, lymphatic, lymphovenous, and capillary malformations (Table 15.1) [3–5].

Natural History of the Disease

The lesions may be localized or diffuse and may have a self-limited course. They may cause cosmetic or functional problems such as pain, osteomuscular limitations, extrinsic airway compression, coagulopathy, hemorrhage, and deformity, in addition to compromising the function of involved organs and, in the most severe cases, leading to death [4].

Most of the time, vascular tumors resolve spontaneously [1, 2]. Therefore, follow-up is, in principle, the only recommendation for asymptomatic and potentially risk-free vascular tumors (including bulky hepatic hemangiomas) [6].

The prognosis of vascular malformations depends on the occurrence of symptoms requiring resection, location, and extension of the lesion, surgery-induced sequelae, compression of vital structures such as the airway, heart, and central nervous system, and risk of bleeding [7]. For example, lesions located in the central nervous system versus those in the extremities, or lesions in the ear lobe versus those affecting an entire lower limb. However, due to the minimally invasive characteristics of the therapies (embolization for high-flow malformations and direct puncture sclerotherapy for low-flow malformations), it is possible to minimize complications, when compared to the surgical treatment [5].

Vascular malformations often increase progressively in size. Treatment is then recommended, except in small asymptomatic lesions located in areas of difficult access [1].

Clinical Presentation and Diagnosis

The diagnosis in most cases is based on clinical parameters, time of manifestation, lesion characteristics, and progression [3]. The extension of superficial lesions may be determined without much difficulty. But in those with deep extension lesions that aren't obvious on physical exam, imaging is required for complete diagnosis [6].

Vascular Tumors

Vascular tumors often present as a reddish lesion with little or no compressibility. They are often warm and may or may not present thrill and bruit [4, 5].

High-Flow Malformations

High-flow malformations have anomalous communications between the arterial and venous systems. This communication may occur directly (arteriovenous fistula) or through entangled vascular loops (*nidus*) without peripheral vascular resistance, directing the arterial flow to the venous sector [3]. Arterial malformations may cause severe clinical problems such as ischemia with tissue necrosis, pain, and skin ulceration in the most severe cases secondary to sequestration of distal arterial flow, in addition to hemorrhage and heart failure caused by volume overload as a consequence of the high-output arteriovenous fistula. On physical examination, the mass is compressible and refills fast. Thrill and murmur are often detected [6].

Low-Flow Malformations

Venous Malformations

In low-flow venous malformations, the mass is compressible but refills slowly. The temperature is generally unchanged, no bruit or thrill is detected, and venous stasis with varicose veins may occur. The skin covering the tumor is usually thin and bluish [5].

Anatomical structures may be locally or extensively affected leading to deformities. These malformations may eventually involve deeper structures such as the subcutaneous tissue or muscles in one of the limbs. In this case, the skin has a normal appearance and the malformation presents as a tumor painful to palpation [5].

Klippel–Trénaunay–Weber syndrome is an example of this category and is defined as the association of hemangioma, venous ectasia, and soft-tissue hypertrophy of the affected body segment. Although a rare congenital condition, its importance is due to its clinical consequences involving the affected limb [7].

Lymphatic Malformations

Lymphatic malformations also involve soft tissues and have a firmer consistency. They occur due to cyst formation as an expression of the lymphatic system anomaly [3]. They frequently develop before the age of 2 years and are more often located in the head and neck (70 %) or axillary areas (20 %) [5], although they may occur in the extremities, pelvis, or retroperitoneum. The skin is generally normal, but the occurrence of small vesicles is common [7].

Imaging Methods

Doppler ultrasound (US) and magnetic resonance angiography are the two most recommended methods to demarcate the malformation, detect associated anomalies, and define the treatment [7].

Doppler Ultrasonography

US allows a dynamic assessment of the vessels and is sufficient to evaluate superficial lesions. Technical contraindications include vascular lesions located close to bone surfaces or cavities with a gaseous content (such as the chest and intestines, and within the cranium) where the echoes generating the images have poor penetration [3, 8, 9].

Magnetic Resonance Angiography

Magnetic resonance angiography has high sensitivity and specificity to assess the angioarchitecture and extension of the vascular lesion and the involved organs throughout the body [9]. However, it has a significantly higher cost and lower availability when compared with US [9].

Computed Tomography

Computed tomography with intravenous contrast (angiotomography) may be used in cases of difficult evaluation by magnetic resonance angiography without compromising the assessment of involved vessels, but with some loss in the assessment of soft parts [9].

Angiography

Diagnostic angiography with catheterization of the vessels of the lesion is indicated in those cases in which other noninvasive diagnostic methods are inconclusive. And when treatment is being performed by showing details about the angioarchitecture helping to decide the best technique to arterial embolization, for example [8, 9].

Differential Diagnosis

In addition to differentiating between the types of vascular anomalies, tumors, or malformations, other diseases not falling under the definition of vascular anomalies should be excluded [1–6]. They include acquired arteriovenous fistulas due to trauma, iatrogenesis, tumor, or secondary to inflammatory processes (such as pancreatitis). Hypervascularized malignant neoplasms are also included in this list, and they have a distinct prognosis and treatment.

Table 15.2 List with the main differential diagnoses related to vascular anomalies [5, 7]

Differential diagnoses
• Reactive lesions (for example, pyogenic granuloma and inflammatory fibroma)
• Hypervascularized malignant neoplasias (for example, hepatocarcinoma, hypernephroma, and vascularized metastases of some tumors)
• Hypervascularized benign neoplasias (for example, leiomyoma and adenofibroma)
• Kaposi's sarcoma
• Petechiae and ecchymoses (generally associated with dyscrasia)
• Varicose veins secondary to venous hypertension
• Scarlet fever
• Contact allergy
• Erythroplasia (cheilitis, buccal mucosa, and red tongue; for example, vitamin B deficiency, iron-deficient anemia, erythematosus lupus, and lichen planus)

Adapted From: "*Hollan KE and Drolet BA. Approach to the Patient with an Infantile Hemangioma. Dermatol Clin. 2013; 31:289–301.*" **and** *"Lee BB, Lardeo J and Neville R. Arterio-venous malformation: how much do we know? Phlebology 2009;24:193–200"*

Benign hypervascularized tumors should not be confused with vascular tumors: while the former is composed of cells and tissues other than blood vessels (for example, uterine leiomyoma), the latter is composed of a proliferation of blood vessels (Table 15.2) [5, 7].

Treatment

Vascular anomalies may present in simple or complex forms; therefore, the type of treatment should be adequate for each case. It is important to be aware of that and to know the objective of the procedures.

Vascular Tumors

In the absence of complications, their management includes follow-up alone until spontaneous regression of the tumor [5–8]. In contrast, treatment—usually surgery—is indicated when these tumors proliferate and invade organs compromising their function and causing deformity, ulceration, or bleeding. When feasible and safe to catheterize the arterial branches feeding the tumor, embolizing agents may be injected to induce ischemia before surgery. This procedure may reduce bleeding and decrease the volume of the tumor to facilitate its resection. Embolization alone does not interfere with the natural course of the disease since it does not allow its control and eradication [4–6, 8].

Clinical Treatment and Laser for Vascular Tumors (Hemangioma) [5]

Some medications are used to treat certain vascular anomalies, but they vary in duration, dosage, and effect. They include: (a) propranolol (antihypertensive and beta-blocker) which is likely to act against vascular tumors by inhibiting angiogenesis and inducing vasoconstriction and apoptosis. The recommended dose is 1–3 mg/kg/day orally divided into two to three daily doses. Hypotension, bradycardia, and bronchospasm (mainly in asthmatics) are the most significant side effects; (b) corticoids may be administered in doses of 2–5 mg/kg/day orally divided into two to three doses. The main side effects are irritability, adrenal suppression, Cushing syndrome, insomnia, growth impairment, osteoporosis due to bone demineralization, and cardiomyopathy. In superficial and small tumors, intralesional injection of corticoids has also been described. Repeated injections may lead to atrophy and skin necrosis; (c) vincristine, a chemotherapeutic agent that inhibits mitosis, is administered to patients with resistance or poor response to corticoids. The usual dose is 1–1.5 mg/m^2. The most relevant adverse effects are constipation and neuromyopathy; (d) interferon, an angiogenesis inhibitor that has proven useful in controlling rapidly growing lesions at a dose of 3,000,000 U/m^2/day. Due to the risk of irreversible diplegia in infants and preschool children, interferon is contraindicated in these age groups; (e) laser, another therapeutic modality, leads to a destruction of telangiectasias and small superficial vessels. Its use is restricted to the treatment of capillary vascular malformations.

Vascular Malformations

Treatment of low-flow malformations consists of percutaneous sclerosis with sclerosing agents (such as alcohol, polidocanol, or ethamolin). But the *nidus*, which results from arteriovenous fistulas in high-flow malformations, should be embolized with a polymer-agent (n-butyl cyanoacrylate—Histoacryl® or ethylene-vinyl alcohol—Onyx®) injected via an arterial access [3, 6, 8].

What Can Non-specialists Do for This Patient?

The most important thing to do is to diagnosis, or to suspect, the vascular anomaly and refer the patient to a specialist. In this regard, it is necessary to classify this defect as a tumor or a vascular malformation. As described above, the time of manifestation and progression are two of the main clinical parameters. In addition, the physical examination helps to identify the affected site (particularly in superficial lesions), investigates the presence of a thrill, which occurs in high-flow malformations, and differentiates between vascular tumor (not compressible) and vascular malformations (usually compressible).

Ultrasound exam is often sufficient to evaluate the extension of vascular lesions, particularly those located in the limbs and extremities. To evaluate complex vascular anomalies located on the face, chest, abdomen, pelvis, and limb roots, magnetic resonance angiography is preferable.

When Should the Patient Be Referred to the Specialist?

Patients presenting deformity, pain, bleeding, and/or loss of function attributed to vascular anomalies and those asymptomatic, but with extensive and complex lesions involving different systems and organs, should be referred to a specialist who will evaluate the lesion and recommend the best treatment.

References

1. Lee BB, Antignani PL, Beraldini V, et al. ISVI-IUA consensus document diagnostic guidelines of vascular anomalies: vascular malformations and hemangiomas. Int Angiol. 2015;34(4):333–74.
2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69:412–20.
3. Lee BB, Baumgartner I, Berlien HP, et al. Consensus Document of the International Union of Angiology (IUA)-2013. Current concepts on the management of arterio-venous malformations. Int Angiol. 2013;32(1):9–36.
4. Lowe LH, Marchant TC, Rivard DC, Scherbel AJ. Vascular malformations: classification and terminology the radiologist needs to know. Semin Roentgenol. 2012;47(2):106–17.
5. Hollan KE, Drolet BA. Approach to the patient with an infantile hemangioma. Dermatol Clin. 2013;31:289–301.
6. Gontijo B, Pereira LB, Silva CMR. Vascular malformations. An Bras Dermatol. 2004;79(1):7–25.
7. Lee BB, Lardeo J, Neville R. Arterio-venous malformation: how much do we know? Phlebology. 2009;24:193–200.
8. Lee BB, Baumgartner I, Berlien P, et al. Diagnosis and Treatment of Venous Malformations. Consensus Document of the International Union of Phlebology (IUP): updated 2013. Int Angiol. 2015;34(2):97–149.
9. Jarrett DY, Ali M, Chaudry G. Imaging of vascular anomalies. Dermatol Clin. 2013;31:251–66.

Aortic Dissection

16

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Abstract

Aortic dissection is the separation of the intima layer from the media muscle layer, after sudden elevation of blood pressure. There are two large lumen paths where blood may pass: [1] a real lumen, which is coated by the endothelium and [2] a false lumen, which is newly formed between the intima and the media layers and has no endothelium.

The false lumen can fully or partially compresses the true lumen. This compression can reduce the blood supply to the brain, abdominal organs or members, which is known as malperfusion syndrome [2].

Other complications of aortic dissection can be caused by weakening of the arterial wall. The impaired wall of the false lumen might expand and form an aneurysm. In severe cases, there may be disruption in the arterial wall.

Aortic dissection is the main cause of death involving sudden aortic disease. The high mortality rates in patients with acute dissection is clear—22.7 % of patients die within 6 h, 50 % within 24 h, and 68 % within 1 week [3]. Therefore, the time taken in the diagnosis and treatment is critically important for patient survival.

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Introduction

Definition

The aorta is a tubular vessel with a cylindrical wall formed by three superimposed layers named intima (inner side), media, and adventitia (outer side). Its lumen is covered by endothelium, a monolayer formed by endothelial cells that covers the entire vascular system and transports blood from the heart.

Aortic dissection is the separation of the intima layer from middle layer after a sudden elevation of blood pressure causing the rupture and consequently detachment of the inner layer allowing the blood to reach the middle layer, creating a new lumen and a flap between both lumens. Thus, two lumen paths are created: (1) the true lumen, covered by endothelium, and (2) the false lumen, just formed between the intima and the media layers with no endothelium (Fig. 16.1). The pressure of the ejected blood leads to circumferential and longitudinal propagation of the dissection vectors, commonly in antegrade way, but occasionally in retrograde way, in the opposite direction of the blood flow [1–3].

Epidemiology

Aortic dissection is the main cause of death in acute aortic diseases, more frequent than ruptured abdominal aortic aneurysms and traumas [1].

It carries high mortality—reaching 22.7 % within 6 h, 50 % within 24 h, and 68 % within the first week [4]. Therefore, timing to take measures is critical for patient survival [4].

Pathophysiology

The false lumen enlarges suddenly and can lead to complete or partial compression of the true lumen; therefore, affecting the emergence of the major aortic branches leading to reduce blood supply to brain, abdominal organs (bowels, kidneys, and/or liver) and/or limbs, which is known as malperfusion syndrome. The sudden enlargement might cause pain, which is very common and often described as severe with a ripping or tearing quality [1, 4].

The two mechanisms of ostial obstruction to blood flow are: (1) dynamic obstruction and (2) static obstruction.

Dynamic obstruction is characterized by prolapse of the false lumen's flap toward the ostium of a major branch during cardiac systole. When the flap touches the ostium, the blood flow for the aortic branch occludes temporally, causing blood flow restriction to the organ. This mechanism is responsible for about 80 % of the total malperfusion syndromes [5].

Static obstruction occurs when the flap occludes continuously and completely the ostium of the aortic branch, leading to the formation of secondary thrombus inside the branch and distal ischemia (Fig. 16.2).

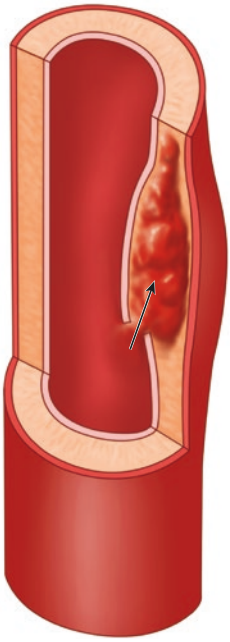

Fig. 16.1 Layers of the dissected artery

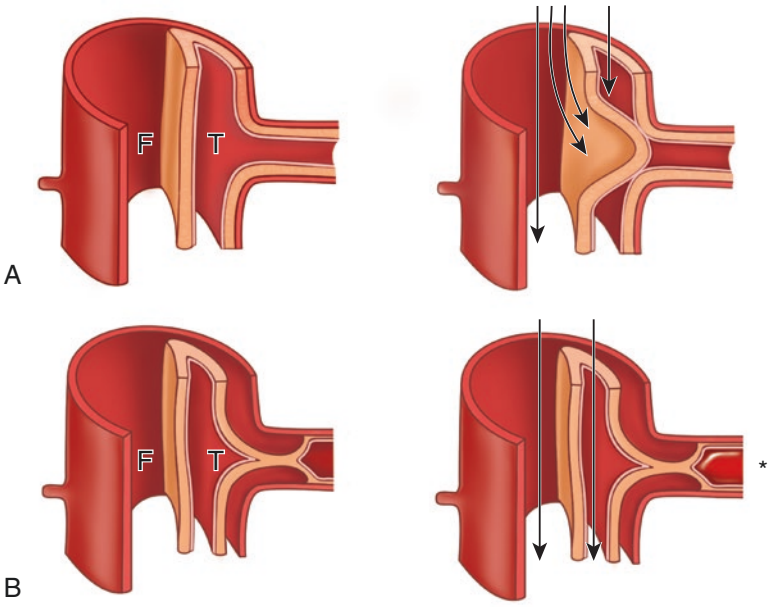

Fig. 16.2 Ostial flow impairment mechanism of the branches of the aortic dissection which leads to malperfusion. (**a**) Dynamic obstruction—ostial obstruction with dynamic flow restriction only during cardiac systole. There is no fixed obstruction, as with during cardiac diastole, when the blade (flap) does not obstruct the ostium of the branch; (**b**) Static obstruction—the blade (flap) obstructs the ostium of the fixed mode branch and leads to secondary thrombus formation in the branch ostium. Subtitles (*T* true, *F* false, *black arrow* blood flow during systole, *asterisk* thrombus)

Other complication of aortic dissection is the weakening of the arterial wall that can form an aneurysm. In the worst case scenario, disruption of the arterial wall can occur leading to bleeding. It can occur in the pericardial, thoracic, or abdominal cavities. In cases of excessive or persistent bleeding, cardiac tamponade or hemorrhagic shock and death are the final outcomes [6].

Classification

Acute Versus Chronic

Dissection is acute when the onset of symptoms occurs within 2 weeks. After 14 days, it is chronic. This time designation is based on autopsy studies that showed higher mortality in the first 14 days [1, 7].

Anatomic

Anatomical presentation of the dissection according to the origin of the intimal tear plays a major role in the prognosis and in the choice of the treatment. There are two main classifications for anatomic aortic dissection: DeBakey and Stanford. The most regular used anatomical classification is the Stanford Classification, categorizing dissection into two types: type A, when the injury in located at the ascending aorta and type B when the lesion is located at the descending aorta [1], as shown in the Fig. 16.3. The Stanford type A dissection comprises about 62.5 % of all cases [1,

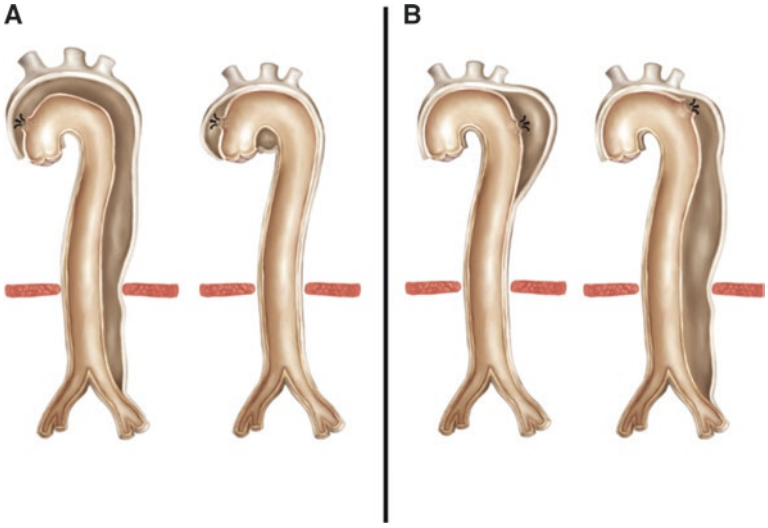

Fig. 16.3 Anatomical classification of acute aortic dissection (Stanford **a** and **b**). (**a**) The origin of the dissection is in the ascending aorta. (**b**) The origin of the dissection is in the descending aorta. Figure copyright by: "Thiago Roberto da Silva"

2]. This classification is important because a Stanford type A is related with a worse natural history, and the treatment is surgery while the Stanford type B has a better prognosis and can be treated with isolated clinical treatment [1, 2].

Risk Factors

1. Hypertension: Hypertension is a major risk factor and plays a crucial role in both increasing the stress on the aortic wall and the subsequent intimal rupture [1].
2. Abnormalities of the aortic wall: Diseases such as aortic coarctation (congenital narrowing of aortic segments), aneurysms, and hereditary conditions such as Marfan syndrome and Ehler–Danlos syndrome and chromosomal abnormalities, like Turner and Noonan syndrome predispose the aortic wall to intima rupture [1, 8].
3. Cardiac disorders: Bicuspid aortic valve is a risk factor for acute type A dissection, due to turbulence from the left ventricle blood jet which stresses against the wall of the ascending aorta [1].
4. Gestation: About 50 % of cases of acute dissection in women under 40 years old occur during pregnancy, especially in cases of hypertensive pregnancy disorders [1, 2, 5].
5. Cocaine use: Present in less than 1 % of dissections, this simphaticomimetic drug leads to systemic hypertension, vasoconstriction, and increased cardiac output.
6. Iatrogenic dissection: aortic dissection can occur during endovascular procedures (diagnostic and/or therapeutic) through the manipulation of catheters, guide wires, and endovascular devices [9].

Atherosclerosis is not a significant risk factor, present in only 31 % of people affected by acute aortic dissection [1].

Clinical Presentation

Pain

Pain has a sudden onset—intense and continuous. It is located in the anterior face of the chest, especially in the type A, or in the back in most cases of type B. However, in some cases, the pain is located in the abdominal area, which raises the suspicion of impairment of mesenteric perfusion. Some patients describe the pain as "stabbing" or feeling "ripped from within" [1, 10].

Neurological Symptoms

Cerebral ischemia occurs due to impairment of blood flow to the supra-aortic trunks, particularly the carotid or vertebral arteries. The incidence of stroke is 6 % in type A dissections, with a mortality rate of 9.4–35.3 % within the first 24 h [1, 2, 11], mostly

in patients with advanced age, systemic hypertension, and atherosclerosis [11]. The most common clinical manifestation is syncope. Other associated symptoms are changes in sensitivity, strength, and motor function in the contralateral brain hemisphere affected [1, 11].

In addition, arterial expansion may cause extrinsic compression of nerves, causing symptoms such as: (1) pain and paresthesia in limbs; (2) Horner syndrome (supraclavicular involvement of the sympathetic ganglion leading to miosis, ptosis, facial anhidrosis, and enophthalmos); or (3) hoarseness, due to left recurrent laryngeal nerve compression that surrounds the aortic arc [1, 12].

In cases affecting the descending aorta, it may have the involvement of the ostia of intercostal arteries, causing spinal cord ischemia in about 2–10 % of cases [1].

Cardiac Complications

In type A dissections, rupture can occur in the ascending aorta, most part of which is located within the pericardial sac. Therefore, bleeding inside the pericardial sac (hemopericardium) leads to cardiac tamponade. The patient may present with Beck's triad: (1) muffled heart sounds, (2) hypotension, and (3) jugular vein engorgement. In these patients, pericardiocentesis is not recommended due to increasing risk of more bleeding and hemorrhagic shock [1].

The coronary arteries may also be involved causing myocardial ischemia. The electrocardiographic findings are consistent with acute coronary syndrome and can lead the doctor to an inadequate administration of thrombolytic agents or anticoagulants, which worsens the prognosis [13].

Malperfusion Syndrome and Limb Ischemia

The impairment of the blood flow to the ostia of the major branches of the abdominal aorta can lead to visceral and lower limbs ischemia, occurring in 31 % of patients [1].

1. Renal arteries: The patient may present oliguria or anuria due to acute renal failure with consequent elevation of urea and creatinine. The presence of this condition triples the mortality rate [1, 14].
2. Mesenteric arteries: This occurs in up to 5 % of cases and increases the mortality rate ninefold. The patient may present with acute abdominal pain, abdominal bloating due to ileus and lower gastrointestinal hemorrhage [1, 14].
3. Lower limbs: The most common site of involvement is the left common iliac artery. The clinical presentation is a classical acute arterial ischemia of the limb, with acute pain, absence of pulses, cold and pale skin, and paresthesia and paresis of the foot. Lower limb ischemia is an isolated factor that triples the rate of mortality [14].

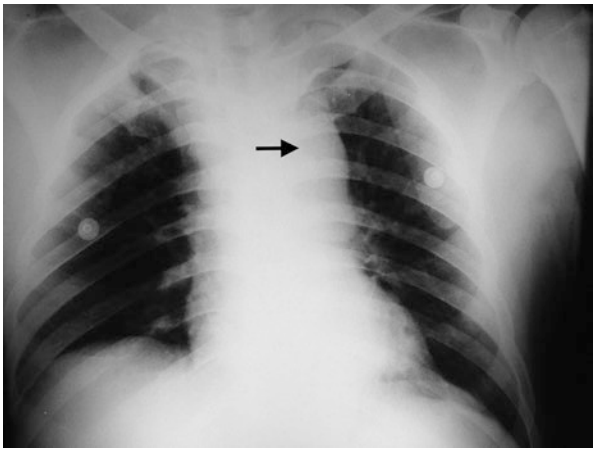

Fig. 16.4 Superior mediastinal widening (*black arrow*)

Diagnosis

Thorax X-ray

This is usually the first exam to be requested, but it is nonspecific. Widening of the superior mediastinum is the most common finding and is associated with calcification of the aortic arch [1] (Fig. 16.4).

Computed Tomography Angiography

The computed tomography angiography in aortic dissection findings are the presence of two aortic lumens, the true lumen and the false lumen, divided by a flap between them (Fig. 16.5). It is possible to determine the site of the intimal tear and its proximal and distal progression as well as the diameters of the lumens. This exam is essential for therapeutic planning and has high specificity, despite showing less sensitivity in the diagnosis of dissections in ascending aorta [15]. A major limitation is that it is not possible to assess aortic valve function and coronary flow in type A dissections [15].

Transthoracic/Transesophageal Echocardiography

Echocardiography is extremely useful in the evaluation of patients with aortic dissection especially in type A. Transesophageal echocardiography has high sensitivity and specificity (98 % and 63–96 %, respectively) [1, 16].

In addition, echocardiography allows assessment of the site of the intimal tear, the diameter of the aorta, the presence of thrombus in the false lumen, blood flow in the false lumen, the impairment of the aortic valve with regurgitation, the

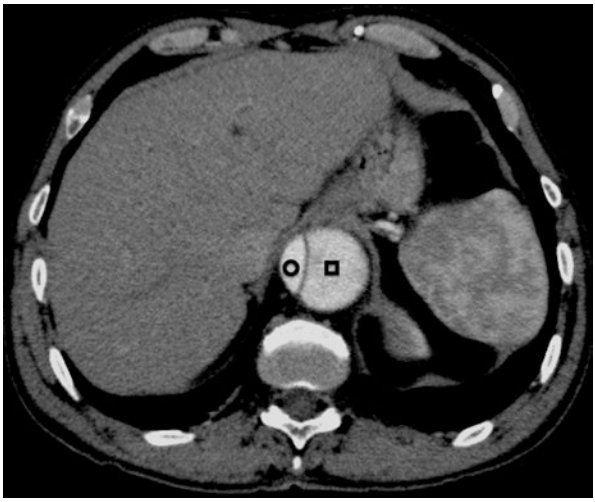

Fig. 16.5 Photograph of computerized angiography of patient with dissection descending aorta. (Legend: *Square* False Lumen, *Circle* True Lumen)

involvement of coronary arteries, and the presence of blood in the pericardium that can lead to cardiac tamponade [1, 16].

Aortography

The exam has a sensibility of 86–88 % and specificity of 75–94 % [1]. This exam can show direct signs that are considered confirmatory for the diagnosis of dissection, such as the detection of a double aortic lumen. Indirect signs, considered suggestive, include deformity of the aortic lumen, abnormalities of its branches and thickening of the aorta wall [1].

Currently, aortography is reserved for intraoperative endovascular treatment of acute dissection.

Nuclear Magnetic Resonance

Nuclear magnetic resonance is a noninvasive method. It can identify the site of the intimal rupture, the distal extent of dissection, the diameter of the aorta, and the commitment of the ostium of the aorta. However, it cannot evaluate the function of the aortic valve and coronary impairment in type A dissections. Nuclear magnetic resonance has high sensitivity and specificity (95–100 %) [1, 17]. However, this exam is not widely available in emergency rooms due to high cost and the longer exam time, making it unsuitable in unstable patients with acute aortic dissection.

Treatment

Patients with acute aortic dissection should have clinical monitoring in an intensive care unit, focusing on acute complications of the disease.

The initial treatment for all types of lesions is lowering the blood pressure with the use of antihypertensive drug, to reduce the heart rate and systolic blood pressure associated with analgesia. By doing this, the extent of the dissection may stabilize reducing the risk of arterial rupture [15].

The surgical treatment of acute aortic dissection depends on the type of dissection (type A or type B), time of installation of the symptoms, and the extent of the injury.

Medical Therapy

Antihypertensive Treatment

The initial choice is often a beta-blocker drug followed by vasodilators [1]. Beta-blockers are used to decrease systolic blood pressure, left ventricular contractility, and heart rate. Vasodilators such as Sodium Nitroprusside are administered in refractory hypertension and should not be used before the heart rate control with beta-blockers [1]. The isolated use of vasodilators stimulates the action of catecholamines by sympathetic reflex, increasing heart rate and contractile force of the left ventricle, worsening the dissection [1].

Esmolol is the preferred drug of choice, but it should be used with caution due to the risk of bronchospasm or in patients with pulmonary obstructive chronic disease. In such cases, cardioselective beta-blockers can be used (Metoprolol or Atenolol) [1].

Analgesia

The pain control can be obtained by morphine or other opiate derivatives. On the other hand, stabilization of pain without use of analgesics is a good criterion for therapeutic efficacy, suggesting control of disease [1].

Interventional Therapy

Type A Dissection

The isolated clinical treatment for patients with Stanford Type A lesions demonstrates mortality rates around 58 % [10]. In contrast, treatment through surgery demonstrates mortality rates of 26 % [10]. Therefore, intervention must be indicated in all cases of dissection type A. The treatment of choice is the replacement of the part of the ascending aorta with the intimal tear. This procedure is performed through median sternotomy and cardiopulmonary bypass. In some very high-risk patients, endovascular intervention can be performed delivering an endograft in the ascending aorta above the coronary ostia. However, this intervention is still experimental currently [1, 18].

Type B Dissection

Unlike type A dissection, interventional treatment should be reserved in complicated cases presenting with: (1) nontreatable pain, (2) malperfusion syndromes, (3) aneurysmal dilatation of the aorta (usually greater than 6 cm diameter), and (4) aortic rupture [19–21]. For patients without complications, medical therapy should be instituted due to the lower mortality rate after 2 weeks—which is 6.4–10.7 %, versus the interventionist approaches such as endovascular schemes, which have a mortality rate of 10.2 % and 17.5–31.4 % for open surgery [1, 10, 22].

The interventional therapy of choice in type B dissection currently is the endovascular approach due to its lower morbidity and mortality in early outcomes [23]. The aim is to deliver an endograft inside the true lumen, sealing the orifice of the intimal rupture. It is performed through the femoral artery under fluoroscopy and digital angiography, avoiding opening of the chest wall. When successful, thrombosis of the false lumen occurs along with remodeling of the aorta and preservation of blood flow in the true lumen [1, 24]. Despite being an excellent surgical alternative in the short term, the correction of endovascular aortic dissection is a recent technique, and the consequences in the long outcomes are not well established [25].

Post-treatment Care

After the acute phase, imaging control with computed tomography angiography or nuclear magnetic resonance should be performed in 6 months. In the event of stable disease, imaging control may be annual [21, 26].

The major chronic complication in patients with aortic dissection is aneurysm. About 25–40 % of patients develop this complication despite the successful initial medication treatment [1, 27, 28]. The resulting aneurysm after acute aortic dissection is more complex and has a higher rate of complications comparing with aorta degenerative aneurysms [1, 27].

What can the nonspecialist do for this patient?

Aortic dissection is a serious and life-threatening disorder that is frequently under-diagnosed. Consider it as a deferential or main diagnosis hypothesis is the most important thing the nonspecialist can do.

The patient with suspected aortic dissection should be monitored in the intensive or intermediate care unit immediately, with invasive measurement of blood pressure, cardiac monitoring, oxygen saturation, urine output, state of consciousness, laboratory tests, and clinical examination series. Controlling blood pressure should be established through use of beta-blockers and sodium nitroprusside [1].

Image exams (CT angiography, transesophageal echocardiography, nuclear magnetic resonance) should confirm the diagnosis.

When to refer to a specialist?

Every patient with acute aortic dissection type A and type B, in conjunction with the complications described above, should be sent as soon as possible to a tertiary center with experts.

References

1. Conrad MF, Cambria RP. Aortic dissection. In: Johnston KW, Cronenwett JL. Rutherford's Vascular Surgery. 8th. Philadelphia: Elsevier; 2014. p. 2169–2188.
2. Januzzi JL, Isselbacher EM, Fattori R, Cooper JV, Smith DE, Fang J, et al. Characterizing the young patient with aortic dissection: results from the International Registry of Aortic Dissection (IRAD). J Am Coll Cardiol. 2004;43(4):665–9.
3. Wilson SK, Hutchins GM. Aortic dissecting aneurysms: causative factors in 204 subjects. Arch Pathol Lab Med. 1982;106(4):175–80.
4. Khan IA, Nair CK. Clinical, diagnostic, and management perspectives of aortic dissection. Chest. 2002;122(1):311–28.
5. Williams DM, Lee DY, Hamilton BH, Marx MV, Narasimham DL, Kazanjian SN, et al. The dissected aorta: percutaneous treatment of ischemic complications—principles and results. J Vasc Interv Radiol. 1997;8(4):605–25.
6. Clouse WD, Hallett JW, Schaff HV, Spittell PC, Rowland CM, Ilstrup DM, et al. Acute aortic dissection: population-based incidence compared with degenerative aortic aneurysm rupture. Mayo Clin Proc. 2004;79(2):176–80.
7. Crawford ES. The diagnosis and management of aortic dissection. JAMA. 1990; 264(19):2537–41.
8. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. Am J Cardiol. 1984;53(6):849–55.
9. Bapat VN, Venn GE. A rare case of aortocoronary dissection following percutaneous transluminal coronary angioplasty: successful treatment using off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg. 2003;24(2):312–4.
10. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA. 2000;283(7):897–903.
11. Bossone E, Corteville DC, Harris KM, Suzuki T, Fattori R, Hutchison S, et al. Stroke and outcomes in patients with acute type A aortic dissection. Circulation. 2013;128(11 Suppl 1):S175–9.
12. Khan IA, Wattanasauwan N, Ansari AW. Painless aortic dissection presenting as hoarseness of voice: cardiovocal syndrome: Ortner's syndrome. Am J Emerg Med. 1999;17(4):361–3.
13. Lentini S, Perrotta S. Aortic dissection with concomitant acute myocardial infarction: from diagnosis to management. J Emerg Trauma Shock. 2011;4(2):273–8.
14. Tolenaar JL, Froehlich W, Jonker FH, Upchurch GR, Rampoldi V, Tsai TT, et al. Predicting in-hospital mortality in acute type B aortic dissection: evidence from International Registry of Acute Aortic Dissection. Circulation. 2014;130(11 Suppl 1):S45–50.
15. Isselbacher EM. Diseases of the aorta. In: Braunwald E, editor. Heart disease. 9th ed. Philadelphia: WB Saunders; 2002. p. 1422–55.
16. Keren A, Kim CB, Hu BS, Eyngorina I, Billingham ME, Mitchell RS, et al. Accuracy of biplane and multiplane transesophageal echocardiography in diagnosis of typical acute aortic dissection and intramural hematoma. J Am Coll Cardiol. 1996;28(3):627–36.
17. Moore AG, Eagle KA, Bruckman D, Moon BS, Malouf JF, Fattori R, et al. Choice of computed tomography, transesophageal echocardiography, magnetic resonance imaging, and aortography in acute aortic dissection: International Registry of Acute Aortic Dissection (IRAD). Am J Cardiol. 2002;89(10):1235–8.
18. Patel HJ, Williams DM, Dasika NL, Suzuki Y, Deeb GM. Operative delay for peripheral malperfusion syndrome in acute type A aortic dissection: a long-term analysis. J Thorac Cardiovasc Surg. 2008;135(6):1288–95. Discussion 95–6.
19. Nienaber CA, Rousseau H, Eggebrecht H, Kische S, Fattori R, Rehders TC, et al. Randomized comparison of strategies for type B aortic dissection: the INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) trial. Circulation. 2009;120(25):2519–28.
20. Elefteriades JA, Lovoulos CJ, Coady MA, Tellides G, Kopf GS, Rizzo JA. Management of descending aortic dissection. Ann Thorac Surg. 1999;67(6):2002–5. Discussion 14–9.

21. Grabenwöger M, Alfonso F, Bachet J, Bonser R, Czerny M, Eggebrecht H, et al. Thoracic Endovascular Aortic Repair (TEVAR) for the treatment of aortic diseases: a position statement from the European Association for Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2012;33(13):1558–63.
22. Fattori R, Cao P, De Rango P, Czerny M, Evangelista A, Nienaber C, et al. Interdisciplinary expert consensus document on management of type B aortic dissection. J Am Coll Cardiol. 2013;61(16):1661–78.
23. He H, Yao K, Nie WP, Wang Z, Liang Q, Shu C, et al. Modified Petticoat technique with preplacement of a distal bare stent improves early aortic remodeling after complicated acute stanford type B aortic dissection. Eur J Vasc Endovasc Surg. 2015;50(4):450–9.
24. Dake MD, Kato N, Mitchell RS, Semba CP, Razavi MK, Shimono T, et al. Endovascular stent-graft placement for the treatment of acute aortic dissection. N Engl J Med. 1999;340(20):1546–52.
25. Shu C, He H, Li QM, Li M, Jiang XH, Luo MY. Endovascular repair of complicated acute type-B aortic dissection with stentgraft: early and mid-term results. Eur J Vasc Endovasc Surg. 2011;42(4):448–53.
26. Isselbacher EM. Thoracic and abdominal aortic aneurysms. Circulation. 2005;111(6):816–28.
27. Panneton JM, Hollier LH. Dissecting descending thoracic and thoracoabdominal aortic aneurysms: part II. Ann Vasc Surg. 1995;9(6):596–605.
28. Hollier LH, Symmonds JB, Pairolero PC, Cherry KJ, Hallett JW, Gloviczki P. Thoracoabdominal aortic aneurysm repair. Analysis of postoperative morbidity. Arch Surg. 1988;123(7):871–5.

Lower Limb Ulcers

17

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Abstract

Ulcer is a loss of lining fabric. It is not a disease but a manifestation of some underlying problem that requires evaluation and treatment. Leg ulcers are a public health problem because it afflicts about 1–2 % of the population in developed Western countries and about 4 % of people over 65 years. The most frequent causes of ulceration are: (1) vascular (venous, arterial, lymphatic, vasculitis); (2) neuropathic (diabetic neuropathy, Hansen's disease, etc.); (3) Mmetabolic (porphyria); (4) neoplastic (Kaposi's sarcoma, basal cell carcinomas, and adenocarcinomas); (5) hematologic (cryoglobulinemia, sickle cell anemia, spherocytosis, polycythemia, etc.); (6) infectious and parasitic diseases (bacteria, fungi, protozoa, and parasites); and undefined. Topical treatment consists in the use of dressings and local agents, and this is only a part of the treatment. It must be stressed that the cause of the ulcer should be treated and interdisciplinary monitoring is required.

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Abbreviations

Ag	Silver
ABI	Ankle-brachial index
mmHg	Millimeters of mercury
pH	Hydrogen potential
WIfI	Wound, ischemia, and foot infection
Psi	Per square inch

Introduction

Ulcer is the loss of tissue coating. In the case of the lower limbs, it is the loss of integument, which can also affect deeper tissues. The lower limb ulcers are slow healing wounds, usually located on the leg and associated with circulatory disorders, especially of the venous system, although there are other causes [1]. Approximately 80 % of the cases result from venous hypertension and 10 %, from arterial insufficiency or a combination of both, the others are the result of neuropathic ulcers, vasculitis among others [2, 3]. These ulcers are different from the cause, location, wound bed, and edges. Neuropathic ulcers show signs arising from sensory abnormalities, autonomic and motor, such as hyperkeratosis, skin dryness, atrophied fingers, among others [1].

Epidemiology

Lower limb ulcers are a public health problem, since it affects approximately 1–2 % of the developed Western countries' population [4, 5] and can reach more than 4 % of people over 65 years [6]. In the United States, about two to four million people have some kind of leg ulcer [7].

Diagnosis

The medical history and physical examination are the initial approach. The following clinical features of the ulcer should be investigated: (1) location, (2) number, (3) size, (4) duration of disease, (5) trigger, (6) presence of pain and its intensity, (7) edges' features, (8) presence and amount of secretion, (9) aspect of wound bed, if it is shallow or deep, and finally (10) the aspect of the skin around the wound should be described [8, 9].

Differential diagnosis of the various causes of ulcers must be considered in order to guide the treatment. The combination of different causes is also frequent [10].

Venous Stasis Ulcers

Concept

Venous stasis ulcers are open chronic wounds that affect the leg (from the ankle to the calf) and are the result of venous insufficiency [11]. They usually present as repeated cycles of ulceration, healing, and recurrence. They are painful, likely to infect, have a foul odor and highly affect mobility and patient quality of life [12, 13].

Epidemiology

Venous stasis ulcers are the most prevalent type of ulcer, affecting 1–2 % of the population and they respond for 60–70 % of lower limb ulcers [14]. Prognosis is poor, taking a long time for healing with high rates of recurrence. Affect the patient's ability to fit in social and occupational activities, reducing quality of life, also imposing financial restrictions. It is estimated a loss of two million working days per year associated with venous stasis ulcers, and it can cause early retirement in up to 12.5 % of workers with this condition. The disease's financial burden are calculated in approximately $ 3 billion/year in the United States. In developed countries, the cost of treatment is estimated at 1–2 % of total health care budget [15].

Pathophysiology

Venous stasis ulcer can occur when venous system fails to return blood to the heart against gravity, condition called chronic venous insufficiency. The presence of reflux and/or venous obstruction or an insufficient action of the calf muscle pump can result in various degrees of chronic venous hypertension, which leads to venous blood accumulation in the affected extremity [1].

Sustained venous hypertension leads to extravasation of plasma and formed elements from blood to the surrounding tissues, especially to the skin and the subcutaneous tissue. Thus, besides the ankle edema, a hardening of subcutaneous tissue takes place, condition called dermatosclerosis. The red cells break down and release hemoglobin, containing the iron ion, which is transformed into hemosiderin and therefore darkens the skin, leading to ocher hyperpigmentation. Finally, there is sequestration of leukocytes that trigger lysosomal enzymes, releasing free radicals and causing tissue injury. The final effect is the ulceration [1].

Prognosis is poor, since only 50 % heal in 4 months, 20 % remain with active ulceration after 2 years and 8 % remain after 5 years, with annual recurrence of 6–15 % [16, 17].

Clinical Presentation

Venous stasis ulcers are usually located in malleolus or at the medial perimalleolar areas. The lesions are superficial with uneven well-defined edges. The bed generally consist of granulation tissue, but may also present fibrin deposition or yellowish secretions, that when associated with foul odor and pain may be infected [18] (Fig. 17.1).

Pain is a common symptom, but its intensity is variable. However, it is usually milder than those of arterial origin, and it is not affected by the size of the ulcer. In general, its intensity increases during the day, worsening in evening times and during long time orthostatic position, improving after lifting the limb [15].

Medical Imaging

Venous duplex scanning is of little help to establish the diagnosis of venous ulcer, which is clinical in most cases. On the other hand, it is very helpful in defining which venous systems are affected: superficial, deep, and/or communicating. It identifies the anatomical abnormalities such as locating precisely which are the compromised veins and systems, if there is acute or chronic superficial or deep thrombosis and collateral vessels. It also adds functional information, determining if there is reflux and/or obstruction in the venous system, providing fundamental information for the proper therapeutic approach [15].

Treatment

Treatment aims wound healing and prevention of recurrence. The main methods are: compression therapy, oral medications, and surgical intervention [15].

Compression Therapy

Compression therapy is the most frequently single therapeutic approach. It promotes symptoms improvement such as pain or heaviness in legs and prevents lower limb edema or allows its resolution, therefore favoring ulcer healing [15]. The available compression methods are: compression socks, multi wraps, bandages, and

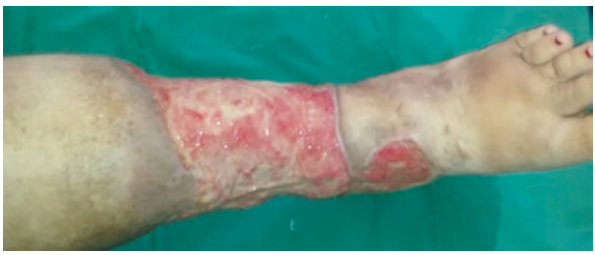


Fig. 17.1 Venous stasis ulcer: uneven edges, but well defined; granulation tissue on the wound bed; ocher dermatitis; edema

pneumatic compression [15]. A systematic review showed that compression with elastic stockings can prevent the recurrence of venous ulcers although not with strong level of evidence [19]. All compression methods are contraindicated in the presence of significant peripheral arterial disease, unless the treatment is authorized by a vascular surgeon, based on the ankle-brachial index [15].

Oral Medications

Medications known as phlebotonic drugs are a heterogeneous group of drugs (e.g., rutosides, hidrosmine, diosmine, calcium dobesilate, chromocarbe, centella asiatica, disodium flavodate, french maritime pine bark extract, grape seed extract, and aminaftone). A systematic review with 44 controlled, prospective and randomized studies, the conclusion was that there is no current evidence of its efficacy in cases of chronic venous insufficiency, requiring more clinical trials [20].

Intervention

Surgical options should be considered in patients with nonhealing venous ulcers despite maximal medical effort. Invasive and surgical options may also be considered in patients who are unable to comply with compression therapy [21]. Nonoperative management of venous ulcer, including compression, elevation, and skin care, is clearly beneficial, such therapy does not correct the underlying pathology [22].

Interventional treatment of superficial venous incompetence can be accomplished by techniques that result in removal, ablation, or ligation of the refluxing venous segment (evaluated by venous duplex ultrasound) [23].

Surgery should be individualized according to the patient's preoperative evaluation. A combination of ligation, axial stripping, and stab phlebectomy may be applied as needed to the great saphenous vein, small saphenous vein, tributary veins, and perforating veins [23].

A systematic review showed that open surgery can improve healing of venous ulcers, but the level of evidence is low, since the comparison was with observational studies [24].

The approach of deep venous system is more complex and includes techniques such as valve repair, valve transplantation, and venous shunts. The recommendation and the results of these techniques are highly controversial, and they are not routinely indicated in daily practice [15].

Endovenous minimally invasive techniques include: (a) endovenous laser and radiofrequency ablation, which promote physical damage to the saphenous vein, occluding it; (b) ultrasound-guided foam sclerotherapy, which promotes chemical occlusion of varicose saphenous and other veins and leads to correction or reduction of venous pressure, allowing the healing of ulcers [15]. Current evidence does not show superiority of endovascular interventions when compared to the isolated compression therapy [24].

Arterial (Ischemic) Ulcers

Concept

Arterial ulcers are caused by the lack of tissues oxygenation secondary to arterial obstruction of the lower limbs. The most common cause is atherosclerosis in about 90 % of cases [25].

Epidemiology

Prevalence of peripheral arterial disease in the United States is estimated at 3–5.5 %, and rises to 10–18.2 % in the population over 70 years of age [26]. Of these, 1–3 % will have peripheral ulcer throughout lifetime [27]. Arterial ulcers account for about 4–10 % of lower limb ulcers. The incidence increases to almost 20 % if mixed ulcers are included [2, 10, 28]. Studies show that these patients have a risk of major limb amputation ranging from 25 to 40 % after 1 year if not revascularized [29, 30].

Pathophysiology

Decreased arterial blood flow leads to ischemia and impaired tissue perfusion. At first, manifesting only during exercise (intermittent claudication). With the progression of the disease, this poor perfusion occurs even at rest, leading, in advanced stages, to necrosis of the underlying dermis and other tissues [25, 31].

Clinical Presentation

The intense pain draws attention in arterial ulcers. Its intensity increases after raising the foot, improving with the use of potent painkillers or keeping the foot down [25, 30, 32].

Ulcers can occur spontaneously or after minor local trauma. It is manifested with necrosis, without granulation tissue (Figs. 17.2 and 17.3). The wound bed is pale, dry, and the edges are irregular [27]. In the presence of secondary infection, there is humidification of necrotic and surrounding tissues, with exudative secretion and stench, condition called wet gangrene [33].

Unlike venous stasis ulcers, arterial ulcers are typically located below the ankle, usually at the distal parts like toes and forefoot [34]. Another common presentation is in bedridden or immobilized patients who develop pressure ulcer in areas of unrelieved pressure, especially in heels [33, 35], but can occur anywhere else in the foot after a local trauma. They can be shallow or deep, with involvement of tendons, muscles, and bones. Arterial ulcers do not heal due to insufficient blood supply. The patient may have other signs of chronic ischemia, such as low skin temperature and

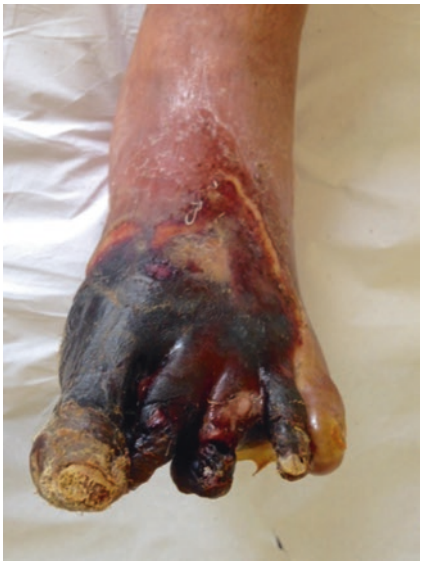


Fig. 17.2 Gangrene restricted to left forefoot saving the fifth toe

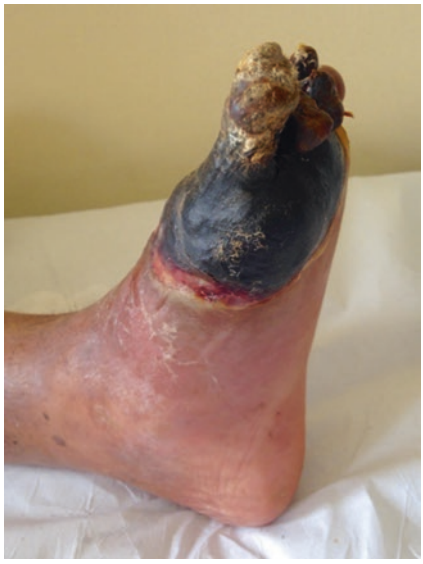


Fig. 17.3 Gangrene restricted to left forefoot saving the fifth toe

reduced peripheral perfusion, thin, pale, and dry skin with no hair and nail dystrophy associated [25, 33].

Diagnosis is clinical. Physical examination shows absence of palpable pulses in the limb. For the objective confirmation of the disease, the ankle-brachial index must be performed, and it is usually under 70 mmHg [27, 36].

Treatment

Treatment of arterial ulcer is complex and leaded by the vascular expert. These ulcers often require restoration of blood flow for wound healing and pain relief. Patients with atherosclerotic arterial ulcers should have medical treatment for systemic atherosclerosis: smoking cessation; strict control of blood pressure, glucose, and cholesterol levels; and use of antiplatelet drugs and statins [37]. Arterial revascularization can be performed by open surgery (artery bypass grafting) or endovascular surgery (percutaneous intervention) [38]. In patients with extensive trophic lesions or impaired limb functionality or those who, for medical reasons, are not candidate for revascularization, primary limb amputation can be the definitive and effective treatment [32]. The WIFi classification, based on wound characteristics, degree of ischemia and infection, helps to establish the risk of amputation and which patient will most benefit with revascularization [39].

Mixed Ulcers

Once the prevalence of chronic venous insufficiency is high in the population, as well as atherosclerosis and its consequences, it is not rare to find ulcers with simultaneous venous and arterial involvement. It is estimated that they affect more than 26 % of lower limbs ulcers [10, 40].

At ectoscopy, signs of chronic venous insufficiency prevail, such as dermatosclerosis, ocher dermatitis, ankle ankylosis, and white atrophy; but at physical examination the peripheral pulses are absent and the ankle-brachial index is lower than 0.9 [10, 41]. Mixed ulcers have features that vary from the aspect of venous ulcers and arterial ulcers, depending on the severity of the arterial component [41].

Patients with mixed ulcers may benefit from limb revascularization surgery [42]. In cases where there is no indication of revascularization, the treatment should proceed the same way as for venous ulcers, with the exception that the compression therapy may be contraindicated, due to the risk of worsening peripheral perfusion. In addition, patients might also not tolerate resting with the lifted limb. These are limiting factors in the treatment of these ulcers [40].

Hypertensive Ulcers

Hypertensive ulcers, also known as Martorell ulcers, are infrequent ischemic vascular ulcers, resulting from a severe and poorly controlled systemic hypertension. It is more common in women between 50 and 70 years of age [43].

High blood pressure leads to arteriolar vasospasm and subsequent skin infarction, leading to ulceration. They are mainly located in the distal third and the anterolateral aspect of the leg, and they are extremely painful. Since there is no macrovascular disturbance, peripheral pulses are commonly palpable. The blood pressure is usually very high. Control of pain and blood pressure levels is the mainstay of treatment [44].

Neuropathic Ulcers

Neuropathic ulcers may occur in patients with loss of sensation in legs and feet, such as in diabetes, Hansen's disease, spinal cord injury, and other conditions. The most common ones are those of diabetic foot (described in Chap. 11). About 25 % of people affected by diabetes will develop foot ulcers [15]. About three million people are affected by Hansen's disease worldwide, and the incidence of neuropathic ulcer due to this condition is more common in India [45]. Patients with such diseases lose limb sensibility due to sensory neuropathy over time, so they are unable to feel pain while using inappropriate shoes or hitting objects on the ground when walking, for example. Thus, sensibility is protective, and those patients may develop ulcers without noticing it [46].

Neuropathic ulcers usually occur through injury and destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limbs, due to the continuous mechanical pressure in a specific area [47], normally the plantar aspect of the foot [45, 46].

Neuropathic ulcers are painless and have a hyperkeratosis halo; being an important gateway to infections. The most frequent location is the plantar surface and the metatarsal heads. Classically neuropathic ulcers have well-defined edges, with depth varying according to the severity and duration of lesion, the presence of necrosis and exudate [45, 47]. The skin around the wound may show calluses, erythema, and maceration. Pulse is generally palpable, but it may be incompressible according to the severity and duration of the disease [45, 47].

Diagnosis is done on clinical basis. Evaluation of associated peripheral artery disease is necessary through the ankle-brachial index or transcutaneous oximetry, the latter recommended in case of diabetes and elderly patients. The application of WIfI (Wound, Ischemia, and foot Infection) classification is very important to evaluate prognosis for major amputation in a year and the benefits of limb revascularization for diabetic patients [39].

Treatment of neuropathic ulcers is based on multidisciplinary care, on control of underlying diseases and wound care, using appropriate dressing and offloading on the area, with the use of special shoes or with frequent position changes, seeking to reduce plantar pressure with use of appropriate footwear and individualized to distribute pressure. Age [45] also states about the importance of health education to prevent recurrence, deformity, and amputation [48].

Other Less Common Causes of Ulcers

1. Vasculitis and collagenosis: group of diseases such as systemic lupus erythematosus, rheumatoid arthritis, and thromboangiitis obliterans, in which the blood vessels are compromised by inflammation. One percent of all the ulcers belong to this group. Location is variable, there may be skin and toes necrosis, and it may be accompanied by purpura, reticular livedo, and white atrophy. The pain ranges from moderate to strong and intensity does not modify with position

changing. Treatment depends on correct diagnosis and consists in treating the underlying disease, suppress inflammatory response, and prevent the deposition of immune complexes. Corticosteroids and immunosuppressive drugs are required [49, 50].

2. Neoplastic ulcers: primary skin tumors rarely affect the lower limbs. The malignant transformation of a chronic ulcer of another etiology is less unusual, though. They normally have high edges and are located in areas of scars or previous chronic ulcer [49].
3. Hematological ulcers: eight to ten percent of homozygous patients for sickle-cell disease and alpha-thalassemia may present leg ulcers. They are located preferably at the medial malleolus area, with high edges, are deeper and often involve muscle fascia, and may contain necrotic tissue. They are usually very painful, bilateral, and tend to chronicity. Systemic symptoms such as malaise, weakness, arthralgia, and fever are ordinarily present [51, 52].
4. Infectious and parasitic ulcers: many agents can cause ulcers, such as bacteria, viruses, fungi, protozoa, and parasites. Some of the most common are:
   (a) Cutaneous leishmaniasis, zoonotic disease caused by protozoa of the genus Leishmania. The typical ulcer is oval and presents with high and infiltrated edges, with bright red background and it can be covered with exudate. Usually, they are unique and can be present in various parts of the body [53–55].
   (b) Cutaneous tuberculosis manifest as erythema induratum of Bazim, then liquefy and form a fistula, with consequent formation of ulcer. It is usually located on the back of the thigh and leg. Treatment of cutaneous tuberculosis is the same as systemic tuberculosis [56, 57].
5. Hansen's disease, caused by *Mycobacterium leprae*, affects skin and peripheral nervous system. Ulcers may be correlated to necrotic erythema nodosum or peripheral neuropathy (neuropathic ulcers). They can commit large areas of the leg [54].
6. Ecthyma is a primary pyogenic infection that leads to ulceration of the skin. It is caused by streptococcus or staphylococcus infections and is more common in the pediatric population. It starts with a vesicle or a pustule that forms an ulcer and may present a bonded crust. It is treated with antibiotics as cephalexin, oxacillin, erythromycin, or azithromycin [58–60].
7. In metabolic diseases, such as porphyria, ulcers can appear in sun-exposed areas [49, 50]
8. Other: pyoderma gangrenosum may cause ulcer, but pathophysiology is unknown. Half of the cases are associated with chronic diseases such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, and cancer. The other half is considered idiopathic. Typical lesions are painful pustules with rapid progression to ulceration and necrosis. They can affect any part of the body. The treatment can be done by intralesional or systemic corticosteroids [49, 50, 61].

For proper treatment of the lower limb ulcers, it is important to be aware of the wide variety of differential diagnoses [10, 62].

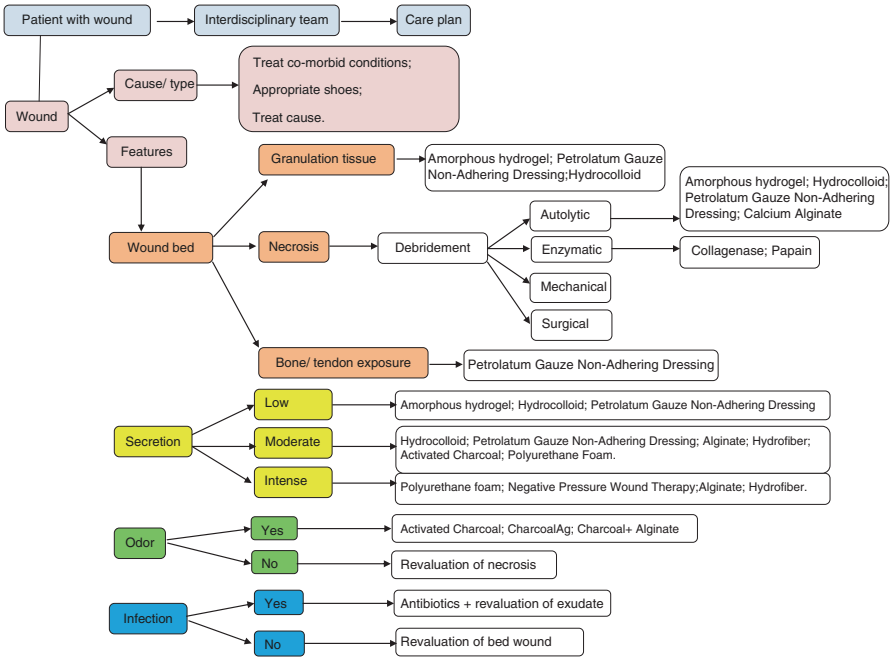
Topical Treatment of the Ulcers

Topical treatment consists in the use of dressings and local agents, and this is only a part of the treatment. It must be stressed that the cause of the ulcer should be treated and interdisciplinary monitoring is required. Thus, associated with the identification of the cause and institution of specific treatment for the underlying disease, local wound care should be initiated [63].

1. Wound cleaning: only nontoxic products should be used [64]. Some studies recommend that the wound must be cleaned with saline solution 0.9 %, since it exhibits the same pH of plasma and does not interfere in the cicatrization process [64]; but systematic reviews concluded that good quality drinking water can also be used for cleaning wounds, if used cautiously [65]. Cleaning must be done with high pressure in continuous or intermittent flow. The applied pressure should go from 8 to 12 lb per square inch (psi), which is enough to remove devitalized tissue and bacteria. Wound cleaning newer systems use pressurized saline solution through a nozzle, between 12,800 and 15,000 per square inch (psi) [66].
2. Debridement: it must be done when there are unviable tissues such as necrosis or excessive fibrin, or signs of infection (exudate, pus, skin redness) to allow the formation of granulation tissue and appropriate epithelialization. To perform the debridement, there is a wide range of methods, including [66]:
   (a) Autolytic: natural process that promotes the maintenance of moist environment through the use of dressings and topical agents. Many of these dressings moisturize and remove necrotic tissue and slough (e.g., hydrogel and Petrolatum Gauze Non-Adhering Dressing) [66];
   (b) Enzymatic: use of ointments with enzymatic action, such as collagenase, fibrinolysin, deoxyribonuclease, and papain. The disadvantages are the need for frequent dressing changes and debridement at a slow rate [66].
   (c) Surgical: consists in aggressively excising the devitalized tissue using surgical techniques. The disadvantages are: hospital facility are needed, anesthetic use is demanded with its associated complications, requires some time of procedure, and may cause pain, bleeding, and healthy tissue excision [66].
   (d) Mechanical: it is a nonselective method, resulting in damage to viable tissue. A possibility to reduce this damage is through the use of wet coverage, which induces separation of devitalized tissue and, once dry, the cover is removed, together with fibrin and necrotic tissue. It is in disuse due to the pain and damage caused to the viable tissue; besides, fibrin can remain in wound bed and the cover does not provide a barrier to bacterial contamination [66].
   (e) Chemical: the use of chemical products is controversial because the benefits need to be balanced against the detrimental effects on the healing process [66].
   (f) Maggot therapy: few studies supporting this therapy is based from the decomposition of nonviable tissue and removes the bacteria the wound [67].

3. Primary dressings: few randomized studies evaluate the effectiveness of dressings. Good quality systematic reviews did not show any superiority regarding wound healing. Good quality systematic reviews did not show any superiority regarding wound healing [64].

   The choice of the ideal dressing must be based on the patient and wound's features: keep wound bed moist; not macerate the edges; be safe, nontoxic, hypoallergenic; good acceptance by the patient; promote relief of pain and odor; not impair mobility; be easy to handle and be cost-effective; be comfortable to the patient [64]. The use of flowcharts (Flowchart 17.1) and the knowledge of the products and information help making the correct choice [64].



Studies conducted in 2013 suggest some evidence that hydrogel and negative pressure therapy have a certain effectiveness in healing diabetic foot wounds and venous stasis ulcers, when compared to other dressings (alginate, hydrocolloid, foam and activated charcoal), but recommend the accomplishment of new studies with better evidence [68–72].

(a) Hydrogel: consists of insoluble polymers (carboxymethyl cellulose) and up to 96 % water [68]. It can be found as amorphous gels and sheet and may be associated with alginate (this increases the power of debridement).

   It is indicated to keep humidity, maintain optimal pH; promote pain relief; assist in autolytic debridement (removal of dead tissue). The exchange period can reach up to 7 days for the sheets and 1 day for the gel [73].

In case of using the gel product, application must be done carefully, once, in large quantities, it can spread and macerate the wound's edge and the skin around [68, 73].

(b) Alginate: it can be found as flat sheets or packing rope for cavities/sinus, combined with silver to increase antimicrobial activity, and it may be composed of calcium alginate and/or sodium alginate [69].

It is indicated for wounds with moderate to intense exudate, so the contact of product and secretion makes up a gel, keeping the wound bed moist and retaining secretion. It is an easy-removal product; it does not adhere to the wound bed. After applying it over the wound, it needs to be slightly humidified with saline [69].

(c) Hydrocolloid: it is available in many shapes, such as paste, powder, and wafer; this latter made of a arboxymethy lcellulose matrix base connected to a vapor permeable film or foam base [70].

It is indicated for wounds with moderate or little exudate. There is also another kind, the fibrous hydrocolloid, or hydrofiber, which is similar to alginate and is suitable for moderate to intense exudation. The exchange period reach up to 5 days or saturation of the product [70].

(d) Foam: it is composed of hydrophilic polyurethane foam and is indicated for wounds with moderate to intense exudate. Associations with silver and with anti-inflammatory drugs are found in the market. It keeps the wound bed moist removing the excess of exudate and contributes to autolytic debridement, thus keeping wound bed in optimal conditions for healing [71].

When combined with silver, it helps in local control of infection. Exchange period reaches up to 5 days or product's saturation. It is recommended at the beginning of treatment with silver association the daily evaluation of the patient because of the possibility of hypersensitivity to silver.

(e) Negative pressure wound therapy: it has not been well established in the literature the exact way it acts yet. It is suitable for complex wounds, with moderate to intense exudation.

Studies have proved benefits described by manufacturers, as to maintain the wet environment, remove excess exudate, remove the microorganism load and the infective material from the wound bed, reduce the foul odor, reduce edema, increase perfusion, and reduce the number of dressing changes [74].

However, there are some disadvantages, such as skin maceration around the wound, prejudice in mobility, and noises that may disturb the patient during sleep—there are currently on the market machines with far less weight and sizes that facilitate mobility, while produce less loud noises [74].

For wounds that need greater stimulation of granulation tissue, some authors report that this therapy is indicated as adjunct therapy to other processes such as the use of grafting [73].

The negative pressure wound therapy works by applying polyurethane foam or sterile gauze sealed with polyurethane film over the wound, and on this dressing, a tube is connected directly to a machine that performs the

negative pressure (vacuum) about 60–180 mmHg, taking the secretion into a reservoir [72].

(f) Activated charcoal: helps in the removal of liquids and toxins that interfere in the cicatrization process [75]. It is indicated for wounds with low to moderate exudation and foul odor [76].

(g) Other currently available dressings:

- Cellulose membrane: it comes in a flat sheets shape, with pores of various diameters. Acts as a temporary skin substitute, maintains humidity, and promotes the regeneration of epithelium [77].
- Made from nanotechnology, after bacterial fermentation, bacterial cellulose nanofibers are set up in three-dimensional network, reproducing the shape imposed by the manufacturer [78]. There are no current studies with good evidence about the use of this product.
- Petrolatum gauze non-adhering dressing: this product is formed by a thin pad impregnated with a mix of petrolatum (vaseline) and 3 % tribromophenate bismuth [79]. It is suitable for wounds with granulation tissues, for dry wounds with little exudate and as an adjunct to other treatments. It may be associated with other products, such as hydrogel, alginate, and activated charcoal.
- In studies conducted by Vaneau et al. (2007), the use of dressings is recommended according to the process of healing: hydrogel for debride; foam and petrolatum gauze for granulation tissue; hydrocolloid and petrolatum gauze to epithelialization. Certain situations are also considered: for fragile skin is indicated the petrolatum gauze; in case of bleeding, the use of alginate; and for odor wounds, such as neoplastic wounds, the use of activated charcoal is recommended [76].

4. Skin culture : the early detection and prompt treatment of infection is necessary, and the culture enables to correlate the clinical features of infection with the laboratory results and local microbiology [80].

   The keratinocyte cell culture, although giving good results, requires specialized technology and consequently is expensive. Unlike acute wounds, chronic wounds are colonized by various pathogens, hampering the correct treatment [80].

5. Grafts: there are three types of grafts: (a) skin autograft, which could be an alternative for the long term ulcers, from the patient's own skin; (b) allograft, applied as a bioengineered skin sheet grown from donor cells, (c) xenografts, through conservation of other animals skins such as pigs [81].

6. Topical antiseptic: they have been indicated for over 150 years to prevent infection [82, 83]. Povidone-iodine is available as powder, impregnated ointment and mesh, and aqueous and alcoholic solutions [82] in concentrations up to 2.5 and 10 %. It can be applied directly to the wound and with use of secondary dressings, as gauze and bandages [83]. There is no good evidence to recommend its use, but in patients with ischemic wounds with no possibility of revascularization at the time, the use of this product is indicated to reduce the risk of infection.

   Some studies have demonstrated the superiority of iodine in controlling infection when compared to silver sulfadiazine, chlorohexidine dressings, and zinc

paste, not to be used in wounds with viability for revascularization and viable tissues [84].

What can the nonexpert do to the patient?

A detailed history and a high-quality physical examination allow the identification of the cause of the ulcer in most cases. Support initial measures and wound care can be early instituted. Identifying the presence of infection and starting early antibiotic therapy can prevent complications and hospitalizations.

When should the patient be referred to the expert?

Patients with arterial impairment should always be referred to the expert since the risk of amputation is high.

Patients with difficult to heal chronic ulcers, after conventional treatment failure, those with frequent complications or patients with ulcers whose diagnosis was not well established should also be evaluated by an expert.

References

1. Muldoon J. Chronic ulcers of the lower limb. In: Flanagan M, editor. Wound healing and skin integrity: principles and practice. 1. Chichester: Wiley-Blackwell; 2013.
2. Moloney MC, Grace P. Understanding the underlying causes of chronic leg ulceration. J Wound Care. 2004;13(6):215–8.
3. Dealey C. The management of patients with chronic wounds. In: Dealey C, editor. The care of wounds. Blackwell; 2008. p. 121–78.
4. Nelzen O, Bergqvist D, Lindhagen A. Leg ulcer etiology—a cross sectional population study. J Vasc Surg. 1991;14(4):557–64.
5. Wille-Jorgensen P, Jorgensen T, Andersen M, Kirchhoff M. Postphlebitic syndrome and general surgery: an epidemiologic investigation. Angiology. 1991;42(5):397–403.
6. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed). 1985;290(6485):1855–6.
7. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care (New Rochelle). 2015;4(9):560–82.
8. Abenhaim L, Clement D, Norgren L, Baccaglini U, Cooke J, Cornu-Thenard A, et al. The management of chronic venous disorders of the leg: an evidence-based report of an international Task Force. Phlebology. 1999;14(1):35–42.
9. Kurz X, Kahn SR, Abenhaim L, Clement D, Norgren L, Baccaglini U, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. Int Angiol. 1999;18(2):83–102.
10. Pannier F, Rabe E. Differential diagnosis of leg ulcers. Phlebology. 2013;28 Suppl 1:55–60.
11. Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. J Am Acad Dermatol. 2001;44(3):401–21. Quiz 22–4.
12. Hickie S, Ross S, Bond C. A survey of the management of leg ulcers in primary care settings in Scotland. J Clin Nurs. 1998;7(1):45–50.
13. Laing W. Chronic venous diseases of the leg. London: Office of Health Economics; 1992.
14. Zenilman J, Valle MF, Malas MB, Maruthur N, Qazi U, Suh Y, et al. AHRQ comparative effectiveness reviews. Chronic venous ulcers: a comparative effectiveness review of treatment modalities. Rockville: Agency for Healthcare Research and Quality (US); 2013.
15. Nouvong A, Armstrong D. Diabetic foot ulcers. In: Cronenwett J, Johnston K, editors. Rutherford's vascular surgery. 8th ed. Philadelphia: Elsevier Health Sciences; 2014. p. 1816–35.
16. Mayberry JC, Moneta GL, DeFrang RD, Porter JM. The influence of elastic compression stockings on deep venous hemodynamics. J Vasc Surg. 1991;13(1):91–9. Discussion 9–100.

17. Dinn E, Henry M. Treatment of venous ulceration by injection sclerotherapy and compression hosiery: a 5-year study. Phlebology. 1992;7(1):23–6.
18. Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. Semin Intervent Radiol. 2009;26(4):286–95.
19. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. Cochrane Database Syst Rev. 2014;9:CD002303.
20. Martinez MJ, Bonfill X, Moreno RM, Vargas E, Capellà D. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2005;(3):CD003229.
21. Howard DP, Howard A, Kothari A, Wales L, Guest M, Davies AH. The role of superficial venous surgery in the management of venous ulcers: a systematic review. Eur J Vasc Endovasc Surg. 2008;36(4):458–65.
22. Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2001;(2):CD000265.
23. Iafrati M, O'Donnell Jr T. Varicose veins: surgical treatment. In: Cronenwett J, Johnston K, editors. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier Health Sciences; 2014. p. 869–84.
24. Mauck KF, Asi N, Elraiyah TA, Undavalli C, Nabhan M, Altayar O, et al. Comparative systematic review and meta-analysis of compression modalities for the promotion of venous ulcer healing and reducing ulcer recurrence. J Vasc Surg. 2014;60(2 Suppl):71S–90S.e1–2.
25. Marston W. Wound care. In: Cronenwett J, Johnston K, editors. Rutherford's vascular surgery. 1. 8th ed. Philadelphia: Elsevier Health Sciences; 2014. p. 1221–40.
26. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation. 2004;110(6):738–43.
27. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5–67.
28. Dean S. Leg ulcers—causes and management. Aust Fam Physician. 2006;35(7):480–4.
29. Benoit E, O'Donnell Jr TF, Kitsios GD, Iafrati MD. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. J Vasc Surg. 2012;55(3):781–9.
30. Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg. 2006;44(1):108–14.
31. Gottrup F, Karlsmark T. Leg ulcers: uncommon presentations. Clin Dermatol. 2005;23(6): 601–11.
32. Hopf HW, Ueno C, Aslam R, Dardik A, Fife C, Grant L, et al. Guidelines for the prevention of lower extremity arterial ulcers. Wound Repair Regen. 2008;16(2):175–88.
33. Becker F, Robert-Ebadi H, Ricco JB, Setacci C, Cao P, de Donato G, et al. Chapter I: Definitions, epidemiology, clinical presentation and prognosis. Eur J Vasc Endovasc Surg. 2011;42 Suppl 2:S4–12.
34. Tam M, Moschella SL. Vascular skin ulcers of limbs. Cardiol Clin. 1991;9(3):555–63.
35. Dosluoglu HH. Lower extremity arterial disease: general considerations. In: Cronenwett J, Johnston K, editors. Rutherford's vascular surgery. 2. 8th ed. Philadelphia: Elsevier Health Sciences; 2014. p. 1660–74.
36. Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA. 2006;295(5):536–46.
37. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.
38. Stranden E, Slagsvold CE. [Arterial ischemic ulcers]. Tidsskr Nor Laegeforen. 2005;125(7): 895–8.
39. Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk

stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220–34.e1–2.
40. Hedayati N, Carson JG, Chi YW, Link D. Management of mixed arterial venous lower extremity ulceration: a review. Vasc Med. 2015;20(5):479–86.
41. Willenberg T. [Mixed leg ulcers]. Ther Umsch. 2011;68(3):149–52.
42. Zhan LX, Branco BC, Armstrong DG, Mills JL. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. J Vasc Surg. 2015;61(4):939–44.
43. Lima Pinto AP, Silva NA, Osorio CT, Rivera LM, Carneiro S, Ramos-E-Silva M, et al. Martorell's ulcer: diagnostic and therapeutic challenge. Case Rep Dermatol. 2015;7(2):199–206.
44. Graves JW, Morris JC, Sheps SG. Martorell's hypertensive leg ulcer: case report and concise review of the literature. J Hum Hypertens. 2001;15(4):279–83.
45. Agale S. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. Ulcers. 2013;2013:9.
46. Conde-Montero E, Horcajada-Reales C, Clavo P, Delgado-Sillero I, Suarez-Fernandez R. Neuropathic ulcers in leprosy treated with intralesional platelet-rich plasma. Int Wound J. 2016;13(5):726–8.
47. Apelqvist J. Diabetic foot disease. In: Flanagan M, editor. Wound healing and skin integrity: principles and practice. 1st ed. Chichester: Wiley-Blackwell; 2013.
48. Reinar LM, Forsetlund L, Bjørndal A, Lockwood D. Interventions for skin changes caused by nerve damage in leprosy. Cochrane Database Syst Rev. 2008;(3):CD004833.
49. Labropoulos N, Manalo D, Patel NP, Tiongson J, Pryor L, Giannoukas AD. Uncommon leg ulcers in the lower extremity. J Vasc Surg. 2007;45(3):568–73.
50. Panuncialman J, Falanga V. Unusual causes of cutaneous ulceration. Surg Clin North Am. 2010;90(6):1161–80.
51. Ndiaye M, Niang SO, Diop A, Diallo M, Diaz K, Ly F, et al. [Leg ulcers in sickle cell disease: a retrospective study of 40 cases]. Ann Dermatol Venereol. 2016;143(2):103–7.
52. Kerstein MD. The non-healing leg ulcer: peripheral vascular disease, chronic venous insufficiency, and ischemic vasculitis. Ostomy Wound Manage. 1996;42(10A Suppl):19S–35.
53. Handler MZ, Patel PA, Kapila R, Al-Qubati Y, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis: clinical perspectives. J Am Acad Dermatol. 2015;73(6):897–908. Quiz 9–10.
54. Guenin-Mace L, Oldenburg R, Chretien F, Demangel C. Pathogenesis of skin ulcers: lessons from the Mycobacterium ulcerans and Leishmania spp. pathogens. Cell Mol Life Sci. 2014;71(13):2443–50.
55. von Stebut E, Schleicher U, Bogdan C. [Cutaneous leishmaniasis as travelers' disease. Clinical presentation, diagnostics and therapy]. Hautarzt. 2012;63(3):233–46. Quiz 47–8.
56. van Zyl L, du Plessis J, Viljoen J. Cutaneous tuberculosis overview and current treatment regimens. Tuberculosis (Edinb). 2015;95(6):629–38.
57. Dias MF, Bernardes Filho F, Quaresma MV, Nascimento LV, Nery JA, Azulay DR. Update on cutaneous tuberculosis. An Bras Dermatol. 2014;89(6):925–38.
58. Trent JT, Federman D, Kirsner RS. Common bacterial skin infections. Ostomy Wound Manage. 2001;47(8):30–4.
59. Edlich RF, Winters KL, Britt LD, Long 3rd WB. Bacterial diseases of the skin. J Long Term Eff Med Implants. 2005;15(5):499–510.
60. Sharma S, Verma KK. Skin and soft tissue infection. Indian J Pediatr. 2001;68 Suppl 3:S46–50.
61. Choucair MM, Fivenson DP. Leg ulcer diagnosis and management. Dermatol Clin. 2001;19(4):659–78. viii.
62. Mekkes JR, Loots MA, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
63. Forster R, Pagnamenta F. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev. 2015;6:CD001836.
64. Flanagan M. Principles of wound management. In: Flanagan M, editor. Wound healing and skin integrity: principles and practice. 1st ed. Chichester: Wiley-Blackwell; 2013.

65. Fernandez R, Griffiths R. Water for wound cleansing. Cochrane Database Syst Rev. 2008;(1):CD003861.
66. Smith F, Dryburgh N, Donaldson J, Mitchell M. Debridement for surgical wounds. Cochrane Database Syst Rev. 2013;9:CD006214.
67. Federman DG, Ladiiznski B, Dardik A, Kelly M, Shapshak D, Ueno CM, et al. Wound healing society 2014 update on guidelines for arterial ulcers. Wound Repair Regen. 2016;24(1):127–35.
68. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;7:CD009101.
69. Dumville JC, O'Meara S, Deshpande S, Speak K. Alginate dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;6:CD009110.
70. Dumville JC, Deshpande S, O'Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;8:CD009099.
71. Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013;6:CD009111.
72. Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev. 2013;10:CD010318.
73. Ribeiro C, Dias F, Fregonezi G. Hydrogel dressings for venous leg ulcers. Cochrane Database Syst Rev. 2013;(9):CD010738.
74. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. Cochrane Database Syst Rev. 2015;7:CD011354.
75. Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010;19(5):208. 210–2, 214–5.
76. Vaneau M, Chaby G, Guillot B, Martel P, Senet P, Téot L, et al. Consensus panel recommendations for chronic and acute wound dressings. Arch Dermatol. 2007;143(10):1291–4.
77. Qiu Y, Qiu L, Cui J, Wei Q. Bacterial cellulose and bacterial cellulose-vaccarin membranes for wound healing. Mater Sci Eng C Mater Biol Appl. 2016;59:303–9.
78. Bottan S, Robotti F, Jayathissa P, Hegglin A, Bahamonde N, Heredia-Guerrero JA, et al. Surface-structured bacterial cellulose with guided assembly-based biolithography (GAB). ACS Nano. 2015;9(1):206–19.
79. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SE. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010471.
80. Edwards-Jones V, Flanagan M. Wound infection. In: Flanagan M, editor. Wound healing and skin integrity: principles and practice. 1st ed. Chichester: Wiley-Blackwell; 2013.
81. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev. 2013;1:CD001737.
82. Durani P, Leaper D. Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. Int Wound J. 2008;5(3):376–87.
83. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev. 2014;1:CD003557.
84. Vermeulen H, Westerbos SJ, Ubbink DT. Benefit and harm of iodine in wound care: a systematic review. J Hosp Infect. 2010;76(3):191–9.

Lymphedema and Erysipelas

18

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Abstract

Lymphedema is the protein-enriched liquid accumulation in the interstitial spaces, due to changes in the lymphatic content, transport deficiency, or failure of extralymphatic proteolysis. It is classified as primary if it is of unknown cause, or secondary or acquired lymphedema. The diagnosis is based on physical examination associated with a careful history. The treatment of the lymphedema should be multidisciplinary and aims to reduce swelling and to prevent its progression. Erysipelas is a skin and mucosal infection caused by the *Streptococcus pyogenes* beta-hemolytic group A of Lancefield classification. It is a common

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condition in clinical daily practice and the most frequent among all lymphangitis. Treatment includes antibiotics, symptomatic medications, and care of skin lesions. Lymphedema is a common complication of erysipelas since the lymph vessels can suffer from fibrosis process. Once established the lymphedema, it predisposes to new infection, given the richness of the protein edema, forming a vicious cycle.

Lymphedema

Concept

Lymphedema is the protein-enriched liquid accumulation in the interstitial spaces, due to changes in the lymphatic content, transport deficiency, or failure of extralymphatic proteolysis [1].

Epidemiology and Classification

There are two types of lymphedema based on its etiology, the primary and secondary lymphedema [2].

Primary Lymphedema

The primary lymphedema is of unknown cause and had been classified based on age of symptoms onset and the presence of cases in the family. Relatively rare, it occurs in approximately 1 in every 6000–10,000 births [2].

Among primary lymphedema, the most common form is the praecox, which affects approximately 80 % of patients. There are also the congenital and the tarda forms, accounting for 10 % each [2]. They are defined as:

- Primary congenital lymphedema: Clinical findings initiate before the first year of life. More frequent in men. The edema is often bilateral and involves the entire leg. The familiar version of congenital lymphedema is known as Milroy's disease and is related to Turner's syndrome [2].
- Praecox primary lymphedema: Clinical findings initiate between 1 and 35 years old and its hereditary version is known as Meige's disease. It is more frequent in women (10:1). Usually the edema is unilateral and extends from distal to proximal. Some authors believe that congenital lymphatic injury remains quiet until puberty. When there is an increase in the size (length) of the limb, increasing local metabolism, there is an imbalance of lymph circulation that can no longer be sufficient to drain the lymph of that particular region, clinically emerging as lymphedema [2].
- Tarda primary lymphedema: Lymphedema initiating clinically after 35 years old [2].

Secondary Lymphedema

Secondary or acquired lymphedema is the most common form in third world countries, mainly due to filariasis. In developed countries, the most common causes of secondary lymphedema are iatrogenic lesions due to resection or ablation of regional lymph nodes after surgery, radiotherapy, tumor invasion, and direct trauma or, less commonly, after lymphangitis (infectious process). Unusual causes are tuberculosis, rheumatoid and psoriatic arthritis, and phlebitis [1].

Natural History

Lymphedema can occur by (1) overproduction of lymph exceeding the capacity of lymphatic vessels transportation or (2) impaired lymphatic flow, due to anatomical or functional changes of the lymphatic system such as lymphatic hypoplasia or aplasia, anatomical absence of lymphatic valves, or vessels contractility insufficiency [1].

This stasis of lymph leads to abnormal accumulation of proteins in the extracellular space leading to increased interstitial oncotic pressure, and water accumulation in the interstitium, emerging clinically as edema. In addition, the abnormal accumulation of the proteins in extracellular space generates an inflammatory response in subcutaneous tissue leading to progressive fibrosis [1].

Clinical Findings

The skin and the subcutaneous tissue of the limb with lymphedema are firm and hardened. The perimalleolus region may have a "tree trunk" shape. The instep enlarges and the toes become thick and rectangular. Pain is mild or absent. With the progression of the condition, the skin undergoes characteristic changes such as hyperkeratosis and lichenification [1, 3].

Generally, lymphedema does not respond to limb elevation, like other edemas, in more advanced clinical stages [1]. It also does not present clinically with hyperpigmentation and ulcers, like typical patients with chronic venous insufficiency.

Lymphedema is manifested in four stages (Table 18.1). Each stage can be subclassified as mild, moderate, and severe [1].

Although the stages do not help in the diagnosis, it allows the evaluation and monitoring of treatment efficacy.

Diagnosis

In most cases, findings in physical examination associated with a careful history establish the diagnosis and may reveal the cause of the edema. Additional tests are used in the diagnosis assistance:

Table 18.1 Lymphedema stages classification

Stages	Characteristics
Latent phase	Presence of fluid accumulation and perilymphatic fibrosis without clinical edema
Grade I	Positive cacifo sign., edema reduces after limb elevation
Grade II	Negative Cacifo sign. Edema does not reduce after limb elevation
Grade III	Irreversible edema. Fibrosis and sclerosis of the skin and subcutaneous tissue

Source: [4]

– *Duplex Scan*: Should be performed for ruling out deep venous thrombosis [1].
  - *Computed tomography* and the *magnetic resonance* may demonstrate the lymphedema characteristics: presence of edema restricted to the subcutaneous tissue, limited by muscular fascia [1].
  - *Lymphoscintigraphy*: It is the diagnostic test of choice. It has a sensitivity of 70–90 % and specificity of nearly 100 % in distinguishing between lymphatic edema and other causes of peripheral edema. It evaluates the lymphatic function through the measurement of radioactive macromolecular marker clearance. It provides important anatomical and functional information if a surgical procedure is required. However, it should not be used for routine diagnosis, since it could worsen the disease [1].
  - *Lymphography*: The exam allows the study of lymphatic anatomy but not of lymphatic function. Due to its high cost, its technical difficulty, and large number of complications, this exam is no longer used in clinical practice [1].
  - *Subcutaneous tissue biopsy*: It may become necessary in some selected cases, especially in the advanced stages, due to the risk of malignancy. The purpose is not to establish the diagnosis of lymphedema but cancer [1].

Treatment

The treatment of the lymphedema should be multidisciplinary [3]. It is primarily based on conservative measures [3]. The approach of secondary lymphedema is to prevent the onset of edema (Table 18.2). In primary lymphedema, the goal is to reduce swelling and to prevent its progression [3, 5, 6].

Most patients will respond to conservative treatment, which can be done with a combination of complex decongestive physiotherapy, intermittent pneumatic compression, drug therapy, and immediate treatment of any suspected infection or lymphangitis [3]. Despite of the treatment modality, intensive skin care with daily cleansing, low pH lotions, and continuous use of cotton clothes are mandatory. Likewise, after any initial treatment, the use of graduated compression stockings or sleeves combined with exercises and limb elevation is part of the treatment. The elastic stockings facilitate venous and lymphatic flow due to gradual compression [1, 3].

Table 18.2 Lymphedema: Preventive measures

Dietary moderation in intake of fluids and sodium
Body weight control
Daily elevation of the lower limb, positioning it above the heart level during sessions of 20–30 min each
Physical activity
Avoid external pressure on the affected limb (e.g., jewelry, tight clothing)
Daily care and cleansing of the skin
Regular use of elastic compression stockings (not exceeding 15–20 mmHg)
Prophylactic antibiotic use in recurrent cases

Source: [1, 3]

Complex Decongestive Physiotherapy

It is nowadays the gold-standard treatment for lymphedema [6, 7].

The Complex Decongestive Physiotherapy comprises two phases. An initial decongestive phase and a maintenance phase.

Phase one is based on manual lymph drainage massage followed by multilayered bandage wrappings. It aims to achieve reduction of the limb diameter, and should be promptly followed by phase two with manual lymph drainage in order to stimulate the lymphatic vessels that are still functioning and to drain the stagnant protein fluid accumulated in the subcutaneous tissue. It should be performed by qualified physiotherapists [7].

The maintenance phase consists of continuous use of graduated compression stockings/sleeves, and physiotherapy-applied or self-applied manual lymph drainage [1, 7].

Intermittent Pneumatic Compression

Air compression pump is another effective therapy method for reducing the volume of the lymphedema limb using a similar principle of the manual lymph drainage but in this case the external compression is done by a sequential gradient pump which forces the lymph flow through the limb [1, 8].

Pharmacologic Treatment

It is based on lymphokinetic medications represented by the benzopyrones [5]. This class of medication has the potential effects of hydrolyzed tissue proteins, enhancing their transport, and to stimulate lymphatic collectors [1]. It comprises the rutosides and the bioflavonoids. The effectiveness of drug treatment alone is controversial [1]. There are several poor quality trials addressing this issue. It is not possible to draw

conclusions about the effectiveness of benzopyrones in reducing limb volume, pain, or discomfort in lymphoedematous limbs [7, 9, 10].

Diuretics do not demonstrate long-term benefits, and therefore have no role in the treatment of lymphedema.

Antimicrobial drugs should be administered if any sign of infection is present. The drugs of choice are oral penicillin, cephalexin, and azithromycin from 7 to 14 days. In case of recurrence—more than two to four episodes per year—prophylactic treatment is required with oral penicillin 7 days once a month or benzatin penicillin once a month [11].

Surgical Treatment

It is reserved for the most severe and refractory cases. The approach may be reconstructive or debulking [1, 12–14]. The reconstructive approach aims to restore the lymphatic function through the making of lymph-venous shunts or transpositions of autologous vessels [14].

The debulking surgery reduces edema by removing the excess tissue, thereby reducing the size and weight of the affected limb, providing improved function and mobility [12, 13].

Erysipelas

Concept

Erysipelas is a skin and mucosal infection caused by the *Streptococcus pyogenes* beta-hemolytic group A of Lancefield classification. It is the most frequent among all lymphangitis [15].

Epidemiology

The erysipelas is a common condition in clinical daily practice, with an estimated incidence of 10–100 cases per 100,000 inhabitants/year. The female is the most affected gender and it primarily affects adults between 40 and 60 years [16]. It is more common among patients with some chronic diseases [17].

More than 40 % of affected people have some other health condition [18]. The lower limbs are affected in more than 80 % of cases. The main risk factors are the presence of (1) lymphedema and (2) obesity [16, 19], but also (3) low socioeconomic conditions, (4) immune-deficiencies states, (5) alcoholism, (6) diabetes mellitus, and (7) chronic venous insufficiency are associated [20, 21].

Natural History

The bacteriological agent needs an inoculation point or a gateway. The most common site of entrance is interdigital mycosis. However, other pathways could be active chronic venous ulcers, skin injuries caused by shoes, insect sting, scarification by scratch, or other injuries of any kind [22, 23].

The evolution depends on the host resistance. It can regress spontaneously without sequel or cause serious systemic infections with hemodynamic instability. It is known that untreated erysipelas have a higher rate of recurrence and leave more sequels in the lymphatic system, with residual and progressive lymphedema than the treated ones [16, 17].

Clinical Findings

A painful lymph node enlargement may be the first sign. Usually the symptoms precede in a few days the skin manifestations. Initial symptoms are local pain, malaise, asthenia, headache, nausea and vomiting, chills and high fever. Systemic manifestations are usually attributed to the high potential lesion of the toxin produced by *Streptococcus sp*. Among the signs it is observed edema and local erythema which give the skin the appearance of an orange peel (Fig. 18.1). Later appear spots and erythematous papules that evolve into vesicles, blisters, and bubbles, which coalesce revealing its citrus liquid, blood, or pus content. It may also lead to scabs and skin necrosis (Fig. 18.2). Vesicles and blisters usually appear late in the course and often after systemic and laboratory improvement [15, 24].

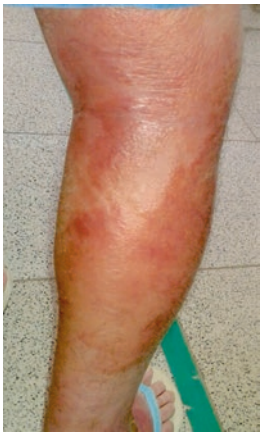

Fig. 18.1 Pacient presenting edema and erythema of the right leg, and an orange peel skin, suggestive of erysipela

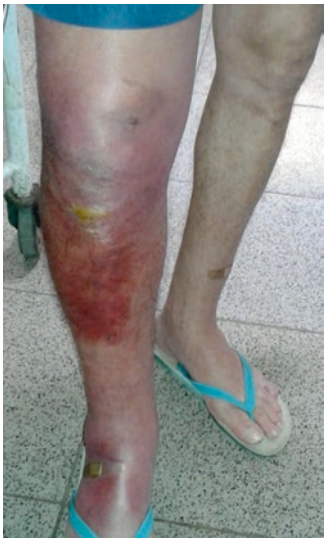

Fig. 18.2 Advanced erysipela showing erythematous papules, vesicles and blisters containing purulent secretion

Table 18.3 Differential diagnosis of erysipelas

Diagnostic	Characteristics
Deep Vein Thrombosis (DVP)	Absence of infectious signs
Systemic diseases: Congestive heart failure (CHF) and Chronic Kidney Disease (CKD)	Usually bilateral edema
Soft tissue injury by trauma	History of trauma
Rupture of Baker cyst	Sudden pain
Tumor extrinsic compressions	Insidious onset, rarely painful

Source: [16]

Diagnosis

The diagnosis of erysipelas is done by clinical examination [17].

Laboratory tests are not necessary for diagnosis but help to monitor the evolution and to exclude other diagnoses (Table 18.3). It is commonly observed leukocytosis and increased C-reactive protein and antistreptolysin O serum levels [22].

Blood culture is rarely positive, which happens in only 5 % of cases [15, 22, 25, 26]. Culture of the vesicles and blisters content and skin biopsy are usually inconclusive and do not help the diagnosis and neither to the isolation of the agent. They are therefore contraindicated [26, 27].

Typical presentations in the absence of comorbidities, additional diagnostic evaluation is unnecessary and the patient may be treated in outpatient settings [15, 28].

Treatment

Antibiotics are the mainstay of treatment for erysipelas. Symptomatic medications and care of skin lesions may also be required [29].

The antibiotic of first choice remains penicillin, oral, intramuscular, or intravenous. Penicillin G benzathine is the gold standard when long-term treatment for *Streptococcus* sp. is intended [11, 30, 31].

In mild cases it is recommended oral antibiotic therapy with penicillin for 5 days. In allergic patients, amoxicillin or erythromycin can be used since they have the same spectrum. Cephalexin, dicloxacillin, and clindamycin are also options [29].

In the presence of systemic symptoms, intravenous treatment with penicillin, ceftriaxone, or clindamycin is recommended for at least 5 days [29].

For severe cases it is recommended broad-spectrum antibiotics such as vancomycin associated with imipenem or meropenem or vancomycin associated with piperacillin—tazobactam [29] (Table 18.4).

Hospitalization is limited to severe or refractory conditions [16]. The main reason for hospitalization is the presence of associated chronic diseases such as diabetes mellitus, obesity, immune-deficiencies status, and alcoholism [31].

Symptomatic medicines can relieve pain and fever. Lymphokinetic drugs, such as benzopyrones or diosmin–hesperidin associations, would help restore the lymphatic flow; however, this benefit has not been proven [9, 10]. Systemic corticosteroids such as prednisone 40 mg/day during 7 days could be considered in nondiabetic patients. Elevation of the affected area also helps to relieve the symptoms [17, 29].

Table 18.4 Antibiotic treatment of erysipelas

Primary treatment			
Penicillin G benzathine	1,200,000 IU	IM	Single dose
Penicillin G potassium	20–30 megaU/day	IV	10–14 days
Amoxicillin	500 mg 8/8 h	Oral	10–14 days
Erythromycin	1–2 g 12/12 h	Oral	10–14 days
Clindamycin	600 mg 8/8 h	Oral	10–14 days
	600 mg 6/6 h	IV	
Cephalexin	500 mg 6/6 h	Oral	10–14 days
Sulfamethoxazole + trimethoprim	800 + 160 mg 12/12 h	Oral	10–14 days
Relapses treatment			
Penicillin G benzathine	1,200,000 IU	IM	21/21 or 30/30 days
Erythromycin	0.5 g 12/12 h	Oral	During 10 days/month
Sulfamethoxazole + trimethoprim	800 + 160 mg 24/24 h	Oral	During 10 days/month

Source: [11, 16, 29–31]

Complications

With proper treatment, the evolution of erysipelas is generally benign (80 %) [16]. The most common complication is the recurrence [17, 32].

Lymphedema is another common complication since the lymph vessels can suffer from fibrosis process. Once established, lymphedema predisposes to new infection, given the richness of the protein edema, forming a vicious cycle [19].

Each recurrence leads to further lymphedema, which in turn predisposes to further infection. Other more serious complications are abscesses, septicemia, endocarditis, acute kidney failure, and deep vein thrombosis [16].

Erysipelas tends to recurrence [16]. Prevention is the best way to avoid it. The proper care of the skin is very important, especially the toes and to fight gateways as skin and nail diseases, fungal infections and chronic wounds. Dealing adequately with edema and, mainly, lymphedema are of equal importance in prevention [29, 32].

In refractory cases, prolonged antibiotic therapy is recommended. Administration of oral penicillin or erythromycin for 4–52 weeks, or intramuscular benzathine penicillin every 2–4 weeks, may be considered in patients showing more than three recurrences per year [16, 33].

What Can the Nonspecialist Do for the Patient with Lymphedema?

In lymphedema, preventive measures may be imposed earlier by the attending physician, avoiding its progression. Limb elevation, hygiene and dietary care, control of predisposing factors, and treatment of the triggering factors such as erysipelas are some of them. Identifying acute erysipelas and initiating early antimicrobial treatment can prevent complications [1, 3, 29].

When to Refer to Specialist?

All patients with lymphedema should see a vascular surgeon at least once. Signs of sepsis and fast progression or initial medical treatment failure in erysipelas are signs of possible complications and require specialist evaluation. Patients with associated vascular diseases also benefit from specialized treatment [34–36].

References

1. Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C, et al. Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2013. Int Angiol. 2013;32(6):541–74.
2. Radhakrishnan K, Rockson SG. The clinical spectrum of lymphatic disease. Ann N Y Acad Sci. 2008;1131(1):155–84.
3. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Taylor ME, Thiadens SR. Lymphedema management. Semin Radiat Oncol. 2003;13(3):290–301.

4. Casleysmith J, Foldi M, Ryan T, Witte M, Witte C, Cluzan R, et al. Summary of the 10th international-congress of lymphology working group discussions and recommendations, Adelaide, Australia, August 10–17. Lymphology. 1985;18:175–80. C/OCL Witte MD 1501 N Campbell Ave Dept Surgery, Tucson, AZ 85724; 1985.
5. Badger C, Preston N, Seers K, Mortimer P. Benzo-pyrones for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev. 2004;(2):CD003140.
6. Ezzo J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI, et al. Manual lymphatic drainage for lymphedema following breast cancer treatment. Cochrane Database Syst Rev. 2015;(5):CD003475.
7. Badger C, Preston N, Seers K, Mortimer P. Physical therapies for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev. 2004;(4):CD003141.
8. Feldman JL, Stout NL, Wanchai A, Stewart BR, Cormier JN, Armer JM. Intermittent pneumatic compression therapy: a systematic review. Lymphology. 2012;45(1):13–25.
9. Badger C, Preston N, Seers K, Mortimer P. Benzo-pyrones for reducing and controlling lymphoedema of the limbs. Cochrane Database Syst Rev. 2003;2.
10. Kerchner K, Fleischer A, Yosipovitch G. Lower extremity lymphedema update: pathophysiology, diagnosis, and treatment guidelines. J Am Acad Dermatol. 2008; 59(2):324–31.
11. Vignes S, Dupuy A. Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. J Eur Acad Dermatol Venereol. 2006;20(7):818–22.
12. Granzow JW, Soderberg JM, Kaji AH, Dauphine C. Review of current surgical treatments for lymphedema. Ann Surg Oncol. 2014;21(4):1195–201.
13. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014;133(4):905–13.
14. Cormier JN, Rourke L, Crosby M, Chang D, Armer J. The surgical treatment of lymphedema: a systematic review of the contemporary literature (2004–2010). Ann Surg Oncol. 2012;19(2):642–51.
15. Bonnetblanc J-M, Bédane C. Erysipelas. Am J Clin Dermatol. 2003;4(3):157–63.
16. Caetano M, Amorin I. Erysipelas. Acta Med Port. 2005;18(5):385–93.
17. Blum C, Menzinger S, Genné D. [Cellulitis: clinical manifestations and management]. Rev Med Suisse. 2013;9(401):1812–5.
18. Oh CC. Cellulitis and erysipelas: prevention. BMJ Clin Evid. 2014;2015.
19. Vaillant L, Gironet N. [Infectious complications of lymphedema]. Rev Med Interne. 2002;23:403s–7s.
20. McKee P, Calonje E, Granter S. Infectious diseases of the skin. In: McKee PH, editor. Pathology of the skin with clinical correlations. 3rd ed. Philadelphia: Elsevier; 2005. p. 872–5.
21. Empinotti JC, Uyeda H, Ruaro RT, Galhardo AP, Bonatto DC. Pyodermitis. An Bras Dermatol. 2012;87(2):277–84.
22. Celestin R, Brown J, Kihiczak G, Schwartz RA. Erysipelas: a common potentially dangerous infection. Acta Dermatovenerol Alp Pannonica Adriat. 2007;16(3):123–7.
23. Mossad S. Common infections in clinical practice: dealing with the daily uncertainties. Cleve Clin J Med. 2004;71(2):129–30. 133–8, 141–3.
24. Bläckberg A, Trell K, Rasmussen M. Erysipelas, a large retrospective study of aetiology and clinical presentation. BMC Infect Dis. 2015;15(1):1.
25. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. N Engl J Med. 1996;334(4):240–6.
26. Denis F, Martin C, Ploy M. [Erysipelas: microbiological and pathogenic data]. Ann Dermatol Venereol. 2001;128(3 Pt 2):317–25.
27. Sachs MK. The optimum use of needle aspiration in the bacteriologic diagnosis of cellulitis in adults. Arch Intern Med. 1990;150(9):1907–12.
28. Lucht F. [Which treatment for erysipelas? Antibiotic treatment: drugs and methods of administering]. Ann Dermatol Venereol. 2001;128(3 Pt 2):345–7.

29. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10–52.
30. Bernard P, Christmann D, Morel M. [Management of erysipelas in French hospitals: a post-consensus conference study]. Ann Dermatol Venereol. 2005;132(3):213–7.
31. Jegou J, Hansmann Y, Chalot F, Roger M, Faivre B, Granel F, et al. [Hospitalization criteria for erysipelas: prospective study in 145 cases]. Ann Dermatol Venereol. 2002;129(4 Pt 1):375–9.
32. Zürcher S, Trellu L. [Recurrent erysipelas and cellulitis: management]. Rev Med Suisse. 2015;11(468):759–62.
33. Mason JM, Thomas KS, Crook AM, Foster KA, Chalmers JR, Nunn AJ, et al. Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. PLoS One. 2014;9(2):e82694.
34. Shimizu T, Tokuda Y. Necrotizing fasciitis. Intern Med. 2010;49(12):1051–7.
35. Elliott D, Kufera JA, Myers RA. The microbiology of necrotizing soft tissue infections. Am J Surg. 2000;179(5):361–6.
36. Frazee BW, Fee C, Lynn J, Wang R, Bostrom A, Hargis C, et al. Community-acquired necrotizing soft tissue infections: a review of 122 cases presenting to a single emergency department over 12 years. J Emerg Med. 2008;34(2):139–46.

Clinical Treatment of Vascular Diseases

19

Joice Cristina Daltoé Inglez

Abstract

Clinical treatment of vascular disease holds several pathologies and their risk factors. The most important are arterial obstructive disease, aortic aneurysm, and acute aortic syndrome.

Obstructive vascular disease reaches all arterial territories, with atherosclerosis as the most important cause. In peripheral artery disease, obstruction of limb arteries will determine the presence of symptoms, such as intermittent claudication and critical limb ischemia (rest pain, gangrene, or ulcers). Clinical management of obstructive disease includes control of risk factors and symptomatic relief, prevention of cardiovascular events and improvement of functional capacity.

The aortic aneurysm and acute aortic syndrome are complex pathologies of aorta. The main goal of medical therapy in aortic aneurysm and acute aortic syndrome is to decrease shear stress on aortic wall (thus reducing rupture and growing rates) and inflammation process since there is a direct relation between diameter, grown and rupture rates.

Obstructive vascular disease is widespread in all arterial territories, reaching cardiovascular, intracranial, and peripheral arteries [1–6]. Prevalence of peripheral artery disease reaches 30 % in patients >70 years although 2/3 are asymptomatic; patients with peripheral artery disease have a larger risk of all-cause and vascular-cause of death [3, 4, 7–10]. In peripheral artery disease, obstruction of limb arteries and limited blood flow will determine the presence of symptoms, such as intermittent claudication and critical limb ischemia (rest pain, gangrene, or ulcers) [6, 9, 10]. Critical limb ischemia is the most severe manifestation of the disease and holds elevated cardiovascular and limb morbidity and mortality [11, 12].

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Atherosclerosis is the leading cause of obstructive disease, and all territories share the same risk factors, such as male gender, smoking, hypertension, hyperlipidemia, diabetes mellitus, and chronic kidney disease [2–5, 13]. Other risk factors related to peripheral disease are the presence of elevated blood levels of inflammation markers (high-sensitivity C-reactive protein), thrombosis factors (homocysteine levels, fibrinogen), and elevated lipoproteins [2, 7]. Low HDL (high density cholesterol) is a major predictor for cardiovascular event [3, 14].

The main goals of treatment are:

- control of the risk factors (involves antiplatelet, antihypertensives, and statins)
- prevent cardiovascular (CV) events
- improve function capacity

Guidelines recommend to calculate cardiovascular risk score in order to predict cardiovascular events in a long period of time [2, 15]. It is based on age, gender, smoking, hyperlipidemia, and blood pressure [15]. There are many risk scores available, such as Framingham, SCORE (Systemic Coronary Risk Estimation), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), Q-Risk, PROCAM (Prospective Cardiovascular Munster Study), and WHO (World Health Organization). The Framingham and SCORE are the most used [15].

The assessment of risk allows to categorize the patient's risk, to identify who will benefit from prevention therapies, and to keep strict surveillance on those with high cardiovascular risk [2, 15, 16]. Once risk factors are continuous, there is no specific threshold to achieve and patients should be reevaluated every 3–5 years if CV risk <5 % and every year if CV risk ≥5 % [2, 15–18].

Categories of Cardiovascular Risk

There are four categories of risk:

- Very high risk: Greater than 10 % risk for fatal atherosclerotic events such as coronary infarction, stroke, or other obstructive arterial event in 10 years. This group includes all patients with documented atherosclerotic disease, type 2 diabetes mellitus, type 1 diabetes mellitus with target organ lesion, and chronic kidney disease (GRF < 60 mL/min/1.73 m^2).
- High risk: Cardiovascular risk ≥5 and <10 % for fatal atherosclerotic events or one elevated risk factor (severe hypertension, familial dyslipidemia).
- Moderate risk: Cardiovascular risk ≥1 and <5 % for fatal atherosclerotic events.
- Low risk: Cardiovascular risk <1 % for fatal atherosclerotic events.

Management of Dyslipidemia

Statins

The correlation between blood levels of cholesterol and cardiovascular disease was established in the twentieth century, and in the 1950s the development of hypolipemiants was started [19]. It took about 35 years for the first statin to be approved by FDA, and now there are semisynthetic (pravastatin and simvastatin) and synthetic statins (fluvastatin, atorvastatin, rosuvastatin, and pitavastatin), with more than 30 million people currently taking statins [19, 20]. Statins are responsible for 25–35 % reduction on plasma levels of LDL-cholesterol and reduce the incidence of heart infarction on 25–30 % [16, 19].

Mechanism of Function: Pleiotropic Effect of Statins

Statins inhibits HMG-CoA reductase (hepatic enzyme responsible for cholesterol synthesis), increases cellular reabsorption of low density lipoprotein cholesterol (LDL) by inducing expression of LDL-receptor and thus, reducing blood levels of LDL-cholesterol, has poor effect increasing serum levels of HDL [20, 21].

It also diminishes the cardiovascular events by reducing endothelial lesion, improving production of nitric oxide and decreasing production of free radicals of oxygen. Statins have anti-inflammatory action and promote atherosclerotic plaque stability, reducing the progression of plaques and diminishing previous lesions [9, 22]. It reduces levels of high-sensitivity C reactive protein, reducing cardiovascular events even though blood cholesterol levels are normal [9, 20, 23, 24].

Most common side effects are myopathy and liver toxicity, in rare cases leading to kidney insufficiency due to rhabdomyolysis [20]. Patients at increased risk for side effects are those at older age, with low body mass index, hypothyroidism, multisystem disease and alcohol abuse, previous renal and hepatic dysfunction, female gender, and in perioperative periods. There are few cases of autoimmune-induced myopathy caused by statins and slight higher rates of diabetes [25]. The risk of side effects is very low especially when compared to impaired risk of cardiovascular event without statin in patients with moderate or high risk [15, 26–28].

Screening

The patients should be assessed individually, but in the absence of other risk factors the screening starts at 40 years for man and 50 years (or postmenopausal) for woman [28]. Patients with risk factors, such as current smoking, diabetes, arterial hypertension, obesity (body mass index above 27, waist circumference ≥93 cm for men and ≥90 for women), familial history of premature coronary artery disease or familial hyperlipidemia, rheumatic or inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel diseases), chronic obstructive pulmonary disease, chronic HIV infection and antiretroviral therapy, chronic kidney disease, abdominal aneurysm, genetic

dyslipidemias (xanthomas, xanthelasmas, FH), and erectile dysfunction must to be investigated for hyperlipidemia independent of age [16, 28, 29].

How to Screen?

Every patient should be evaluated by medical history, physical examination, and blood levels dosage of total cholesterol (TC), LDL, HDL, TG, glucose, and renal function (glomerular filtration rate, GFR). If dosage of LDL isn't available and triglycerides <400 mg/dL, LDL can be calculated with Friedewald formula LDL = TC − HDL − TG/2.2 (mmol) and LDL = TC − HDL − TG/5 (mg/dL).

Calculating non-HDL cholesterol (total number of atherosclerosis particles) and Apoprotein B promotes better risk evaluation when compared to LDL only in patients with diabetes mellitus or metabolic syndrome. Non-HDL = VLDL + IDL + LDL (VLDL = TC/TG, if TG < 400).

Other markers such as Apoprotein B, Apoprotein A1, and Lipoprotein(a) may be considered for risk evaluation. Apoprotein B is the most atherogenic of the lipoprotein and has a good correlation with LDL levels. It is considered a second-line marker in risk evaluation and a good predictor of cardiovascular risk [30]. On the other hand, Apoprotein A1, as the major protein of HDL, is correlated with HDL blood levels. Lipoprotein(a) provides complementary information in families with premature cardiovascular disease [15, 16, 28, 29].

Who Should Take This Drug?

Statins are indicated for high blood levels of LDL-cholesterol and for patients with cardiovascular risk ≥7.5 % [31]. For every reduction of 40 mg/dL in LDL-cholesterol, there is a corresponding 24 % reduction in major cardiovascular events [15, 17, 32, 33].

Statins should also be considered for patients with atherosclerosis [9, 31, 34], diabetes mellitus, asymptomatic patients with multiple risk factors (>5 % cardiovascular risk in 10 years), hypertriglyceridemia (TG > 500 mg/dL need statins combined to fibrates), and >21 years with elevated LDL [33]. Low levels of HDL-cholesterol are independent and are an inverse predictor of cardiovascular disease, since for every 1 mg/dL increase in HDL, there is a lowering in 2–3 % for the risk of coronary artery disease.

Special Situation

(a) Hemodialysis: There is no contraindication to statins, but the dose must be calculated for stages 3–5 of chronic kidney disease. Reduction of LDL and high-sensitivity C reactive protein decreases in 17 % incidence of major atherosclerotic events [15, 23, 35, 36].

(b) Peripheral vascular surgery: Statins have a protective effect on cardiovascular causes of death, improving pain-free walking distance and controlling inflammatory state and progression of atherosclerosis [2, 6, 8, 9, 11, 31]. It also decreases rates of amputation, patency rates after procedures, and limb salvage [8]. Although starting statins perioperatively increases the incidence of myopathy, risk is outweighed by benefits [15, 34].

(c) Liver disease: Use of statins is safe in patients with altered liver enzymes (less than 3 times upper limit) leading to the decrease of cardiovascular events in 68 %. The risk-to-benefit ratio was greater in patients with altered liver test, elevated dosage of ALT, and a high relation ALT-to-AST is a strong predictor of severe coronary disease. The benefits of statins in patients with altered liver enzymes above 3 times the upper limit remains unclear [15, 29, 37].

Targets of Treatment

There is no target LDL-cholesterol to achieve [6, 11, 12, 17]. The main objective of treatment is to decrease LDL level by 50 % or more. For every 1 mmol/L (40 mg/dL) reduction of LDL, cardiovascular morbidity decreases in 22 % [15, 27, 33].

Benefits are seen in reduction:

- Very high risk patients: LDL-cholesterol < 1.8 mmol/L (<70 mg/dL) [6, 15, 31];
- High risk: LDL-cholesterol < 2.5 mmol/L (<100 mg/dL) [9, 11, 12, 15, 31];
- Moderate risk: LDL-cholesterol < 3 mmol/L (<115 mg/dL); [15].

Regular blood tests, such as cholesterol and fractions, liver function, and non-HDL (includes also apolipoprotein B), should be evaluated to confirm response to treatment and adhesion to treatment [15, 16, 32].

Intensive statin regimens reduce 15 % more cardiovascular events than less intensive therapy and are indicated for patients with peripheral artery disease [8, 9, 38], with 13 % reduction of coronary death and nonfatal myocardial infarction, 19 % reduction of coronary revascularization, and 16 % reduction of ischemic stroke, but with elevation of hepatic enzymes [31, 39]. In more intensive regimens, for each 1 mmol/L (40 mg/dL) reduction in LDL, all-cause mortality and coronary artery disease were reduced in 10 % and 20 %, respectively [15, 17, 18, 27, 29, 40]. Intensive regimen is recommended for patients with >7.5 % CV risk and >75 years without contraindications [33].

Statin Therapy: Daily Doses

High intensive regimen: Atorvastatin 80 mg and rosuvastatin 20–40 mg [33].

Moderate intensive regimen: Atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin 40 mg bid, fluvastatin XL 80 mg, pitavastatin 2–4 mg [33].

Low intensity regimen: Simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, pitavastatin 1 mg [33].

Hipolipedemiant Non-statin Drugs

(a) Bile acid sequestrants (cholestyramine, colestipol, and colesevelam): Such class of drugs binds to bile acid during digestion impeding their reabsorption and increasing clearance of hepatic cholesterol for production of new bile acid, therefore increases LDL-receptor activity and decreases serum rates of LDL-cholesterol [15, 33]. Doses of 24 g of cholestiramine, 20 g of colestipol, or 4.5 g of cholestagel decreases LDL-cholesterol in 18–25 % with no effect on HDL. Side

effects are gastrointestinal (flatulence, constipation, dyspepsia, and nausea), reduced reabsorption of fat-soluble vitamins and important drug interaction (administration 4 h before or 1 h after other drugs) [15]. When used in association with statins, there is an additional decrease of 10–20 % of LDL-cholesterol [15].

(b) Cholesterol absorption inhibitors (ezetimibe): Such class of drugs reduces absorption of cholesterol and bile acid without intervene in fat-soluble vitamins metabolism [15]. As sole treatment, diminishes LDL-cholesterol levels in 15–22 % and combined to statins, lowers LDL-cholesterol in 30–44 %. Second-line treatment, normally prescribed with statins [15, 36]. Side effects are related to alteration of hepatic function and muscle pain. The recommended dose is ezetimibe 10 mg daily [15].

(c) Nicotinic acid: In a daily dose of 2 g, such drugs increase HDL by 25 %, decrease LDL in 15–18 % and TG in 20–40 %, and reduce Lipoprotein(a) in more than 30 %. They are better indicated in familial hyperlipidemia and metabolic syndrome patients [15].

(d) Fibrates: Such class of drugs is for the treatment of hypertriglyceridemia, generally when triglycerides are >2.3 mmol/L (or >200 mg/dL). It can reduce cardiovascular disease in 13 % [15]. Side effects are related to gastrointestinal disturbance, myopathy, elevation in hepatic enzymes, skin rash, pancreatitis, and deep vein thrombosis (impaired metabolism of homocysteine) [15].

Antiplatelet Therapy

Platelets have a significant role in atherothrombosis: Rupture of an atherosclerotic plaque induces platelet aggregation and vasoconstriction resulting in acute arterial occlusion [1, 6, 13, 41]. Antiplatelet therapy prevents platelet aggregation and represents, beside statins, one of pillars of treatment of cardiovascular disease [1, 5, 7, 11, 13, 41–43]. In patients with moderate risk, antiplatelet therapy reduces 10–15 cardiovascular events per 1000 [9, 43]. In high risk patients, antiplatelet reduced in 23 % incidence of cardiovascular events (vascular death, nonfatal myocardial infarction, and nonfatal stroke) [9, 18, 42, 43]. Similar benefits are demonstrated when aspirin is initiated after stroke and transient ischemic attack [43]. In patients with intermittent claudication, antiplatelet therapy lowers the rates of all-cause and cardiovascular death [7, 9, 44].

Aspirin

Aspirin has a commercial use as anti-inflammatory drug since beginning of 1900, but its antiplatelet action was reported only in 1953 and elucidated in 1971 [42]. It causes irreversible inactivation of cyclooxygenase, inhibiting conversion of arachidonic acid into thromboxane A2 and prostaglandin I1 [1, 13, 22, 41–43, 45, 46].

The effect of aspirin is dose dependent and cumulative and endures all life span of platelets (8–10 days), with 75 mg of aspirin reaching antiplatelet effect [42, 43, 45]. Doses of 75–150 mg/daily shows similar effects when compared to moderate

and high doses (160–1500 mg), but doses >325 mg/daily show an increased risk of bleeding and gastrointestinal side effects [3, 18, 42, 43, 47].

The use of doses of aspirin 75–325 mg/daily decreases in 12–14 % cardiovascular events (myocardial infarction, stroke, and cardiovascular death), diminishes in 21 % the risk of cardiovascular death, and prevents recurrent stroke in 1.5 % [6, 41–43, 45, 47]. The secondary prevention effect is well established in coronary artery disease, peripheral artery disease, and cerebrovascular disease [6, 8, 41]. there is no reduction in cardiovascular events in patients without established cerebrovascular or peripheral artery diseases and there is an increased risk of bleeding [6, 48].

Aspirin side effects relate to upper gastrointestinal symptoms and an increased risk of gastrointestinal bleeding (<1 %), vasoconstriction of renal circulation, and a nonsignificant increase in hemorrhagic stroke [41, 44, 45]. There are almost 20 % of aspirin resistance cases in population [1, 42, 46].

Thienopyridines (Clopidogrel, Ticlopidine, and Prasugrel)

Thienopyridines are selective and irreversible blockers of ADP-receptor which has its antiplatelet effect due blockade of glycoprotein IIb/IIIa complex [1, 6, 9, 22, 41, 42, 46, 49, 50]. It also has anti-inflammatory effects by reducing high-sensitivity C reactive protein, stabilizing atherosclerotic plaque, and diminishing intimal hyperplasia after endothelial lesion [42]. Ticlopidine has shown better results in reducing stroke, myocardial infarction, and vascular death when compared to placebo [6].

Clopidogrel shows better results in preventing secondary coronary artery disease, peripheral artery disease, and recurrent stroke when compared to aspirin. Clopidogrel reduces in 8.7 % the risk of ischemic stroke and death from vascular causes and also decreases in 23.8 % the incidence of myocardial infarction, with no increased risk of bleeding [2, 3, 6, 8, 9, 11, 12, 18, 22, 31, 42, 43, 47, 49]. Incidence of resistance to clopidogrel is 16–25 % [1, 6, 42, 49, 50].

Prasugrel is an irreversible thienopyridine approved only for the treatment of acute coronary syndrome and patients undergoing percutaneous coronary intervention. It demonstrates reduction of 19 % in death, nonfatal MI or stroke when compared to clopidogrel [1, 41, 47]. Has elevated risk of fatal bleeding in patients >75 years and underweight (<60 Kg) [47]. Side effects of thienopyridines are related to bone marrow depression (neutropenia), rash, and diarrhea [41, 44, 49]. Ticlopidine is taken at 250 mg twice a day and clopidogrel at 75 mg/daily with loading doses of 300 mg [42].

Other Antiplatelet Drugs

(a) Thrombin protease-activated receptor (PAR-1) blockers (vorapaxar and atopaxar): Decrease cardiovascular risk but at a cost of an increased risk of bleeding [2, 8]. When applied for peripheral artery disease, vorapaxar decreases

the risk of acute limb ischemia and peripheral revascularization [1, 2, 8, 11]. Vorapaxar is taken at dose of 2.5 mg daily [8].

(b) Glycoprotein IIb/IIIa receptor blockers (abciximab, tirofiban, and eptifibatide): Have an antiplatelet effect due blocking fibrinogen binding site [1, 41, 46]. Their use is intravenous and restricted to acute coronary syndrome and patients undergoing percutaneous coronary intervention [1]. Studies suggest perioperative benefits of abciximab in patients with critical limb ischemia or poor distal out-flow [22]. Side effects are related to thrombocytopenia [1].

(c) Ticagrelor: Reversible antagonist of P2Y12-receptor (binds in a different site on ADP-receptor of clopidogrel) that demonstrates superiority on prevention of cardiovascular death, myocardial infarction, and stroke when compared to clopidogrel, however with higher rates of intracranial bleeding [1, 6, 11, 41, 47]. Their side effects are bradyarrythmias, dyspnea, and impairment of renal function [47]. Is indicated only in dual therapy with aspirin for the treatment of acute coronary syndrome and for patients undergoing percutaneous coronary intervention [6, 41, 47].

(d) Truflusal: Is a new COX-1 inhibitor under investigation, preliminary studies demonstrate similar efficacy to aspirin in preventing recurrent vascular events with less intracerebral bleeding [47]. Not FDA approved.

(e) Sarpogrelate: Decreases platelet levels of 5-hydroxy-tryptamine (5-HT); it's been studied in peripheral artery disease with similar results to aspirin with less bleeding [47].

(f) Dipyridamole: Inhibits platelet phosphodiesterase 5 intensifying inhibitory effect of prostacyclin; its effects in primary and secondary prevention are not well established [41, 47].

(g) Picotamide: Inhibitor of thromboxane A2 synthase and thromboxane A2 receptor. Demonstrates inconclusive results in peripheral artery disease, suggesting benefits [13, 51].

Dual Platelet Drugs

Residual risk of cardiovascular events is high in the use of aspirin alone, and adding another antiplatelet drug increases antiplatelet effect [6, 42, 43]. Combination of aspirin and other antiplatelet (clopidogrel, ticlopidine, ticagrelor) has shown 20–36 % additional decreasing in cardiovascular risk in patients and is indicated in the management of acute coronary syndrome and patients undergoing percutaneous coronary or peripheral intervention, with slightly higher rates of bleeding [8, 31, 41–43, 51, 52]. In patients with previous stroke or peripheral artery disease, dual antiplatelet therapy didn't show benefits in preventing new events and had an increased risk of major bleeding and death [2, 3, 9, 12, 18, 31, 42, 47, 51, 53].

The combination of aspirin with intravenous infusion of glycoprotein IIb/IIIa blockers reduces the risk of acute occlusion in coronary arteries and stent in short time [43]. There isn't evidence of benefits of aspirin + dipyridamole [43].

Who Must Take This Drug?

All patients with moderate, high, or very high cardiovascular risk or evidence of symptomatic peripheral artery disease such as intermittent claudication should take aspirin 75–325 mg/daily [2, 11, 12, 22, 31, 54]. Even with the lack of improvement on symptoms, there is a significant reduction in cardiovascular events in patients with previous disease, particularly myocardial infarction and stroke [2, 3, 12, 13, 42–44, 51]. However, clopidogrel has been proved superior; relation cost-effectiveness favors aspirin [3]. In cases of contraindication for aspirin use, clopidogrel 75 mg/daily is indicated [3, 8, 43, 49, 54]. In asymptomatic patients with peripheral artery disease, there are no benefits of antiplatelet therapy that being indicated only in secondary prevention for coronary artery and cerebrovascular diseases [2, 3, 5, 7, 8, 13, 31, 48, 51, 55]. Dual antiplatelet therapy (aspirin and clopidogrel) is indicated after percutaneous procedures with implant of stents for 1–3 months [8, 22, 38].

Antihypertensive

Hypertension is a major risk factor for peripheral artery disease, affecting 55 % of these patients [4, 9, 31]. Solely, it is related to 7.5 million deaths every year, representing 13 % of all causes of death, specially cardiovascular related mortality [56]. In patients with peripheral artery disease, intensive blood pressure controls reduce cardiovascular events and death [2, 4]. Initially, it was believed that just by reducing blood pressure rates (independent of antihypertensive class), morbidity and mortality would decrease. However, now it's known that some antihypertensives, such as angiotensin-converting-enzyme inhibitor, have an additional effect on reduction of cardiovascular events. But this evidence isn't applicable in peripheral artery disease patients [2, 56].

The primary goal of the treatment is reduction of blood pressure and, if possible, reduction of cardiovascular events [57]. When choosing an antihypertensive therapy, one should consider pressure level target, quality of life, impact on other cardiovascular events, and comorbidities (renovascular disease, primary hyperaldosteronism, and diabetes) [4, 57].

Renovascular Disease

Renal blood flow is controlled by renin-angiotensin-aldosterone system and in the presence of obstructive disease in renal arteries, the use of angiotensin-converting-enzyme inhibitor may worsen renal function by decreasing renal perfusion [4, 31]. When angiotensin-converting-enzyme inhibitor is introduced for patients with renovascular disease there is an increasing of >20 % of creatinine in more than 50 % of patients [4]. Because the prevalence of renovascular disease is higher in peripheral artery disease patients [4], patients with hypertension and severe peripheral artery disease, or peripheral artery disease and resistant hypertension or impaired renal function must be screened for renal artery stenosis and renal function must be assessed regularly [4].

Renin-Angiotensin-Aldosterone Inhibitors

In peripheral artery disease patients, the use of renin-angiotensin-aldosterone inhibitors reduces in 5 % all-cause mortality and 7 % in cardiovascular mortality. Such effects are related not only because of the reduction of blood pressure, but due to additional blockade of pleiotropic effects of angiotensin II [4, 58]. These results are related to angiotensin-converting-enzyme inhibitor, which is responsible for a 10 % reduction, compared to no reduction with angiotensin-receptor blockers [4, 56, 59].

Angiotensin-converting-enzyme inhibitor is the first choice for patients with peripheral artery disease due to the reduction of cardiovascular risk [2, 9, 12, 18, 31, 59]. In patients taking daily 10 mg of ramipril was observed a reduction of 14 % in vascular death, nonfatal stroke, and nonfatal myocardial infarction [2, 4, 6, 9, 18, 31, 59]. These benefits are twofold high in patients with low ankle-brachial index and ramipril is associated with improvements in pain-free walking and maximal walking distance [4, 31].

Beta-Blockers

There is no evidence that beta-blockers worsen peripheral artery disease [2, 4, 9, 18, 31, 59, 60], on the contrary, adding beta-blockers seems to reduce cardiovascular death or myocardial infarction after peripheral artery reconstruction [4, 6, 9, 12, 18, 22]. The combination of beta-blockers and calcium channel blockers decreases maximum walking distance by 9 % [4]. If change in antihypertensive therapy is necessary, it is recommended the progressive decreasing of beta-blocker dose to prevent sympathetic events [4] and such class of drug should be avoided in patients with asthma, chronic obstructive pulmonary disease, cardiac failure, and low cardiac rate, and beware of hypoglycemia in diabetic patients [4].

Calcium Channel Blockers

There are two classes of calcium channel blockers: dihydropyridines (vasodilators that increase renal excretion of sodium and water) and cardioselectives (verapamil and diltiazem, which reduce cardiac output by diminishing cardiac rate and inotropism) [4]. In peripheral artery disease, it is suggested that verapamil reduces restenosis rates after intervention, but without showing differences in ankle-brachial index [59]. There are no differences comparing the use of beta-blockers, aldosterone-receptor blockers, and calcium channel blockers for cardiovascular events reduction in patients with peripheral artery disease [4, 59].

Options for Treatment

Optimal thresholds are defined as a reduction of blood pressure ≤140×90 mmHg and ≤130×80 mmHg for diabetic and in chronic renal disease patients [4, 6, 11, 18, 54]. However, there are recent trials proposing that systolic blood pressure should be under 120 mmHg for patients with high cardiovascular risk [2].

There is an inverse relation between ankle-brachial index and cardiovascular events. With intensive blood pressure control, this relation is lost [4], decreasing the risk of cardiovascular events, despite the concern with reduced flow and related organ ischemia [4].

There is no specific antihypertensive drug of choice for peripheral artery disease patients and hypertension [4], but there are some general recommendations:

- In non-black patients with less than 55 years—start with angiotensin-converting-enzyme inhibitor [4].
- Black ethnicity or >55 years—start with calcium channel blocker or thiazide diuretic [4].
- If necessary, add calcium channel blocker, and after thiazide diuretic [4].

Handling of Symptoms

Patients with peripheral artery disease usually manifest with intermittent claudication, progressing sometimes to critical limb ischemia [22]. Critical limb ischemia is defined by ischemic rest pain in leg or foot, gangrene, and ulcers [22]. Patients who cannot be revascularized or attempts of revascularization have failed have 50 % rates of amputation in 6 months and 25 % of patients with critical limb ischemia die in the first year from cardiovascular causes [22]. Management of symptoms of peripheral artery disease focuses on the improvement of quality of life, pain control, increasing walking distance, and limb salvage [6, 22].

Pain Control

In patients with critical limb ischemia, pain control is a major concern while surgical decision is not taken (revascularization or amputation) [22]. Starting with paracetamol and nonsteroidal anti-inflammatory medications for relief of pain and usually progressing to opioids, such as morphine, and antidepressant [6, 22, 61]. Nonsteroidal anti-inflammatory in patients with chronic kidney disease and hypertension should be avoided [22].

Pentoxyfilline

Pentoxyfilline is a methylxanthine derivative [9] which alters red blood cells conformability, diminishing blood viscosity and platelet aggregation, improving tissue

perfusion and oxygenation, and lowering fibrinogen levels [9, 31]. It was the first medication approved by FDA for intermittent claudication treatment, but today pentoxyfilline use is limited due to heterogeneity effects and data and diminished efficacy when compared to cilostazol [8, 9, 62]. Many studies have shown benefits on the use of pentoxyfilline compared to placebo, with unpredictable improvement in pain free and maximal walking distance [9, 22, 31] and no evidence of improvement on ankle-brachial index [31]. Although side effects are nausea, headache, drowsiness, and anorexia [31], pentoxyfilline is generally well tolerated and safe [31]. The dose is 400 mg taken 3 times per day [31, 54].

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor which increases intracellular levels of cyclic AMP [6, 8–10, 22, 31, 63, 64]. It has pleiotropic effects, such as antiplatelet aggregation, vasodilatory effects, improves HDL blood levels, and impairs triglycerides levels [9, 22, 31, 62]. It also works preventing restenosis rates after peripheral artery procedures [22, 31, 64]. Cilostazol associated to exercise is the first-line treatment for intermittent claudication. This drug improves in 50–70 % on pain-free walking distance and in 25 % maximum walking distance when compared to pentoxyfilline or placebo [2, 6, 8–10, 12, 22, 31, 63, 64]. There is no reduction on cardiovascular events, such as myocardial infarction, stroke or death, or evidence of increased bleeding complications when associated to aspirin and clopidogrel [6, 9, 10, 62]. Cilostazol side effects are headache, diarrhea, and palpitations, which determines difficulties in long-term adherence of patients [2, 8, 9, 64]. Recommended dose is 100 mg twice daily, and it's contraindicated in heart failure due to proarrhythmic effects [2, 8, 9, 31, 54, 62–64].

Naftidrofuryl (Nafronyl)

Naftidrofuryl is a 5-hydroxytryptamine-2 receptor antagonist which promotes vasodilatation in ischemic tissues [2, 8, 9, 31, 62, 63]. This drug class has shown better results in improving intermittent claudication, increasing maximum pain-free walking distance in 92 % compared to placebo (17 %) [2, 8, 9, 31, 63]. Dose is 100–200 mg, 3 times daily [62]. Prescribed in Europe, is non-FDA approved [2, 8, 9, 12, 31, 62, 63].

Prostanoids (Iloprost, Beraprost, Prostaglandin E1, and Prostacyclin)

endotheliumProstanoids are prostaglandin analogues that preserve vascular endothelium and prevent activation of leucocytes and aggregation of platelets. [9, 22]. Their use is usually restricted to patients with critical limb ischemia without perspective of revascularization or in whom surgical treatment has failed [22]. Intravenous infusion

of iloprost has shown 21 % increase in pain control and/or ulcer healing and diminishing amputation rates (23 % × 39 %) compared to placebo [6, 9, 12, 22]. Oral administration of iloprost is not effective on reduction of amputation rates or death, but improves mean maximum walking distance by 30 % [9, 12]. Better results are seen in administration for longer periods, of 4 or more weeks [6, 12, 22]. Side effects are facial flushing, headache, diarrhea, vomiting, and transient hypotension [6, 22, 54].

Other Peripheral Artery Disease Medical Therapy

Homocysteine

Hyperhomocysteine is an atherothrombotic risk factor in coronary, peripheral, and cerebrovascular diseases [9], inducing oxidative damage in endothelial cell and proliferation of vascular smooth muscle cells [9]. In patients with peripheral artery disease, homocysteine blood levels are elevated in 30 % of patients [31] and raising homocysteine in 1 μmol/L increases the risk of all-cause mortality in 3.6 % and cardiovascular death in 5.6 % [9]. The use of acid folic reduces in 25 % levels of homocysteine and cobalamin (vitamin B12) reduces in 7 % [31]. There is no evidence of reduction of cardiovascular events when decreasing homocysteine levels [9, 31, 54].

Levocarnitine (L-Carnitine)

Levocarnitine is a dietary supplement which serves as substrate for aerobic metabolism in skeletal muscle and acts on mitochondrial membrane transporting acylated fatty acids and acetate [9, 31]. It has shown an increase of 73 % in maximal and pain-free walking distance in patients with intermittent claudication compared to placebo (46 %) [9, 31]. Non-FDA approved for peripheral artery disease [9].

L-Arginine

In patients with peripheral artery disease, it works as vasodilator by increasing nitric oxide [9]. Preliminary studies, show increasing in 155 % in maximum walking distance when compared to placebo [9].

Gingko Biloba

Gingko biloba is an herbal extract with antiplatelet, vasodilatory, and antioxidant action used as dietary supplement [9]. Studies suggest nonsignificant improvement in walking distance although results are variable because of purity and potency of extract [9, 65]. Non-FDA approved.

Medical Therapy in Aortic Aneurysm and Acute Aortic Syndrome

The acute aortic syndrome is represented by three aortic pathologies: aortic dissection, intramural hematoma and penetrating atherosclerotic ulcers. [66, 67]. The common mechanism of lesion is a rupture in the media of aorta, with bleeding in intramural hematoma, or separation of intimal and media along the aorta in dissection, or ulceration of atherosclerotic plaque in intima in penetrating ulcer [66–68]. Aortic ulcers and intramural hematoma can lead to acute aortic dissection, pseudoaneurysm, or aorta rupture [68]. Surgical treatment is indicated in aortic rupture and intractable pain [68].

Aortic dissection represents the most prevalent aortic emergency [67]. The type A aortic dissection affects aortic root and arch and has 30 % mortality within first 24 h and 40 % mortality within 48 h [67, 68], the treatment of choice in this pathology is surgical, diminishing mortality in 1-month from 90 % in clinical treatment to 30 % in surgical treatment [67, 68]. Type B aortic dissection affects descending aorta and gold standard treatment is clinical management (78 % survival in 3 years after discharge) [67–69]. If complicated, with signals of organ ischemia, rupture, incontrollable blood pressure or refractory pain, surgical treatment is indicated [67–69]. Complicated type B aortic dissection have poor prognosis with 50 % mortality [67, 69].

Aortic aneurysm is a complex disease characterized by aortic dilatation of more than 50 % the normal aortic diameter due to media degeneration [70–72]. There is a direct relation between diameter, grown and rupture rates (in aortic diameter over 5 cm, for each 1 cm growth the rupture risk doubles) [70, 72, 73]. The major cause of death of aortic aneurysm is related to dissection and rupture and if untreated, approximately 80 % will progress to rupture [72]. The surgical treatment is specific for each aortic segment and individualized for every patient, usually including size criteria between 5 and 6.5 cm, growth rate >1 cm/year or pain [70, 72, 73].

The main goal of medical therapy in aortic aneurysm and acute aortic syndrome is to decrease shear stress on aortic wall (thus reducing rupture and growing rates), through blood pressure control, cardiac contractility and reduction of inflammation status [66–69, 72, 74].

Beta-Blockers

First-line therapy in both, acute aortic syndrome and aortic aneurysm, due to systolic blood pressure control and to reduce aortic wall stress [66–69]. Their use seem to improve survival [66–69, 71] in acute aortic syndrome and also appear to decrease aneurysmal degeneration in aortic dissection and late dissection-related procedures [68, 71]. Their use in aortic aneurysms remain unclear and contradictory, with some studies showing benefits in prevention on rupture and other studies demonstrating

reduction in aortic wall elasticity [68, 70, 74]. There is no significant evidence that use of beta-blockers reduce aneurysm expansion rate, but studies suggest lower growth rates [70–72].

Beta-blockers are indicated to maintain systolic blood pressure around 100–120 mmHg and heart rate 60–80 bpm [66–69, 74]. For blood pressure control, consider sodium nitroprusside in acute events, if necessary [69]. For patients with aortic aneurysm, consider duration of treatment (lifetime treatment) before beta-blockers introduction [74].

There is additional benefit when beta-blockers are initiated before surgery due to reduction in cardiovascular morbidity, but this benefit is only seen at least 1 month before surgery [70]. If it's started in perioperative period, there is an increased risk of intraoperative bradycardia and hypotension [70].

Calcium Channel Blockers

Calcium channel blockers have been related with survival improvement, but their role remains uncertain [68, 69]. Their use is indicated in patients with chronic obstructive pulmonary disease and in patients who don't tolerate beta-blockers [67, 69].

Angiotensin-Converting-Enzyme Inhibitors

Some studies have shown interference in aneurysm enlargement, but results are inconclusive [71]. This drug class was not associated to survival improvement [68, 72].

Angiotensin-Receptor Blockers

Seems to reduce aortic enlargement in patients with Marfan syndrome, but the studies are controversial [68, 72, 74]. No data related to prevention of aortic dissection [68, 72].

Statins

Small studies suggest benefits of use of statins in slowing enlargement rates of aortic aneurysm, and this drug is responsible for reduction in cardiovascular mortality and morbidity related to atherosclerotic disease [70]. Statins should be started 1 month before surgical treatment and maintained for life-long, mostly because their effect on reduction of cardiovascular events [70, 72].

Tetracycline and Macrolides (Doxycycline and Roxithromicin)

This drug class is a nonspecific matrix methaloproteinases inhibitor. In cases when there is overexpression of methaloproteinases, their use reduces elastin degradation

and consequently dilatation of artery [72]. Studies demonstrate no significant benefits on their use in aneurysmatic disease, with some series demonstrating trend in reduction of expansion rate [68, 71, 72, 74].

Antiplatelet Therapy

It seems to reduce cardiovascular risk and thrombus-related complication, such as rupture of aortic aneurysm, without significant raising in risk of bleeding [68, 70]. Association of antiplatelet therapy (aspirin) and statin seems to decrease abdominal aortic aneurysm growing rates, but data is not conclusive [68]. One should start aspirin and statins at diagnosis of aortic aneurysm in patients with atherosclerotic comorbidity due to reduction in major cardiovascular events and vascular death [68, 70, 72].

References

1. Buch MH, Prendergast BD, Storey RF. Antiplatelet therapy and vascular disease: an update. Ther Adv Cardiovasc Dis. 2010;4:249–75.
2. Solomon CG, Kullo IJ, Rooke TW. Peripheral artery disease. N Engl J Med. 2016;374:861–71.
3. Tangelder MJD, van Hattum ES. Antithrombotic therapy in peripheral artery disease—antiplatelet therapy, anticoagulants, both or none. Thromb Haemost. 2010;104:196–9.
4. Singer DRJ, Kite A. Management of hypertension in peripheral arterial disease: does the choice of drugs matter? Eur J Vasc Endovasc Surg. 2008;35:701–8.
5. Qian J, Yang XH. A meta-analysis of randomized controlled trials on antiplatelet agents versus placebo/control for treating peripheral artery disease. Medicine. 2015;94:e1293.
6. Di Minno G, et al. Systematic reviews and meta-analyses for more profitable strategies in peripheral artery disease. Ann Med. 2014;46:475–89.
7. Katsanos K, et al. Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. PLoS One. 2015;10:e0135692.
8. Olin JW, White CJ, Armstrong EJ, Kadian-Dodov D, Hiatt WR. Peripheral artery disease. J Am Coll Cardiol. 2016;67:1338–57.
9. Stoyioglou A, Jaff MR. Medical treatment of peripheral arterial disease: a comprehensive review. J Vasc Interv Radiol. 2004;15:1197–207.
10. Bedenis R, et al. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014;10:CD003748.
11. Vemulapalli S, Patel MR, Jones WS. Limb ischemia: cardiovascular diagnosis and management from head to toe. Curr Cardiol Rep. 2015;17:57.
12. Elsayed S, Clavijo LC. Critical limb ischemia. Cardiol Clin. 2015;33:37–47.
13. Violi F, Basili S, Berger JS, Hiatt WR. Handbook of experimental pharmacology, vol. 210. Berlin: Springer; 2012. p. 547–63.
14. Barter P, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007;357:1301–10.
15. Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–818.

16. Anderson TJ, et al. 2012 update of the Canadian cardiovascular society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29:151–67.
17. Ray KK, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J. 2014;35:960–8.
18. Endorsed by: the European Stroke Organisation (ESO), et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries * The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2851–906.
19. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci. 2010;86:484–93.
20. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001; 5:378–87.
21. Ridker PM, Cook NR. Comment statins: new American guidelines for prevention of cardiovascular disease. Lancet. 2013;1–4. doi:10.1016/S0140-6736(13)62388-0.
22. Lumsden AB, Davies MG, Peden EK. Medical and endovascular management of critical limb ischemia. J Endovasc Ther. 2009;16(2 Suppl 2):II31–62.
23. Fellström BC, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
24. Ridker PM, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
25. Longo DL, Mammen AL. Statin-associated autoimmune myopathy. N Engl J Med. 2016;374:664–9.
26. Sattar N, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–42.
27. Collaboration CTTC. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
28. Collaborators CTTC. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
29. Authors/Task Force Members, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2012;33:1635–701.
30. Boekholdt SM, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012;307:1302–9.
31. Conte MS, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2015;61:1–40. doi:10.1016/j.jvs.2014.12.009.
32. Schulte JM, Rothaus CS, Adler JN. Starting statins—polling results. N Engl J Med. 2014;371:e6.
33. Stone N. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. 2013;1–85. doi:10.1161/01.cir.0000437738.63853.7a/-/DC1.
34. Schouten O, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med. 2009;361:980–9.
35. Wanner C, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.

36. Baigent C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
37. Athyros VG, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376:1916–22.
38. Kinlay S. Management of critical limb ischemia. Circ Cardiovasc Interv. 2016;9:e001946.
39. LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.
40. Nicholls SJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365:2078–87.
41. Cheng JWM. Updates in antiplatelet agents used in cardiovascular diseases. J Cardiovasc Pharmacol Ther. 2013;18:514–24.
42. Manolis AS, Tzeis S, Andrikopoulos G, Koulouris S, Melita H. Aspirin and clopidogrel: a sweeping combination in cardiology. Curr Med Chem Cardiovasc Hematol Agents. 2005;3:203–19.
43. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.
44. Wong PF, Chong LY, Mikhailidis DP, Robless P, Stansby G. Antiplatelet agents for intermittent claudication. Cochrane Database Syst Rev. 1996;(11):CD001272. doi:10.1002/14651858.CD001272.pub2.
45. Wood A, Patrono C. Aspirin as an antiplatelet drug. N Engl J Med. 1994;330(18):1287–94.
46. Clappers N, Brouwer MA, Verheugt FWA. Antiplatelet treatment for coronary heart disease. Heart. 2005;93:258–65.
47. Vidal SGM, Ruland S. Platelet antiaggregants in stroke prevention. Neurol Clin North Am. 2013;31:633–57.
48. Seshasai SRK. Effect of aspirin on vascular and nonvascular outcomes. Arch Intern Med. 2012;172:209.
49. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348:1329–39.
50. Savi P, Nurden P, Nurden AT, Levy-Toledano S, Herbert JM. Clopidogrel: a review of its mechanism of action. Platelets. 1998;9:251–5.
51. Berger PB, et al. bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial. Circulation. 2010;121:2575–83.
52. Mauri L, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014;371:2155–66.
53. The SPS3 Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012;367:817–25.
54. Lambert MA, Belch JJF. Medical management of critical limb ischaemia: where do we stand today? J Intern Med. 2013;274:295–307.
55. Fowkes F, Price JF, Stewart M, Butcher I. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303(9):841–8.
56. van Vark LC, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J. 2012;33:2088–97.
57. Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. Combination therapy in hypertension. J Am Soc Hypertens. 2010;4:42–50.
58. Shahin Y, Khan JA, Samuel N, Chetter I. Atherosclerosis. Atherosclerosis. 2011;216:7–16.
59. Treatment of hypertension in peripheral arterial disease (Review). 2013;1–48.

60. Paravastu SCV, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease (Review). 2012;1–32.
61. Bailey M, Griffin K, Scott D. Clinical assessment of patients with peripheral arterial disease. Semin Intervent Radiol. 2014;31:292–9.
62. Agrawal K, Eberhardt RT. Contemporary medical management of peripheral arterial disease. Cardiol Clin. 2015;33:111–37.
63. Knepper JP, Henke PK. Diagnosis, prevention, and treatment of claudication. Surg Clin North Am. 2013;93:779–88.
64. Rogers KC, Oliphant CS, Finks SW. Clinical efficacy and safety of cilostazol: a critical review of the literature. Drugs. 2015;75:377–95.
65. Nicolaï SP, et al. Ginkgo biloba for intermittent claudication. Cochrane Database Syst Rev. 1996;(6):CD006888. doi:10.1002/14651858.CD006888.pub3.
66. Nienaber CA, Powell JT. Management of acute aortic syndromes. Eur Heart J. 2012;33:26–35.
67. Thrumurthy SG, Karthikesalingam A, Patterson BO, Holt PJE, Thompson MM. The diagnosis and management of aortic dissection. BMJ. 2012;344:d8290.
68. Erbel R, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. Eur Heart J. 2014;35:2873–926.
69. Karthikesalingam A, Holt PJE, Hinchliffe RJ, Thompson MM, Loftus IM. The diagnosis and management of aortic dissection. Vasc Endovasc Surg. 2010;44:165–9.
70. Moll FL, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41:S1–58.
71. Goldfinger JZ, et al. Thoracic aortic aneurysm and dissection. J Am Coll Cardiol. 2014;64:1725–39.
72. Danyi P, Elefteriades JA, Jovin IS. Medical therapy of thoracic aortic aneurysms: are we there yet? Circulation. 2011;124:1469–76.
73. Bobadilla J, Orr N, Minion D. Thoracoabdominal aortic aneurysm repair: current endovascular perspectives. Vasc Health Risk Manag. 2014;10:493. doi:10.2147/VHRM.S46452.
74. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm. J Am Coll Cardiol. 2010;55:841–57.

Appendix A: Doppler Ultrasound and Ankle–Brachial Pressure Index

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Abstract

The ankle–brachial index is one of the simplest, costless, and with utmost importance tool for the diagnosis, screening, and segment of peripheral arterial disease and we need to know how to use it. The simplicity of the examination with Doppler ultrasound is undoubtedly the factor that most contributes to the adoption of this device as vascular preliminary tool. As a blood velocity detector, Doppler ultrasound can be used to determine the systolic pressure of the arteries, which are the targets of the study. In this case, a sphygmomanometer is also required. They will be used in determined limb segments (upper and lower limbs) to temporarily occlude the blood flow and consequently assess the related blood pressure. The normal value of the index is 0.9–1.1. Values less than 0.9 indicate peripheral arterial disease and it is correlated with increased risk of future cardiac events. The index can be related with symptoms according to its value. When the ABI falls to 0.7–0.8 it is associated with lameness, 0.4–0.5 indicates pain, and 0.2–0.3 is typically associated with gangrene and nonhealing ulcers.

Doppler Ultrasound

The Austrian physicist Johann Christian Andreas Doppler (1803–1853) observing the different colorations that certain stars had questioned why this phenomenon. In 1842, he discovered the modifying effect of the vibration frequency caused by the relative movement between the source and the observer. This became known as the "Doppler effect." The Doppler effect is a part of the modern theories of the early universe (Big Bang and the red shift). It is currently used in radar, navigation, the study of the movement of the stars, and the study of cardiovascular diseases.

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In vascular diseases, the Doppler effect applies to the frequency change caused by the speed of the blood cells. Portable Doppler apparatus used in clinical practice sends continuous wave ultrasound produced by a crystal. The other crystal located in the same transducer receives the echo. It works with frequencies between 5 and 10 MHz. Since these are wide frequencies, the lower (5 MHz) capture deeper vessels because they have greater tissue penetration power; and the highest (10 MHz) capture more superficial vessels, being better for the study of the distal veins of the limbs.

The simplicity of the examination with Doppler ultrasound is undoubtedly the factor that most contributes to the adoption of this device as vascular preliminary tool. As a blood velocity detector, Doppler ultrasound can be used to determine the systolic pressure of the arteries, which are the targets of the study. In this case, a sphygmomanometer is also required. They will be used in determined limb segments (upper and lower limbs) to temporarily occlude the blood flow and consequently assess the related blood pressure.

Sphygmomanometer

The correlation between the size of the pneumatic cuff and ankle circumference is not well established, so it should adopt the same ratio used in the upper limb. Therefore, the pneumatic cuff should cover at least 40 % of the limb circumference in which will be measured the systolic blood pressure. Schematically the technique for obtaining the ankle–brachial index is:

- Make sure that the patient did not smoke at least 2 h before the test.
- Put the patient in the supine position with the head and heels completely supported on the bed. Next, we should expect a rest period, which varies between 5 and 10 min.
- Ask the patient to remain still during the examination.
- The sequence of statements should preferably be in this order: right arm, right ankle (preferably the posterior tibial artery), left ankle, left arm, and right arm again. Repeat the first step performed to avoid falsely high values resulting from anxiety or ‘white-coat effect.’
- Place the sphygmomanometer involving at least 40 % of limb, apply the gel on the Doppler sensor and place it on the pulse zone at an angle of 60° with probable trajectory of the vessel analyzed. Ordinarily it means 60º to 45º with the skin. The probe must be moved until the clearest sound is audible.
- The cuff should be progressively inflated to 20 mmHg above the level of disappearance of the flow signal, and then deflated slowly to detect the pressure level at the reappearance of flow signal.

After this, divide the value of the target artery pressure by the value of the brachial artery pressure. Usually, the index is expressed in terms of the highest value in the tibial arteries; it is called the ankle–brachial pressure index. It can be similarly determined the index of popliteal pressure or from the arteries of the arms with respect to each other.

Ankle–Brachial Pressure Index

The normal value of the index is 0.9–1.1. Values less than 0.9 indicate peripheral arterial disease and it is correlated with increased risk of future cardiac events. The index can be related with symptoms according to its value. When the ABI falls to 0.7–0.8 it is associated with lameness, 0.4–0.5 indicates pain, and 0.2–0.3 is typically associated with gangrene and nonhealing ulcers.

In general, diseases like diabetes and chronic renal failure leave patients to have calcified arteries and this may be difficult for the index measurement, because it can have aberrant pressure reading above 1.4. In these cases, additional noninvasive studies are required, such as pulse volume recording, which gives a waveform, typically not affected by medial calcification.

In addition to the application of the index to characterize the degree of limb ischemia, their use is recommended for routine evaluation of the following patients for the detection of peripheral arterial disease:

- all patients who present symptoms in the lower limbs in walking;
- all patients aged between 50 and 69 and have a cardiovascular risk factors (diabetes or smoking);
- all patients aged 70 or older regardless of cardiovascular risk factor; and
- all patients with a risk score of Framingham between 10 and 20 %.

This is one of the simplest, costless, and with utmost importance tool for the diagnosis, screening, and segment of peripheral arterial disease and we need to know how to realize the ankle–brachial index.

Appendix B: Vascular Imaging Techniques

Alexandre de Tarso Machado

Abstract

This chapter is about the most frequent diagnostic exams in angiology and vascular surgery practiced nowadays. The highlights of ultrasound, computed tomography, magnetic resonance imaging, and scintigraphy are described in topics divided into definition, basic physical principle, best indications, and limitations.

Ultrasonography (Ultrasound)

Ultrasonography is characterized as innocuous, noninvasive, relatively cheap, and widely spread tool that uses the echo produced by sound from the body tissues' reflections to generate images [1]. The images in grayscale, named as Mode B, are bidimensionals and they can be associated with blood flow velocity (Doppler) resulting in duplex ultrasound, useful in the study of arterial and venous systems [1]. The lymphatic system cannot be well studied by US due to its small diameter resulting in limited indications [1].

In vascular imaging, the ultrasonography stands out for allowing study of the vessels anatomy, by determining the caliber, tortuosity, branches, stenosis, thrombus, and blood flow velocity [1, 2]. The most frequent indications involve venous and arterial systems of upper and lower limbs, carotid, aorta and iliac arteries, iliac veins, inferior vena cava, visceral arteries (especially liver and kidney), vascularized tumors, malformations, and arteriovenous fistulae [1–3].

Also, it is possible to perform image-guided procedures using the ultrasonography, such as vascular punctures or arteriovenous malformation embolizations3.

Due to the inability to generate images from air and bones, ultrasonography is not indicated to study the lungs, gastrointestinal tract, vessels, or other structure

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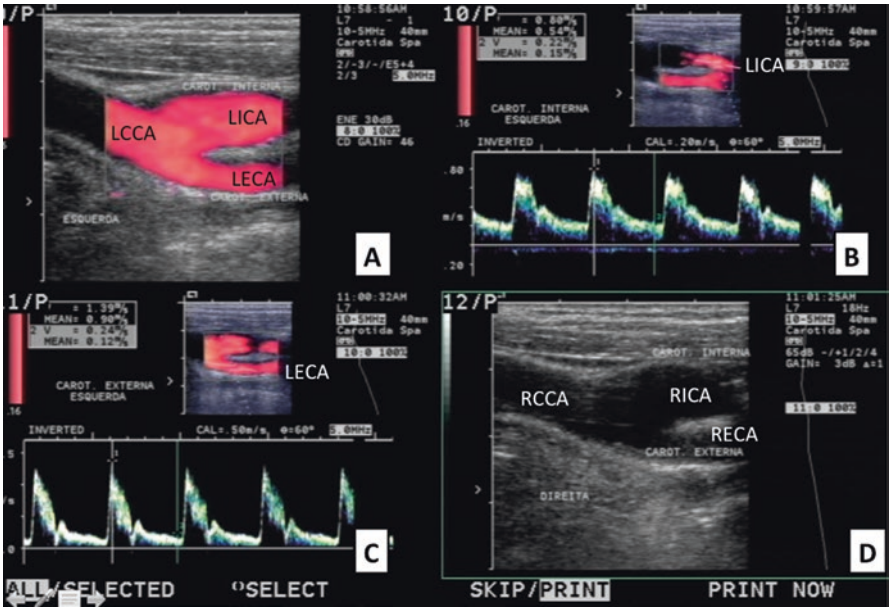

Fig. B.1 Echo Color Doppler imaging of carotid vessels. (**a**) Left common carotid artery (LCCA), left internal carotid artery (LICA), and left external carotid artery (LECA) are patent demonstrated by color and bidimensional mode ultrasonography (Duplex scan). (**b**, **c**) Left internal carotid artery (LICA) with monophasic flow and left external carotid artery (LECA) with biphasic flow obtained by duplex with Doppler ultrasonography. (**d**) Right common carotid artery (RCCA), right internal carotid artery (RICA), and right external carotid artery (RECA) in bidimensional mode ultrasonography (grayscale). Note that in this last case, the blood flow cannot be identified and studied

hidden inside or near the bones such as the cranium, chest, maxilla, or vertebral column, for example. Besides that, it is an operator-dependent diagnostic method that could compromise the quality of the exams.

Computed Tomography

It is one of the main diagnostic imaging for the evaluation of anatomical structures throughout the body. The images are obtained from the detected x-ray voltage values and converted into grayscale images based on digital units (Hounsfield Unit) [1]. It is possible to generate three-dimensional and multiplanar reconstructions to calculate stenosis and to manipulate images with the postprocessing resources, increasing its potential in diagnostic and therapeutic planning. For example, detailing the anatomy of the aortic aneurysm to choose the best technique and material to be used in this situation [4]. Computed tomography angiography (or simply angiotomography) details the vascular anatomy using iodinated contrast media administered intravenously [1]. Unlike the ultrasound that is incompatible with the analysis

of structures close to the bone and air, angiotomography has application in the whole body, being indicated in the study of the intracranial circulation (as ischemic or hemorrhagic stroke, aneurysms, tumors, bruises, and arteriovenous malformation); in intrathoracic cardiovascular system (such as heart and cardiac vessels, pulmonary circulation, stenosis, aneurysms, dissections, ulcer, fistula, trauma, and compression); in arterial and venous circulation of the limbs, abdomen, and pelvis [4]. There is limited application of the computed tomography in the lymphatic system due to its small anatomy [4].

Its major disadvantages are the generation of ionizing radiation related to radiation injury in very high doses, bone marrow aplasia, genetic mutations, teratogenesis and cancer, and the risk of nephrotoxicity (2–5 %) and anaphylactic shock (<1 %) induced by iodinated contrast. Besides that, compared to ultrasound, computed tomography needs a more complex room with dedicated structure and it is expressively more expansive, resulting in a relatively low availability in certain places [1, 2, 4].

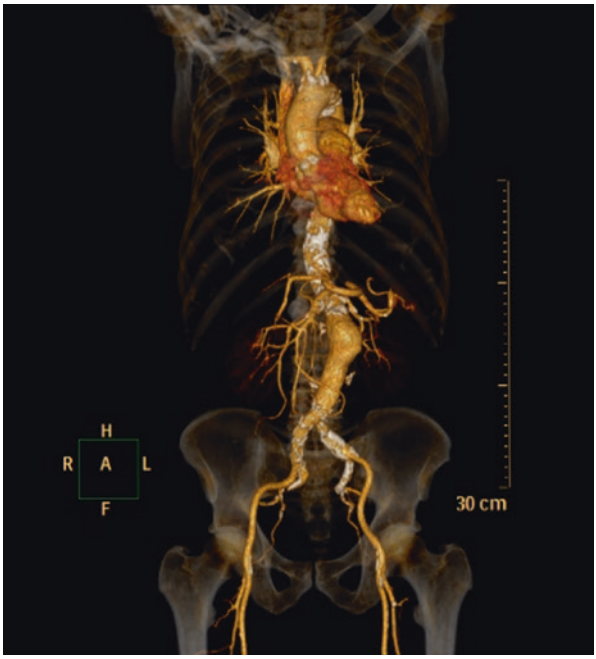

Fig. B.2 Three-dimensional reconstructed computed tomography revealing anatomic details of a patient with abdominal aortic aneurysm with atheromatosis (white plaques throughout the aorta and iliac arteries)

Magnetic Resonance Imaging

Noninvasive imaging method based on a powerful magnetic field capable of aligning the direction of the orbits of hydrogen electrons, providing accurate anatomical details of the body [1]. Like computed tomography, it is possible to edit images after their acquisition, generating three-dimensional and multiplanar reconstructions to increase the accuracy and therapeutic planning [5]. It can also be used in intravenous contrast media (in this case, the gadolinium) to study the vascular system, but with low sensitivity to diagnosis lymphatic diseases [6].

Its indications stand out over the study of musculoskeletal system; arteriovenous malformations, especially those that involves soft tissue; biliary tract; pelvic organs; central nervous system; and fetal anomalies (this last because magnetic resonance does not use ionizing radiation) [5]. Besides that, are equivalent to computed angiography in exploring the cardiovascular system (vascular anatomy, stenosis, aneurysms, dissections, ulcer, fistula, trauma, and compression) [5, 6].

Despite the gadolinium does not cause anaphylactic reaction as the iodine contrast media, it can cause nephrogenic systemic fibrosis. A rare, progressive, and lethal disease committing less than 1 % of patients with renal impairment. Other limitations are claustrophobia; higher cost and lower availability (when compared to computed tomography and ultrasonography); and incompatibility with ferromagnetic materials such as stretchers, prostheses, and metallic needles [1, 2, 5].

Scintigraphy

Diagnostic test used in nuclear medicine considered as a functional exam and not only an anatomic test as ultrasonography, computed tomography, and magnetic resonance imaging [7]. It is based on radioactive media administered intravenous, oral, inhalation, or subcutaneous with natural affinity to different organs and tissues according to its pathophysiological characteristics. After reaching the target, the radiation emitted by the radiopharmaceutical is converted to images as their distribution and time elimination [8]. The main limitations of the scintigraphy are low resolution for anatomical images, availability of some special radiotracers and study time (up to an hour depending on the physiological process), and potential complication of worsening obstruction secondary to the dye in some situations [7, 8]. The major indications are in the cardiovascular field (coronary scintigraphy), allowing to locate and to assess the severity of ischemic damage, to detect collateral branches, and to estimate the improvement in cardiac function after myocardial revascularization and drug treatment [7]; and in the study of the lymphatic system (lymphoscintigraphy), to locate lymph node basis of risk for metastatic disease (especially ambiguous drainage tumors, as the midline); to identify "in transit metastasis," proved essential in predicting the risk of micrometastasis in patients with cancer (sentinel lymph node); and in lymphedema assessment in order to confirm the diagnosis, detect anatomical sites more precisely and follow up [8].

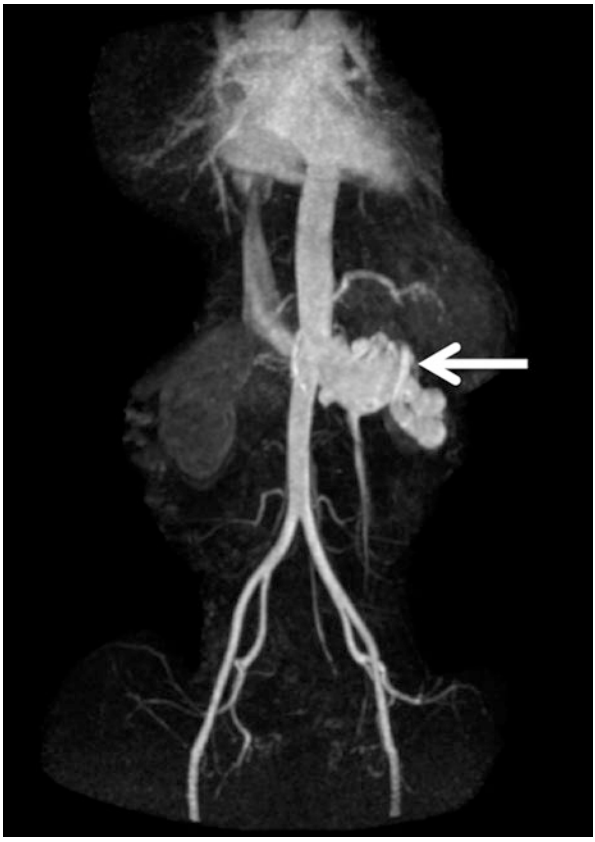

Fig. B.3 Three-dimensional reconstructed magnetic resonance from a patient with arteriovenous fistulae in the left kidney. Note the nidus (*arrow*) and the early contrast media in inferior vena cava

References

1. Collins R, Cranny G, Burch J, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. Health Technol Assess. 2007; 11(20):1–184.
2. Berger FH, Nieboer KH, Goh GS, Pinto A, Scaglione M. Body packing: a review of general background, clinical and imaging aspects. Radiol Med. 2015;120(1):118–32.
3. Marin JR, Lewiss RE. Point-of-care ultrasonography by pediatric emergency medicine physicians. Pediatrics. 2015;135(4):e1113–22.
4. Caputo ND, Stahmer C, Lim G, Shah K. Whole-body computed tomographic scanning leads to better survival as opposed to selective scanning in trauma patients: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2014;77(4):534–9.
5. Ohno Y. New applications of magnetic resonance imaging for thoracic oncology. Semin Respir Crit Care Med. 2014;35(1):27–40.

6. Berman DS, Hachamovitch R, Shaw LJ, et al. Roles of nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance: assessment of patients with suspected coronary artery disease. J Nucl Med. 2006;47(1):74–82.
7. Mieres JH, Makaryus AN, Redberg RF, Shaw LJ. Noninvasive cardiac imaging. Am Fam Physician. 2007;75(8):1219–28.
8. Vignes S. Treatment of varicose veins and limb lymphedema. J Mal Vasc. 2014;39(1):57–61.

Glossary

Activated partial thromboplastin time (aPTT) A sample of the plasma is extracted from the blood sample. An activator of the intrinsic pathway of coagulation (such as silica, celite, kaolin, ellagic acid) is added, and the time the sample takes to clot is measured optically.

Acute aortic syndrome aortic pathologies caused by disruption in media layer of aorta, and holds aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection represents the most prevalent aortic emergency.

Amaurosis Complete or partial blindness without damage to the eyeball. It may be caused by diseases of the optic nerve, retina, spinal cord, or brain.

Amplification phase Second phase the cell-based model hemostasis, occurs on surfaces of platelets, with activation of these and clotting factors.

Ankle–brachial index The systolic pressure at the ankle, divided by the systolic pressure at the arm.

Antihypertensive medication which controls blood pressure thus reducing cardiovascular events and death.

Antiplatelet therapy interrupts atherothrombotic process through inhibition of platelet aggregation, is a cornerstone therapy in treatment of atherosclerotic disease.

Aortic aneurysm is a complex disease characterized by aortic dilatation of more than 50 % the normal aortic diameter due to media degeneration.

Aortic dissection is the separation of the aortic layers after a sudden elevation of blood pressure causing the rupture and consequently detachment of the inner layer, creating a new lumen.

Artery dissection tear inside an artery. When the inner layers of the artery separate from the outer layers. The pressure of the pooling blood can make a short tear much longer and blood trapped between the layers can form a blood clot.

Artery kinking abnormal elongation of internal carotid artery with an angulation of the artery of 90° or less. Often associated with stenosis of the artery.

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Atherosclerosis cholesterol deposits in and fibrosis of the inner layer of the arteries.

Autograft when the donor and recipient are the same.

Baropodometry is a method of measuring pressures on the surface of the foot during standing or walking. Used most often for biomechanical analysis of gait and posture.

Branched an offshoot or a division of the main portion of a structure. In this case a division of an endograft.

Cardiovascular event myocardial infarction, stroke, and other obstructive arterial event.

Catheterization is the insertion and navigation of a catheter into the vessels for diagnostic and interventional purposes.

Cell-based model of the hemostasis Current model of secondary hemostasis, which has three phases: initiation, amplification, and propagation.

Claudication ischemic leg or foot pain during exertion, caused by obstructive vascular disease on peripheral arteries.

Coagulation Following enzymatic reactions that culminated in the formation of fibrin.

Coagulation factors An activated proenzyme will activate others proenzymes in a sequential cascade of reactions that will form fibrin eventually.

Coalesce To unite in one body or in a larger whole.

Confidence interval gives a range of values which is likely to include an unknown parameter.

Critical limb ischemia most severe manifestation of obstructive disease, which includes rest limb pain, gangrene, and ischemic ulcers.

Cytotoxic toxic to cells.

Debridement or debridement, cleaning process, removal of necrotic tissue adhered or bodies/foreign particles in the bed of the wound using surgical technique, mechanical and/or chemical.

Deep venous thrombosis Formation of thrombi (blood clots) in the deep veins of the vascular system of the members. It is most common in the lower limbs and can complicate as pulmonary embolism or postthrombotic syndrome.

Diabetic neuropathy Is a type of nerve damage that can occur in people with diabetes, most often in legs in feet. Depending on the affected nerves, symptoms of diabetic neuropathy can range from pain and numbness to muscle weakness; loss of balance and coordination; and serious foot problems, such as ulcers and infections. Peripheral neuropathy is the most common form of diabetic neuropathy. Signs and symptoms of peripheral neuropathy are often worse at night.

Doppler effect Change in frequency of a wave for a moving observer in relation to its source.

Dressings products used for prevention and treatment of wounds.

Dyslipidemia alteration of serum levels of lipidis (e.g., HDL, LDL, triglycerides).

Dyslipidemia altered metabolism of cholesterol and their fraction, is a major risk factor for cardiovascular obstructive disease.

Ectoscopy global vision of the patient, including general health and any physical and psychological characteristics evident.

Eczema erythematous dermatitis which may progress to blistering, weeping, or eruption of the skin.

Ehlers–Danlos syndrome is a hereditary disease of the connective tissue that inhibits the synthesis of collagen that is present in the skin, joints, muscles, ligaments, blood vessels, and visceral organs. The lack of collagen turns these structures susceptible to deformities.

Embolism a bubble of air, a solid mass of blood that has become hard, or a small piece of fat that blocks an artery.

Embolization endovascular procedure used to treat bleeding or some types of tumors (including high-flow malformations) by deliberately blocking blood vessels with small particles, coils, or polymer agent.

Endarterectomy is a surgical procedure to remove the atheromatous *plaque* material, or blockage, in the lining of an artery constricted by the buildup of deposits. It is carried out by separating the plaque from the arterial wall.

Endograft A graft introduced using endovascular methods.

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Endothelium cell layer that is internally lining the blood vessels.

Endovascular relating to a surgical procedure in which a catheter containing medications or miniature instruments is inserted through the skin into a blood vessel for the treatment of vascular disease.

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Endovascular Therapy interventional radiology techniques to treat disease inside blood vessels. The techniques involve the introduction of a catheter percutaneously into a large blood vessel (usually femorals). The catheter is injected with a radio-opaque contrast dye that can be seen on fluoroscopy (live X-ray). As the contrast courses through the blood vessels, characteristic images are seen by experienced viewers and can assist in the diagnosis and treatment of diseases.

Endovenous ablation thermal energy that obliterate the vein.

Enzyme Protein capable of catalyzing chemical reactions.

Erythema Redness of the skin caused by dilatation of capillaries—usually a sign of inflammation.

Esthesiometry The measurement of sensory (as tactile) discrimination.

Exudate liquid with a high content of serum proteins and leukocytes produced in response to tissue damage and blood vessels.

Fenestrated to pierce with one or more openings.

Flebotônicas are a heterogeneous class of drugs containing plant extracts (e.g., flavonoids) and synthetic compounds (e.g., calcium dobesilate).

Foot care Daily foot care for people likely to develop foot problems. It involves all aspects of preventative and corrective care of the foot and ankle.

Footprinting mat A tool made of a rubber mat that is used for taking footprints to screening for foot ulceration.

Gait analysis The systematic study of human motion that uncovers precisely how the body is moving. It is done using the eye of observers, augmented by instrumentation for measuring body movements, body mechanics, and the activity of the muscles.

Gangrene Necrotic slough.

Hazard ratio A measurement of how often an event happens in one group compared to other group, over time.

Hematemesis the vomiting of blood.

Hematemesis the vomiting of blood.

Hemostasis set of mechanisms that keeps the blood fluid inside the vessel without causing bleeding and without cause thrombosis.

Heptest It is an alternative to aPTT. Test consists of incubating an undiluted plasma or whole blood sample with an equal volume of factor Xa. This reaction mixture is then recalcified by the addition of RECALMIX—a reagent containing optimal concentrations of calcium chloride and brain cephalin in a bovine plasma fraction rich in factor V and fibrinogen. It is used to monitor anticoagulant effect.

Hoarseness a rough quality of the voice.

Hydronephrosis cystic distension of the kidney caused by the accumulation of urine in the renal pelvis as a result of obstruction to outflow and accompanied by atrophy of the kidney structure and cyst formation.

Hyperemia is an increase in the amount of circulating blood in a given location.

Hyperglycemia increased glucose in the bloodstream.

Hyperkeratosis is thickening of the stratum corneum (the outermost layer of the epidermis), often associated with the presence of an abnormal quantity of keratin, and also usually accompanied by an increase in the granular layer.

Hypoallergenic Product with less potential to cause allergic reactions.

Initiation phase first phase cell-based model of hemostasis, occurs on cell surfaces containing tissue factor, which produces an insufficient amount of thrombin, but of importance for amplification stage.

Intermittent claudication Intermittent claudication is a pain in the leg that a person experiences when walking or exercising. The pain is intermittent and goes away when the person rests.

Ischemia a medical problem in which there is not enough blood flowing to a part of the body.

Ischemia Reduction or interruption in the blood supply of certain vascular territory.

Keratinocytes keratinocytes or differentiated cells are of epithelial tissue (skin) and invaginations of the epidermis to the dermis (such as hair and nails). Keratinocytes form the epidermal five layers: basal layer, spinous layer, granular layer, lucid layer, and stratum corneum.

Lacunar infarcts type of stroke that results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures.

Lichenification is a skin condition that results in thick, leathery patches of skin. This thickening of the skin is caused by the deposits of dead skin cells that stick to the skin;s surface; this result is actually meant to be a form of defense from future itching or rubbing. Occasionally, cracks form in the skin, bearing a frightening resemblance to tree bark.

Livedo reticularis is a skin found, characterized by the appearance of reddish or bluish traces on the skin, with irregular borders that follow exactly the arrangement of veins.

Lower limb amputation The surgical removal of a leg, foot, or toes from the body. The major categories of lower limb amputation include foot, toe, transtibial, transfemoral amputations, knee and hip disarticulation.

Lumbar puncture It is a medical procedure in which a needle is inserted into the spinal canal, most commonly to collect cerebrospinal fluid for diagnostic testing.

Malperfusion syndrome is caused by the involvement of aortic branches in dissection and reduces blood supply to the organs involved.

Marfan syndrome is an inherited disease of the connective tissue that affects organs such as heart, eyes, blood vessels, and skeleton. The clinical manifestations are varied and can present increased stature, elongated members, alterations in the spine, aortic dilation, mitral valve prolapse, and changes in lens.

Meta-analysis a statistical method to combine the results of independent studies.

Nidus vascular malformation forming the transition between the feeding artery and draining vein.

Nonvitamin K antagonists oral anticoagulants New oral anticoagulants drugs. There are two distinct action methods: directly inhibit the factor Xa of the coagulation cascade, as rivaroxaban, or directly inhibit thrombin, as dabigatran.

Number needed to treat (NNT) is the average number of patients who need to be treated to prevent one additional bad outcome. Is an epidemiological measure used in communicating the effectiveness of a healthcare intervention, typically a treatment with medication.

Obstructive vascular disease obstruction of artery where atherosclerosis represents main cause, is widespread in arterial territories, and peripheral manifestation is claudication and critical limb ischemia.

Oncotic pressure or colloid osmotic pressure is a form of osmotic pressure exerted by proteins, notably albumin, in a blood vessel's plasma that usually tends to pull water into the circulatory system. It is the opposing force to hydrostatic pressure.

Orthostatic Body position vertical, standing.

Osteomyelitis Infection in a bone. There are several different ways to develop the bone infection. The first is for bacteria to travel through the bloodstream (bacteremia) and spread to the bone or spreading from nearby tissue. Infections can also begin in the bone itself if an injury exposes the bone to germs.

Pericardiocentesis this procedure is the drainage of the area between heart and pericardium by needle puncture. The pericardium is the membrane that surrounds the heart.

Peripheral arterial disease Atherosclerosis of limb arteries resulting in blood flow impairment. Ultimately it will lead to intermittent claudication, rest pain, or dry gangrene.

Phlegmasia cerulea dolens It is the most serious deep vein thrombosis clinical manifestation and it presents as venous gangrene. It is a serious and rare condition and can be associated to cancer, heparin-induced thrombocytopenia, and depletion of protein C induced by warfarin.

Phosphodiesterase III enzyme that metabolizes cyclic adenosine monophosphate (cAMP) in vascular smooth muscle.

Pigmentation brownish darkening of skin, resulting from extravasated blood.

Pinprick sensation The cutaneous pain sensation involving small-fiber sensory nerves.

Polymer agent embolic agent used to block blood flow by injecting it into the target. After a few seconds these agents have the capacity to polymerize occluding the vessel.

Polytetrafluoroethylene (PTFE) A type of synthetic polymer.

Popliteal pressure blood pressure in the popliteal artery.

Propagation phase third phase of the cell-based model hemostasis, characterized by recruitment of large numbers of platelets and complex formations that cause scaling in the formation of fibrin.

Protective sensation Enough residual deep pressure sensation to reduce the risk of ulcers secondary to light touch diminution in detection due to various peripheral neuropathies.

Pseudoaneurysm differs from a true aneurysm in that its wall does not contain the components of an artery, but consists of fibrous tissue, which usually continues to enlarge, creating a pulsating hematoma.

Pulmonary embolism It is when the blood clot breaks in the vascular system and reaches the pulmonary arteries. The presence of a clot in the pulmonary arteries restricts a proper gas exchange, resulting in hypoxemia, thus preventing the blood on flowing from the right ventricle to the left side of the heart. This causes hypotension, shock, and can lead to death.

Renovascular disease obstructive disease of renal arteries, interfere on treatment of hypertension.

Reticular vein dilated subdermal vein, usually tortuous and 1–3 mm in caliber.

Risk ratio The ratio of the probability of an event occurring in an exposed group to the probability of it occurring in a nonexposed one.

Saline solution common name of sodium chloride isotonic solution is one in relation to the body liquids containing 0.9 % by weight NaCl in distilled water, that is, each 100 mL of aqueous solution containing 0.9 g of salt, sterile solution used for intravenous infusion, wound cleaning, nasal irrigation, and others. Antiseptic substances used to degrade or inhibit the proliferation of microorganisms.

Sclerotherapy is a procedure commonly used to treat low-flow malformations (venous or lymphatic malformations) by injecting medicine into the lesions, which makes them shrink due to the sclerosis.

Sensory dysfunction Impair sensation function caused by disease affecting sensory nerves. Symptoms include loss of function (negative) symptoms, including numbness, tremor, impairment of balance, and gait abnormality. Gain of function (positive) symptoms include tingling, pain, itching, crawling, and pins and needles.

Shock a state of profound depression of the vital processes of the body that is characterized by pallor, rapid but weak pulse, rapid and shallow respiration, reduced total blood volume, and low blood pressure and that is caused usually by severe especially crushing injuries, hemorrhage, burns, or major surgery.

Systolic pressure Highest blood pressure. Corresponds in general terms to the pressure exerted by the blood on the vessel wall during ventricular systole.

Stenosis Narrowing of the vascular lumen.

Stenting Insertion or application of a stent (an appliance or material intended to support a graft or keep a passage open).

Supine position Lying on his back.

Systematic review Systematic review is a review of the literature with an explicit method that collects and critically analyzes multiple others studies or papers, particularly primary studies, in order to answer an especific research question. A qualified systematic review includes a quality assessment of the studies collated, i.e., a judgment of the risk of bias of each included study.

TASC The Transatlantic InterSociety Consensus Classification of femoral and popliteal lesions.

Telangiectasia confluence of dilated intradermal venules less than 1 mm in caliber.

The Semmes–Weinstein 10 g monofilament Is a nylon monofilament precisely calibrated and equal length used to evaluate the sensory perception threshold. It is a noninvasive, low cost, rapid, and easy-to-apply test often used as a screening device for identifying patients living with diabetes who are at risk of foot ulceration. When it is placed against the foot and slightly bent due to the pressure of pushing it onto the foot, a person with normal sensation should feel it.

Therapeutic footwear Refers to an extra depth shoe. A depth or custom or those specially custom-molded shoes intended to reduce the risk of skin breakdown in individuals with coexisting foot disease.

Thromboangiitis obliterans known as Buerger's disease, inflammatory occlusive vascular disease. It involves arteries and small and medium-caliber veins, usually in the distal portions of the lower and upper limbs.

Thrombolysis lysis of blood clots by pharmacological means. It works by stimulating secondary fibrinolysis by plasmin through infusion of analogs of tissue plasminogen activator, the protein that normally activates plasmin.

Thrombosis a medical condition in which the flow of blood in the body is blocked by a clot (= half solid mass) of blood.

Total contact cast A specially designed cast designed to take weight of the foot (off-loading) used to treat serious and deep sores in patients with foot ulcers. It consists of a fiberglass shell that fits around the leg and foot very closely and

has a bar on the bottom that keeps weight off of foot when the patients are standing or walking.

Transaminases The group is represented by two enzymes: serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). Both SGOT and SGPT are normally found primarily in liver and heart cells, are released into the bloodstream as the result of liver or heart damage, and so serve as tests of the liver and heart.

Ulcer A disruption of the mucocutaneous surface, resulting in a craterlike lesion.

Varicose vein tortuous vein, dilated and elongated, with loss of valvular function and wall changes related to venous hypertension.

Venous hypertension increased blood pressure in the veins.

Venous thromboembolism It is when thrombi (blood clots) are formed in the venous system. It includes deep venous thrombosis and pulmonary embolism that can occur at the same time or separately.

White-Coat effect increase in blood pressure levels of patients due to the presence of health professionals.

Index

T.P. Navarro et al. (eds.), *Vascular Diseases for the Non-Specialist*,
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