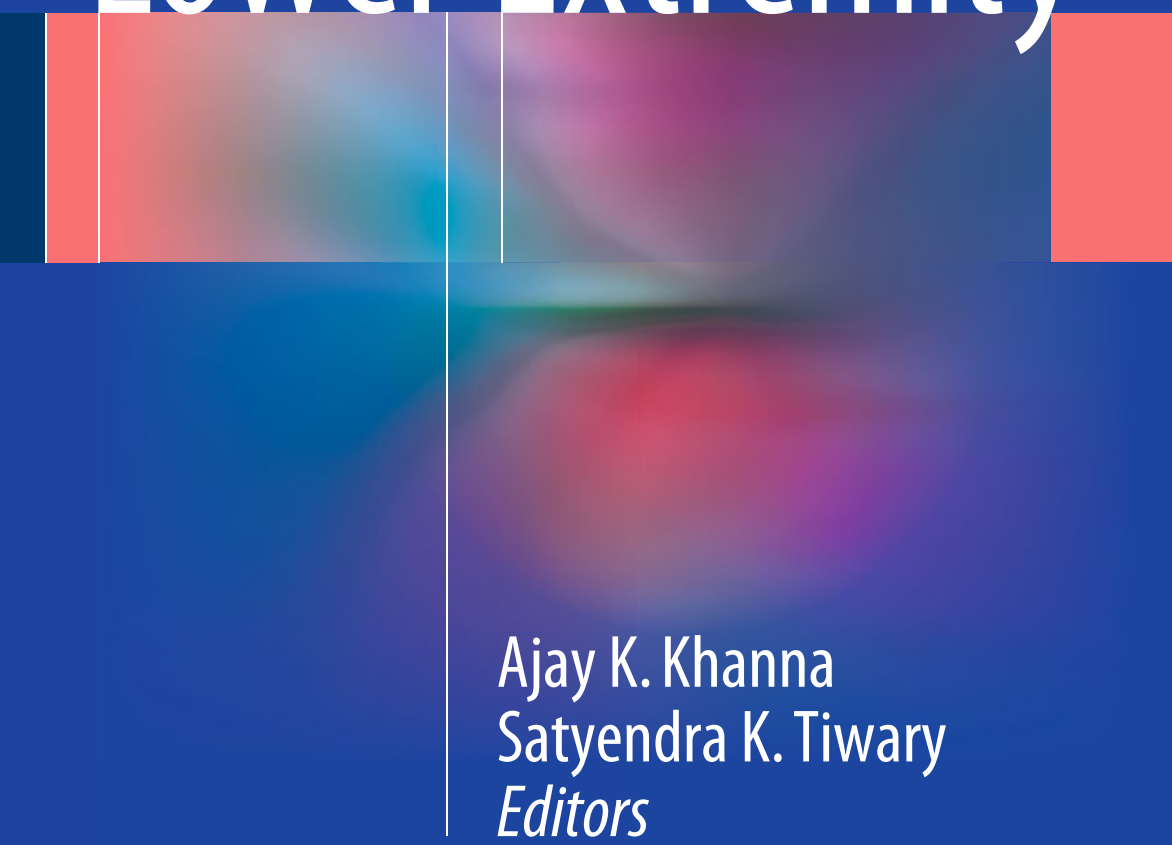
Ulcers of the Lower Extremity



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Springer

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Foreword

This book addresses a number of important aspects of wounds and wound healing. It is written by experts from a range of academic and clinical disciplines and illustrates the complexity of the issue and the need for multidisciplinary teams to care for patients with wounds. It provides a comprehensive and practical approach to what is a major health problem globally.

Wounds have existed since the beginning of time, and apart from developments in previous centuries driven by conflict and trauma, we are still struggling to ensure patients with wounds receive an accurate diagnosis and effective treatment in many parts of the world. The changing patterns of disease and population demographics in different countries mean that wounds will increase in number and complexity as we go forward and the urgency for education, training, and research in this area will unquestionably expand rapidly.

It is interesting to reflect on the current situation where many patients can be cured of cancer and organ transplantation is seen as a routine procedure, but we cannot guarantee a patient with a wound will receive care from an educated, informed, and up-to-date clinician. This book will go a long way to helping both clinicians and patients to provide and receive care that is more appropriate for the twenty-first century. I commend it to you as a source of valuable information as you will find useful information that will assist your practice.

Regards,
Keith

Prof. Keith Harding, CBE, FRCGP, FRCP, FRCS, FLSW
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Foreword

Ulcers are one of the most common pathological conditions affecting lower limbs, easy to be diagnosed with the naked eye. However, what we see is only an external picture of tissue changes. This is barely a symptom of pathological events taking place in soft tissues, caused by various noxious factors. To identify these factors the naked eye is not enough. Modern imaging, blood flow evaluation, bacteriology, immunohistopathology, and other methods, these are what we need to identify the etiological factors of ulcer. Even with these methods in hand, we do not exactly know what is the initiating factor in most types of ulcers. The result is that our treatment efforts are not always satisfactory. There are four basic elements in the pathomechanism of formation and persistence of ulcers. These are local predisposing factors, bacterial flora, high reactivity of infiltrating granulocytes and macrophages, and lack of skin regeneration. The predisposing factors are venous hypertension with high tissue fluid pressure damaging the epidermal barrier from inside, arterial hypoperfusion with cell apoptosis or necrosis, and lack of tissue fluid flow away in lymphedema with lymph leakage. These changes create favorable conditions for penetration of deeper tissues by bacteria and fungi normally residing on the epidermal surface. Our own microbes peaceful while on the skin surface become virulent in tissues. Furthermore, bacteria attract immune cells. So do necrotic keratinocytes, fibroblasts, and dying granulocytes. The scavenging process of microorganisms and our own cellular debris is a type of an almost endless autoimmune reaction. This can be confirmed by the enlargement of inguinal lymph nodes and subsequent depletion of their immune cells. The fourth factor is lack of regeneration of the skin with all its layers. Keratinocytes migrate upon the granulation tissue; however, they lack fibrils attaching them to the ulcer bed ground matrix which is a substitute of the nonexisting basement membrane. There is no papillary and reticular layer with blood and lymphatic capillaries. Moreover, no ulcer (wound) contraction can take place, as it happens in other type of wounds, because the foot or calf skin cannot be mobilized.

The described process illustrates how important it is to study the mechanism of ulcer formation and conduct the treatment trials. Refreshing knowledge of the basic and clinical processes of the so frequent development of inflammation/necrosis foci in human lower limbs becomes indispensable. The content of this book fulfills this requirement. It is the most actual summary of today's clinical experience in ulcer pathogenesis and treatment in the contemporary medicine. The variety of etiology,

kinetics of development, topography, methods of treatment, epidemiology, and medical documentation have been presented in a comprehensible style. It will serve medical professionals in their efforts to use modern methods of treatment, based on the knowledge of pathophysiology. Elimination of the predisposing factors must become a priority before the topical treatment is started. Finally, it would direct our attention more to the role of microorganisms in ulcer delayed healing, as our lower limbs are so much exposed to them, colonized from the perineal region and feet touching the ground full of microlife.

I am extremely happy to note that Prof. Khanna with his colleague is bringing out such a book which will be helpful for every person interested in lower limb ulcers. This book has 29 chapters tackling almost all types of ulcers of the lower extremity. As this book has many color photographs, it will definitely invite more interaction with the readers. Most of the chapters are well written and provide a complete scenario of such ulcer.

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Preface

Ulcers of the lower extremity are extremely common. When I thought of writing this book on ulcers of the lower extremity in my mind, I thought there will be many books on this subject being such a common entity. But when I started searching and I asked my colleagues if have they seen a comprehensive book on this subject, their answer negated it. In fact I could only trace one book on this subject which has been written by a nurse. Though many textbooks of medical sciences had various chapters at various places on this subject, I thought that I should accumulate and comprehend such type of book which will have at one place all aspects of chronic ulcers of the lower extremity. With this idea in my mind, I met Dr. Naren Agarwal, Executive Editor, Clinical Medicine, Springer, in one of our society meeting. On putting this idea, Dr. Naren got so excited that even without asking anything about the book, he immediately agreed to publish this book. In one of our annual national meeting of the surgeons, I moderated a symposium on ulcers of the lower extremity, and I found that a full hall of a capacity of 1500 persons was jam-packed to hear this subject. So I could understand that this book may be worth writing.

I thought of what can be the various chapters which can be included in such type of book, and I along with my coeditor and other colleagues could pinpoint 29 chapters starting right from the epidemiology, impact of ulceration, approach and investigations to an ulcer, pathophysiology of healing of an ulcer, microbiology of ulcer, common type of ulcers like venous, arterial, and diabetic and then uncommon type of ulcers, various types of malignant ulcers, various flaps for ulcers, amputation, pain management, and the documentation of ulcer. I selected the various authorities on the subject very carefully across the world, and in this book, chapters have been written by authors from the USA, Europe, UK, West Indies, and India. I think that there may still be many topics which might not have been covered in this book.

Two giants in the field of wound healing Prof. Keith Harding, Cardiff, UK, and Prof. Olszewski from Warsaw, Poland, are writing the forewords for this book. Prof. Keith Harding is the editor of several journals related to wounds. Prof. Olszewski is a lymphologist and the mastermind of the concept of various diseases related to lymphology. Now he is giving the new concept of the role of bacteria in nonhealing ulcers.

The book is full of figures, and I am sure that the readers will enjoy perusing the chapters and looking at the various pictures.

I acknowledge the help of my coeditor Dr. Satyendra K. Tiwary and my other colleagues in the department who have taken all pains to bring out this book. I acknowledge the help of Dr. Naren Agarwal and Ms. Teena Bedi of Springer in bringing out this concept in the present form. I am indebted to my family Anuradha, Divya, and Soumya who provided me the moral support and will forgive me for the ignorance which was unintentional.

I dedicate this book to all those patients who have suffered from this painful disease, and I hope that their misery will soon turn into a boon.

Varanasi, India Ajay Kumar Khanna

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Epidemiology of Leg Ulcer

1

Divya Khanna and Ajay Kumar Khanna

1.1 Introduction

Leg ulcers have plagued mankind since ancient times and still pose a considerable burden for both patients and carers in most countries of the world. Ulcers can be defined as wounds with a "full-thickness depth" and a "slow healing tendency." Ulcers of skin can result in complete loss of the epidermis and often portions of the dermis and even subcutaneous fat [1]. Chronic leg ulcer disease also known as chronic lower-limb ulcer is a chronic wound of the leg that shows no tendency to heal after 3 months of appropriate treatment or is still not fully healed at 12 months [2].

According to most of the Western and European studies, the most common type of leg ulcer is venous ulcer, the others being neuropathic ulcer and arterial ulcers (Table 1.1) [3, 4]. These three kinds of ulcers account for almost 90 % of cases of lower-leg ulceration. Approximately 70 % of the limb ulcers are caused by venous diseases. Rest 30 % are due to vascular diseases, diabetic, malignant ulcers, traumatic ulcers, chronic lymphedema, and a few medical conditions [4].

Chronic ulceration of the lower legs is a relatively common condition among adults. The spectra of symptoms in chronic leg ulcer disease include increasing pain, friable granulation tissue, foul odor, and poor wound healing. This not only results in social distress and considerable increase in healthcare and personal costs but also loss of productivity and poor quality of life [5, 6].

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Table 1.1 Causes of leg ulcers [4]

Vascular	Venous
	Arterial
	Mixed
Neuropathic	Diabetes
	Tabes
	Syringomyelia
Metabolic	Diabetes
	Gout
	Prolidase deficiency
Hematological	Sickle-cell disease
	Cryoglobulinemia
Trauma	Pressure
	Injury
	Burns
Tumors	Basal cell carcinoma
	Squamous cell carcinoma
Infections	Bacterial
	Fungal
	Protozoal
Panniculitis	Necrobiosis lipoidica
	Fat necrosis
Pyoderma	Gangrenosum
Special cases	Hypertensive ulcers

1.1.1 Global Burden of Leg Ulcer

Globally various studies have reflected burden of leg ulcer in terms of prevalence, incidence rate, morbidity, and mortality associated with leg ulcer and health cost involved in its management. Chronic leg ulcers affect 0.6–3 % of population aged over 60 year and increasing to more than 5 % of those aged 80 years and above. Rayner et al. (2009) have stated that chronic leg ulcer disease is an important cause of morbidity with prevalence in the community ranging from 1.9 to 13.1 % [7]. Sasanka et al. (2012) have stated in their study that in the course of a lifetime, nearly 10 % of the population will develop a chronic wound, with a wound-related mortality rate of 2.5 % [6].

According to Cheng et al. (2011) about 15 % of elderly adults in the United States suffer from chronic wounds and in chronic leg ulcer disease predominantly venous stasis ulcers, pressure ulcers (bedsores), and diabetic (neuropathic) foot ulcers. In America yearly 2–3 million new cases are diagnosed with various types of chronic wounds [8]. The prevalence of vascular ulcer in the United States is estimated at 500,000–600,000 and increases with age. Estimated annual incidences of leg ulcer in Switzerland and the United Kingdom are 0.2 and 3.5 per 1000 individuals, respectively [9, 10].

Faria et al.'s (2011) study in Botucatu, Sao Paulo, Brazil, reported a 35.5 % prevalence of varicose veins and 1.5 % prevalence of severe chronic venous

insufficiency with an ulcer or an ulcer scar [11]. The peripheral artery disease commonly associated with non-healing wounds affects about 8 million Americans and 12–20 % of Americans of age group 65–72 years. An estimated over 7.4 million population suffer from pressure ulcers around the world where estimation was possible. This estimate is not including a major number of developing countries [12].

In Western Australia, 1994, leg ulcers were found to affect nearly 1.1 per 1000 population (0.11 % point prevalence). The study of Baker et al. (1994) demonstrated that 24 % of the population suffered from ulcers for 1 year, 35 % had a problem of ulceration for 5 years, 20 % had experienced 10 or more episodes of ulceration, and 45 % of the sufferers were housebound [13]. Jull et al. (2009) stated that although the period prevalence of leg ulcers in New Zealand was at 79 per 100,000 per year, capture analysis suggested a more accurate estimation, which was between 393 and 839 per 100,000 per year [14].

According to data from epidemiological studies, the incidence of chronic ulcers in surgically hospitalized patients in China is 1.5–20.3 %. In one study of the 580 wound areas in 489 patients, 366 or 63 % were ulcers on the lower extremities [15, 16]. Korber et al. (2011) stated in their study conducted in Germany that venous insufficiency was the predominant causative factor in 47.6 % and arterial insufficiency in 14.5 % and 17.6 % of ulcers were due to combined arterial and venous insufficiency [17].

1.1.1.1 Indian Scenario

In tropical countries like India, there is a deficiency of epidemiological studies for prevalence and etiology of chronic leg ulcer diseases. One study estimated the prevalence at 4.5 per 1000 population. The incidence of acute wounds was more than double at 10.5 per 1000 population [18].

1.1.2 Socioeconomic Impact of Chronic Leg Ulcer Diseases

Ruckley (1997) has stated that chronic venous insufficiency affects approximately 5 % and chronic leg ulcer approximately 1 % of the adult population of developed countries. Recent quality-of-life studies highlight major disability and social impairment associated with chronic leg ulcer disease, but they also reflect that this condition is characterized by chronicity and relapse and hence giving rise to massive healthcare expenditure. This expenditure was accounted in the United Kingdom to be around E400 million per annum. Venous diseases are consuming 1–2 % of the healthcare budgets of European countries. In France too, the costs of venous disease represented 2.6 % of the total healthcare budget in 1995, thus confirming other data from European studies and an early health survey in the United States [19–21].

Similarly in the United States, treatment costs for venous ulcers in more than 6 million patients approached $2.5bn (£1.6bn; €1.8bn), and 2 million workdays were lost annually because of venous ulcer disease [22, 23]. A recent prospective study performed in 23 specialized wound centers throughout Germany calculated the mean total cost of a venous ulcer per patient per year to be €9569 (€8658 (92 %) direct costs and €911 (8 %) indirect costs [23, 24].

1.1.3 Importance of Prevalence Data

Epidemiological studies are used to assess the prevalence of diseases or conditions within populations in order to ascertain the magnitude of a certain problem. Mostly cross-sectional studies have been used to assess the number of patients with a certain disease within the healthcare system. Large randomized samples have been used to assess populations, and such samples have the advantage of knowing people who are suffering from chronic leg ulcer disease but are self-treating and are out of reach to the healthcare system.

Prevalence data from such studies will serve as a valuable basis for the planning of appropriate actions to deal with the problem. Impact and effectiveness of current treatment modalities can be assessed by doing repeated prevalence based studies in a defined geographical region and subsequently these studies can suggest for need of improvements in current treatment strategies [25–32]. For example, in an observation of Skaraborg, the prevalence of leg ulcer decreased by 46 % within the healthcare system from first epidemiological studies (1988–1992) compared to a repeat study in 2002, giving a strong indication that our changed management strategy was successful. In the absence of repetitive planned prevalent studies, it would have been much more difficult to detect the result of this change of management strategy [26–32].

1.1.4 Definitions of Incidence and the Various Forms of Prevalence Estimates [32]

Incidence: Number of new cases per unit time and population; usually one year
Point prevalence: Proportion with a certain disease at any point of time; time period usually shorter than three months
Period prevalence: Proportion with a certain disease within a longer period of time; usually one year or more
Overall prevalence: Proportion that have ever had a certain disease; lifetime period; lifetime prevalence

1.1.5 Methodological Pitfalls in Prevalence-Based Study

For a prevalence data to be reliable, the study has to be large enough. Validation of all or a randomly selected sample of the reported patients is mandatory to determine the number of false positives (described later) and to establish the diagnosis. It is not appropriate to rely on a venous ulcer diagnosis by the healthcare giver without verification from a previous objective noninvasive assessment. Without objective validation there is a high risk of overestimating venous leg ulcer prevalence [32].

One example is a study from Ireland that only assessed ankle pressures to diagnose arterial ulcers and most other ulcers were considered as being venous, clearly

resulting in an overestimation of venous ulcer point prevalence [33]. False-positive cases, for example, erosions from eczema can be confused with leg ulcers and thereby contribute to increased false positive rates. This underlines the importance of validating studies of patients/caretakers claiming a history of ulceration to avoid overestimates of prevalence of venous ulceration [32].

A hospital-based cross-sectional study can contribute selection bias as only patients treated within the healthcare system will be in chronic leg ulcer disease prevalence. Such a study will reflect the workload for healthcare professionals, but we know a large population of people who are self-treating their ulcers. In such a scenario, a population sample can overcome this bias by including all people within the selected sample. However, such studies need to be fairly large for a reliable prevalence estimate. These studies are not only expensive but also time consuming and difficult to perform [32].

1.2 Risk Factors Associated with Leg Ulcers

The incidence of ulceration is rising as a result of the ageing population and increased risk factors for atherosclerotic of chronic leg ulcer disease such as smoking, obesity, and diabetes [4, 23, 37]. Prevalence of leg ulceration increases dramatically with age, although ulcers can occur in quite young people and there are records of people suffering with venous ulcers for up to 60 years [4, 34].

People 65 years of age and older constitute one of the fastest growing segments of the population in the United States and Europe. In the next 40 years, this group is expected to double in size [34]. Venous leg ulcers account for 40–70 % of chronic lower-extremity wounds, with a disproportionate percentage of individuals with venous leg ulcers being elderly or women [4, 34].

One of the studies reflects that venous leg ulcers were overall more likely to occur in women than in men. However, the overall difference in incidence between men and women probably reflects the greater number of women as compared with men that survive to the oldest ages, thereby increasing the overall rate for women [34].

Family history of venous ulceration, obesity, phlebitis, deep venous thrombosis, and leg injuries were also found to be a significant risk factor in various studies [4, 23, 30]. Sedentary-style habits such as jobs involving prolonged sitting or standing especially among men is also associated with increased risk of occurrence of venous leg ulcers [23, 35]. Similarly obesity was also associated with venous leg ulceration. A study also reflected that BMI >33 kg/m^2 and walking distance shorter than 200 m during the day are indicators of poor wound healing [35].

Recurrent pregnancy also was found to be an important risk factor contributing to increased risk of venous ulceration. Several studies reflected that women who had more than one pregnancy had a higher risk of venous ulceration even after adjusted for increasing age [4, 23, 37].

Korber et al. stated in their study conducted in Germany that venous insufficiency was the predominant causative factor in 47.6 % and arterial insufficiency in 14.5 % and 17.6 % of ulcers were due to combined arterial and venous

insufficiency. Other rarer causes associated with leg ulcers include leg vasculitis (5.1 %), exogenous factors (3.8 %), and pyoderma gangrenosum (3.0 %) [14].

A study from one center in India suggests leprosy (40 %), diabetes (23 %), venous disease (11 %), and trauma (13 %) causes of lower-extremity wounds. Other causes included atherosclerosis and tuberculosis [4, 7, 18]. Other major causes include venous ulcers, pressure ulcers, vasculitis, and trauma. The most common causes of vasculitis ulcers are rheumatoid arthritis, systemic lupus, and polyarteritis nodosa. The blood dyscrasias that most commonly lead to leg ulceration are sickle-cell disease, thalassemia, thrombocythemia, and polycythemia rubra vera [36]. An important factor that further contributes to chronicity of leg ulcers is inappropriate treatment of acute traumatic wounds [4].

Conclusion

Leg ulcers are common and very debilitating and carry a huge impact on the patient's life, the society, and the government. Venous ulcers are the most common of all ulceration followed by arterial and mixed variety. With the increase in the incidence of diabetes, more and more diabetic foot ulcers will be more prevalent.

References

1. Van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. Br Med J. 2010;341(7782):1092–6.
2. Kahle B, Hermanns HJ, Gallenkemper G. Evidence based treatment of chronic leg ulcers. Dtsch Arztebl Int. 2011;108(14):231–7.
3. Sarkar PK, Ballantyne S. Management of leg ulcers. Postgrad Med J. 2010;76(901):674–82.
4. Agale SV. Chronic Leg Ulcers: Epidemiology, Aetiopathogenesis, and Management. Ulcers. 2013;2013:9. Article ID 413604. doi:10.1155/2013/413604.
5. Gonz'alez-Consuegra RV, Verd'u J. Quality of life in people with venous leg ulcers: an integrative review. J Adv Nurs. 2011;67(5):926–44.
6. Sasanka CS. Venous ulcers of the lower limb: where do we stand? Indian J Plast Surg. 2012;45(2):266–74.
7. Rayner R, Carville K, Keaton J, et al. Leg ulcers: atypical presentations and associated comorbidities. Wound Pract Res. 2009;17(4):168–85.
8. Cheng CF, Sahu D, Tsen F, et al. A fragment of secreted Hsp90α carries properties that enable it to accelerate effectively both acute and diabetic wound healing in mice. J Clin Invest. 2011;121(11):4348–61.
9. Rahman GA, Adigun IA, Fadeyi A. Epidemiology, etiology, and treatment of chronic leg ulcer: experience with sixty patients. Ann Afr Med. 2010;9(1):1–4.
10. Mekkes JR, Loots MAM, van der Wal AC, et al. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
11. Faria E, Blanes L, Hochman B, et al. Health-related quality of life, self-esteem, and functional status of patients with Leg ulcers. Wound. 2011;23(1):4–10.
12. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763–71.
13. Baker SR, Stacey MC. Epidemiology of chronic leg ulcers in Australia. Aust N Z J Surg. 1994;64(4):258–61.

14. Jull A, Walker N. Parag Vet al. Venous ulcer management in New Zealand: usual care versus guideline recommendations. N Z Med J. 2009;122(1295):9–18.
15. Fu X, Sheng Z, Cherry GW, et al. Epidemiological study of chronic dermal ulcers in China. Wound Repair Regen. 1998;6(1):21–7.
16. Fu X. Skin ulcers in lower extremities: the epidemiology and management in China. Int J Low Extrem Wounds. 2005;4(1):4–6.
17. K¨orber A, Klode J, Al-Benna S, et al. Etiology of chronic leg ulcers in 31, 619 patients in Germany analyzed by an expert survey University Clinic. J Dtsch Dermatol Ges. 2011;9(2):116–21.
18. Shukla VK, Ansari MA, Gupta SK. Wound healing research: a perspective from India. Int JLow Extrem Wounds. 2005;4(1):7–8.
19. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology. 1997;48:167–9.
20. Callam MJ, Ruckley CV, Harper DR, et al. Chronic ulceration of the leg: extent of the problem and provision of care. BMJ. 1985;290:1855–6.
21. Van den Oever R, Hepp B, Debbaut B, et al. Socio-economic impact of chronic venous insufficiency. An underestimated public health problem. Int Angiol. 1998;17(3):161–7.
22. Phillips T, Stanton B, Provan A, et al. A study of the impact of leg ulcers on quality of life: financial, social, and psychological implications. J Am Acad Dermatol. 1994;31:49–53.
23. Van Gent WJ, Wilschut ED, Wittens C. Management of venous ulcer disease. BMJ. 2010;341:c6045. doi:10.1136/bmj.c6045.
24. Purwins S, Herberger K, Debus ES, et al. Cost-of-illness of chronic leg ulcers in Germany. Int Wound J. 2010;7:97–102.
25. Forssgren A, Fransson I, Nelzén O. Leg ulcer point prevalence can be decreased by broad-scale intervention: a follow-up cross-sectional study of a defined geographical population. Acta Derm Venereol. 2008;80:252–6.
26. Nelzén O, Bergqvist D, Lindhagen A. The prevalence of chronic lower-limb ulceration has been underestimated: results of a validated population questionnaire. Br J Surg. 1996;83:255–8.
27. Nelzén O, Bergqvist D, Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. Br J Surg. 1994;81:182–7.
28. Nelzén O, Bergqvist D, Lindhagen A. Leg ulcer etiology — a cross-sectional population study. J Vasc Surg. 1991;14:557–64.
29. Nelzén O, Bergqvist D, Hallböök T, et al. Chronic leg ulcers: an underestimated problem in primary health care among elderly patients. J Epidemiol Community Health. 1991;45:184–7.
30. Nelzén O, Bergqvist D, Fransson I, et al. Prevalence and aetiology of leg ulcers in a defined population of industrial workers. Phlebology. 1996;11:50–4.
31. Nelzén O, Bergqvist D, Lindhagen A. Long term prognosis for patients with chronic leg ulcers: a prospective cohort study. Eur J Vasc Endovasc Surg. 1997;13:500–8.
32. Nelzen O. Prevalence of venous leg ulcer: the importance of the data collection method. Phlebolymphology. 2008;15(4):143–50.
33. O'Brian JF, Grace PA, Perry IJ, et al. Prevalence and aetiology of leg ulcers in Ireland. Ir J Med Sci. 2000;169:110–2.
34. Margolis DJ, Bilker W, Santanna J, et al. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol. 2002;46:381–6.
35. Dragan J, MilicSasa S, ZivicDragan C, et al. Risk factors related to the failure of venous leg ulcers to heal with compression treatment. J Vasc Surg. 2009;49(5):1242–7.
36. London NJM, Donnelly R. ABC of arterial and venous disease. Ulcerated lower limb. Br Med J. 2000;320(7249):1589–91.
37. Jennifer L, Beebe-DimmerJohn R, PfeiferJennifer S, et al. Epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol. 2005;15(3):175–84.

Impact of Ulceration

2

Sanjeev Kumar Gupta

2.1 Introduction

Wounds, particularly chronic wounds, are an area of concern for patients and clinicians alike. They not only represent a significant health problem but also have a profound socioeconomic impact. Chronic wounds are conventionally defined as wounds that have failed to progress in an orderly and timely reparative process over a maximum period of 6 weeks to restore the anatomic and functional integrity of the injured site.

2.2 Prevalence

There are wide geographical variations in both the prevalence and the etiology of chronic wounds. In Europe, the prevalence ranges from 0.18 to 1 % with venous ulcers accounting for the majority of these cases followed by diabetes and arterial disease. Data from India are limited. The etiology of chronic wounds in the hospital setting is different from that seen in the community. While hospital-based studies are easier to carry out, they do not reflect the true population-based statistics. In a community-based study from Northern India, the prevalence of chronic wounds was 4.48 per 1000 population with lower-extremity involvement being much more common than the involvement of the upper extremity [1]. The most common etiology for chronic ulcers in the above study was untreated or improperly treated acute traumatic wound followed by diabetes. In contrast, most studies indicate that diabetic ulcers are the most common cause of lower-extremity ulceration in the hospital setting [2, 3].

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2.3 Quality-of-Life Issues

Chronic wounds represent a heterogeneous group which shares the common characteristic of delayed wound healing due to an underlying disease. Most patients have a poor quality of life including pain, physical discomfort, functional limitations, social and economic burden, and psychological distress. The negative socioeconomic impact of chronic ulceration plays a huge strain not only on the patient and his/her family but also on the society. In the United States, chronic wounds affect around 6.5 million patients resulting in expenditure of an estimated US$ 25 billion annually on treatment. In the Scandinavian countries, the cost of treatment of chronic wounds accounts for 2–4 % of the total healthcare expenses. In developed countries approximately 1–2 % of the population will experience a chronic wound during their lifetime. The economic burden is growing rapidly across the globe due to increasing healthcare costs, an aging population, and an increasing incidence of diabetes [4–6].

2.4 Cost of Ulcer Prevalence

According to the Center for Disease Control and Prevention, 7.8 % of the population in the United States had diabetes in 2007 which equals almost 24 million persons. In the same year, diabetes and its complications cost the exchequer $174 billion of which $116 billion were in direct costs and the rest $58 billion were indirect costs such as loss of productivity, disability, and early mortality. An analysis of Medicare claims from 1995 to 1996 showed that expenditures for diabetic foot patients were three times higher than for the general population ($15,309 vs. $5526) yielding a total Medicare cost of $1.5 billion in 1995. In a study in which patients with diabetic foot ulcers were prospectively followed up, it was shown that 54 % patients healed in 2 months, 19 % healed in 3–4 months, and 27 % healed in >5 months. Healing without amputation costs an average of $6664 against healing by amputation which averaged $44,790. The Wagner grade was also related to the cost, being $1892 for Wagner grade 1 ulcer while a Wagner grade 4/5 ulcer averaged $27,721. Presence of vascular disease and neuropathy adds to the costs of treating diabetic foot ulcers. In India, the expenditure incurred in treating diabetic foot ulcers (DFU) varied from Rs. 10,000 in patients in urban areas to Rs. 6260 in patients in rural areas. Patients in urban areas spent a significantly higher amount on medications as well as for laboratory tests and consultations than patients in rural areas. The median costs of surgical treatment were also considerably higher in urban patients (Rs. 21,000 vs. Rs. 6500). Expenditure increased with increased duration of diabetes as well as with the number of complications in both groups. In a recently published study, the cost of treating DFU in five different countries was estimated based on a hypothetical model [5]. While the cost of treatment varied from the lowest in Tanzania to the highest in the United States for two different types of diabetic foot ulcers, the burden for the patient cannot be determined by the adjusted absolute cost but by the patients' responsibility for bearing the cost. The

cost to the patient is a function of both insurance cover and annual per capita purchasing power parity (PPP) adjusted gross domestic product (GDP). The authors concluded that India is the most expensive country for treatment of DFU, where approximately 5.7 years of income are required to pay for treatment compared to only 3 months of income in Chile and in China [5]. Several investigators have reported marked differences between the costs in urban versus rural settings, being considerably higher in the latter. These differences are due to poor access to healthcare facilities and mismanagement due to lack of adequately trained healthcare providers. It is thus obvious that in countries where the cost of treatment to the patient is so high, many patients will decline treatment, while those who chose treatment will face financial ruin [6].

2.5 Risk of Amputation

Diabetic neuropathy contributes to foot deformities and ulcers, which, if left untreated, increase the likelihood of lower-extremity amputations. It is estimated that up to 25 % of diabetics will develop a foot ulcer. In the United States, nearly 71,000 lower-limb amputations were performed in people with diabetes in 2004 costing approximately 3 billion dollars per year. 67 % of all lower-extremity amputations have diabetes. Majority of the amputations (nearly 80 %) are preceded by an ulcer. Every year 5 % of diabetics develop foot ulcers and 1 % will require amputation. Recurrence rate of diabetic foot ulcers is 66 %, and the amputation rate rises to 12 % with subsequent ulcerations. The age-adjusted lower-extremity amputation rate for people with diabetes (5.5 per 1000 people) was 28 times higher than in people without diabetes (0.2 per 1000 people). Amputation rates also rise with increasing age varying from 3.9 per 1000 in diabetics who are less than 65 years of age to 7.9 per 1000 in diabetics more than 75 years of age. Amputation rates are also influenced by race being 1.5 times more common in blacks than in whites. Men are twice as more likely to have a lower-extremity amputation than women. The 5-year survival rate after a major lower-extremity amputation is about 50 %. Once amputation occurs, 50 % will develop an ulcer in the contralateral limb within 5 years. According to estimates, a staggering $9 billion were spent on the treatment of diabetic foot ulcers in 2001 [4].

2.6 Venous Ulceration and Cost

In developed countries, venous ulcers account for 70–90 % of ulcers on the lower leg. In the United States, 1.69 % of the population aged 65 years or older are affected by venous ulceration. The prevalence of venous ulcers is approximately 600,000 annually. The annual cost of treating these ulcers ranges from $ 2.5 to 3.5 billion. Similar figures have been observed in Europe and Scandinavian countries. In Germany, the average cost of treating a patient with venous ulceration ranged from 9900 to 10,800 Euros. The incidence of venous ulceration increases with increasing

age. The recurrence rates following healing are high with up to one third of treated patients experiencing four or more recurrences. Estimates suggest that venous ulcers lead to loss of 2 million working days per year in the United States [7].

The socioeconomic burden of wound complications is worsened by the aging global population. As the global population ages, so does the population of elderly in the hospitals which leads to increased socioeconomic burden in caring for people with lower-extremity ulcerations.

2.7 Loss of Work

Patients with chronic wounds are often forced to abstain from their work in order to get proper medical management of their wounds. Some of them may be unable to carry out their occupation due to wound-related disability. Chronic wounds cause disability which in turn is associated with poor outcome leading to a vicious cycle. The loss of wages places a heavy socioeconomic burden not only on the patient but also on his/her family and the society. Venous ulcers lead to an early retirement in nearly 12.5 % of workers. Venous ulcers are responsible for a staggering 2 billion dollars in lost wages. An overwhelming majority of patients complain that their mobility is adversely affected by the ulcer. In younger, working patients, leg ulceration correlated with time lost from work, job loss, and deleterious effects on their finances. They found caring for their wounds burdensome leading to feelings of anger and resentment. Majority of the patients felt that chronic wounds had a profound negative emotional impact and were associated with feelings of fear, social isolation, anger, depression, and negative self-image [8]. Accurate assessment, prompt treatment, and suitable follow-up are essential for minimizing the long-term disability caused by chronic wounds.

2.8 Psychological Impact

Pain is also a major problem for venous leg ulcer patients which leads to depression, irritation, and reduced social activity. The pain is often worsened during dressing changes. In a multicenter cross-sectional study from Italy, it was seen that women with venous ulcers had more pain and worse quality of life than men. Venous ulcers had high mean values of visual analog score (VAS) during the day and night (44.4 and 44.9, respectively). A higher value was observed during dressing change (57.5). There was direct correlation between pain and quality of life, being worse for ulcers with longer duration and larger area [9]. Chronic leg ulcers also affect self-esteem and social life. In a study from the United Kingdom based on a questionnaire administered to 198 patients, it was observed that bad odor and excessive exudates from the wound had adverse psychological effects leading to feelings of disgust, self-loathing, and low self-esteem. The net result was social isolation and depression. 52 patients (27 %) scored as depressed, while 50 (26 %) scored as anxious on the hospital depression and anxiety (HADS) scale [10]. In another study, 38 patients

completed a health-related quality-of-life questionnaire, and the data obtained was used to evaluate the impact of ulceration. Older patients had worse health-related quality-of-life issues as did those with pain and non-healing ulcers. Pain, itching, altered appearance, loss of sleep, functional limitation, and disappointment with treatment were identified as the psychological effects of chronic ulceration [11]. It is thus important that wound management guidelines should also include recommendations for management of pain, lifestyle modifications, compliance and other quality-of-life issues. In another study from Brazil, the diminished quality of life observed in patients with chronic venous ulcers was attributed to both the physical aspects and functional ability [12]. Routine activities like climbing or moving down stairs or simply standing without support even for short periods become difficult. This physical limitation of mobility entails multiple restrictions which force people with chronic venous ulcers to restructure their daily activities and increase dependence upon others which also hamper social relationships. These patients feel socially isolated, depressed, and constrained due to the dressings. They also feel discriminated against by their family as well as the society. The presence of chronic leg ulcers also affects their mental health as evidenced by the low quality-of-life (QOL) scores in the domains of emotional aspects and mental health. Many studies have shown that persistent pain is a constant reminder of their ulcer and contributed to the feelings of sadness and loss of control. Pain was also related to loss of mobility and sleep disorders.

Health-related quality of life (HRQOL) is worse in diabetics with complications than in diabetics without complications. Foot ulcers increase the risk of death by 2.4-fold as compared to diabetic patients without ulcers. These ulcers are associated with reduced mobility and restriction of daily activities that adversely affect HRQOL. Both qualitative and quantitative studies have confirmed the huge negative psychological and social effect in diabetic foot ulcer patients including reduction in social activities, increased family tensions for patients and their caregivers, limited employment, and financial hardship [13]. A systematic literature review of HRQOL issues in diabetic foot ulcer patients reported that these posed a threat to physical functioning and a negative impact on psychological and also social functioning. The major factors were limited mobility, sleep disturbances, lack of energy, limitations in work and leisure activities, worries and frustration, and a lack of self-esteem [11].

Conclusion

Chronic leg ulcers have a profound economic, psychological, and social effect on the lives of the patients and their immediate families. The cost of caring for these patients also imposes a huge economic burden on healthcare facilities and providers. Manpower constraints and limited resources aggravate the problem. The immense economic and social impact of wounds call for allocation of more resources and funds not only to increase research funding for a better understanding of the complex biological mechanisms of wound healing but also to harness the technology for development of better wound care products which help in the early healing of chronic wounds thereby minimizing the cost of treatment and the socioeconomic burden.

References

1. Gupta N, Gupta SK, Shukla VK, Singh SP. An Indian community based epidemiological study of wounds. J Wound Care. 2004;13:323–5.
2. Persoon A, Heinen MM, van der Vleuten CJ, et al. Leg ulcers: a review of their impact on daily life. J Clin Nurs. 2004;13(3):341–54.
3. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763–71.
4. 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;52:17S–22.
5. Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu Z. Cost of treating diabetic foot ulcers in five different countries. Diabetes Metab Res Rev. 2012;28 Suppl 1:107–11.
6. Ramachandran A, Ramachandran S, Snehalata C, et al. Increasing expenditure on health care incurred by diabetic subjects in a developing country. Diabetes Care. 2007;30:252–6.
7. Dias TYAF, Costa IKF, Melo MDM, et al. Quality of life assessment of patients with and without venous ulcer. Rev La Am Enfermagem. 2014;22(4):576–81.
8. Alexander SJ. Time to get serious about assessing and managing psychosocial issues associated with chronic wounds. Curr Opin Support Palliat Care. 2013;7:95–100.
9. Guarnera G, Tinelli G, Abeni D, et al. Pain and quality of life in patients with vascular leg ulcers: an Italian multicentre study. J Wound Care. 2007;16(8):347–51.
10. Jones J, Barr W, Robinson J, Carlisle C. Depression in patients with chronic venous ulceration. Br J Nurs. 2006;15(11):S17–23.
11. Goodridge D, Trepman E, Embil JM. Health-related quality of life in diabetic patients with foot ulcers: literature review. J Wound Ostomy Continence Nurs. 2005;32(6):368–77.
12. Wachholz PA, Masuda PY, Nascimento DC, Taira C, Cleto NG. Quality of life profile and correlated factors in chronic leg ulcer patients in the mid-west of Sao Paulo, Brazil. An Bras Dermatol. 2014;89(1):73–81.
13. Fejfarova V, Jirkovska A, Dragomirecka E, et al. Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with Diabetes mellitus? J Diab Res. 2014;2014:371938. doi:10.1155/2014/371938. Epub 2014 Mar 25.

Types of Ulcers of Lower Extremity

3

Patrick Harnarayan, Michael J. Ramdass, Ravi Maharaj, and Vijay Naraynsingh

3.1 Introduction

One of the most debilitating, painful, recurrent, malodorous, and costly conditions seen in the practice of surgery is the leg ulcers. These have always been a challenge for clinicians in terms of diagnosis and understanding of its pathophysiology. For instance, although the association between ulceration of the leg and varicose veins was observed more than 2000 years ago by Hippocrates [1], he thought that these ulcers were the site of release of the "evil humors" that plagued the body causing untold maladies. Thus, healing of the ulcers was frowned upon, and these ulcers were frequently reopened as described by Chadwick et al. [2]. Table 3.1 shows the various types of ulcers of the lower extremity. We herein look at the types of ulcers which are commonly seen in our surgical practice including the following: venous, arterial, mixed arterial, and venous; diabetic; neuropathic; hematological; lymphatic; Marjolin's; malignant (primary and secondary); vasculitic; infective (necrotizing fasciitis, osteomyelitis, tuberculosis, and syphilitic); trauma; decubitus; calciphylaxis; hypertensive; and Bazin's.

3.2 Venous Ulcer (Fig. 3.1)

Chronic venous insufficiency affects about 5 % of the adult population, and 1 % may have chronic leg ulcers in developed countries and a prevalence of 3–5 % in the population above 65 years of age [3, 4]. Ulcers of primarily venous origin can range between 54 and 57 % of chronic leg ulcers [5, 6]. Ulceration can begin before age

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Table 3.1 Types of ulcer

Vascular	Venous
	Arterial
	Mixed
Neuropathic	Diabetes
	Tabes
	Syringomyelia
Metabolic	Diabetes
	Gout
	Prolidase deficiency
Hematological	Sickle-cell diseases
	Cryoglobulinemia
Trauma	Pressure
	Injury
	Burns
Tumors	Squamous cell carcinoma
	Marjolin's ulcer
	Basal cell carcinoma
	Melanoma
	Sarcomas
Infection	Bacterial
	Fungal
	Protozoal
Others	Hypertensive ulcer, Bazin's disease, pyoderma gangrenosum, fat necrosis, necrobiosis, calciphylaxis

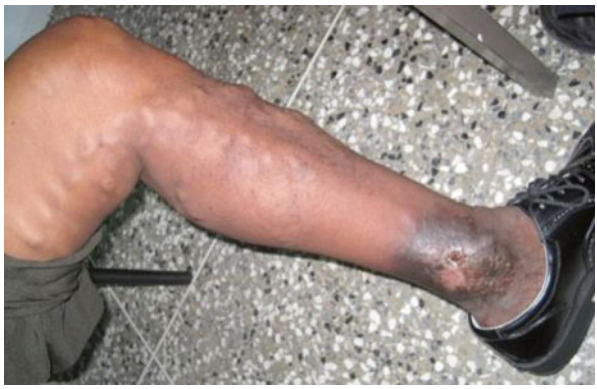

Fig. 3.1 Varicose ulcer due to saphenofemoral incompetence

3.of 40 [7], and many patients live with one throughout their entire adult life without seeing resolution. Venous disease utilizes 1–2 % of the health budgets of European countries with annual cost estimates being around £ 400 million in the United Kingdom and $1 billion in the United States [1, 8].

Before 40, the gender incidence is equal, but above this the disease afflicts mainly the women [7] probably due to earlier pregnancies and hormonal factors [5, 6]. Venous disease has a multifactorial origin with prolonged standing, obesity, aging, pregnancy, and hereditary factors all playing a part [6].

Primary disease can be congenital when patients are born with valvular defects which herald themselves in the late teens or early twenties or familial when it affects generations and a familial factor does exist if one parent was involved and this is increased further if both parents had venous disease [5]. Secondary valvular problems range from trauma to the surrounding tissue, motor vehicular accidents with bony fractures and crush injuries, and post-thrombotic syndrome [5]. Deep vein thromboses (DVTs) associated with chronic leg edema, pigmentation, and ulceration were known as "postphlebitic syndrome" [9].

The pathology here is one of elevated venous pressure (venous hypertension) due to venous reflux through valves which are either primarily diseased or through pathological changes in the vein wall. In primary valve failure, there is degenerative change in the valve annulus and leaflets, while secondary failure is due to the diseased vein wall with secondary widening of the commissures leading to incompetence and reflux.

Venous disease is chronic, and venous ulcers tend to be more often recurrent when compared with the non-venous ulcers [10] and those with venous ulcers had a higher body mass index. Elevated venous pressure is the underlying cause of skin and soft tissue changes seen in chronic venous insufficiency (CVI) that ultimately lead to venous ulceration.

Increased venous pressure is transmitted to the venules and capillaries of the subcutaneous tissue causing a level with elongation of the capillary bed, increased type IV collagen in the basement membrane [9], and pericapillary fibrin cuff forms [11]. These capillaries which are not normal seem to have increased permeability to larger molecules. Protein such as fibrinogen and red cells then leak into the interstitium, and this fibrinogen converts to fibrin in the pericapillary space [11] and the fibrin is deposited together with hemosiderin [12], released during red cell destruction. Fibrinolytic activity appears deficient in patients with venous ulceration deposition so there is decreased fibrin clearance and reduced lymph drainage [13, 14]. In addition, fragmentation and obliteration of cutaneous lymphatics and decreased lymphatic flow correlate with the degree of venous hypertension [15–17]. Microscopically, capillaries also demonstrate microthrombi that are occlusive and white cells sludge [18]. Stagnation of blood flow and decreased oxygen levels occur, and the protein laden, edematous area then acts to decrease oxygen diffusion into the area leading to tissue hypoxia [19, 20]. There is good evidence that there is reduced cutaneous oxygenation [21]. This actually improves with oxygenation which indicates that a diffusion barrier exists and not an oxygen transport problem causing low oxygen tissue content which presumably plays a major part in genesis of the ulcer. This improves if oxygen is supplied to the area [19, 20].

Venous ulcers typically occur on the lower medial leg in the so-called gaiter area, but they can be seen nearly anywhere on the lower leg or dorsum of the foot [7]. They may be single or multiple, painful, and shallow with a red

granulating floor, and usually there is a zone of stasis dermatitis and brown-to-black hemosiderin deposits [22] called lipodermatosclerosis. Edges may be clear-cut or irregular, and they extend onto the dorsum, up the leg, or become circumferential, and if present the ulcer will be found within this hyperpigmented area. Venous ulcers can be found on the lateral aspect of the dorsum as well especially when there is severe sapheno-popliteal reflux into the short saphenous venous system [23].

The skin becomes heavily pigmented and bound down to the subcutaneous tissue with extensive fibrosis which constricts the limb. This lipodermatosclerosis (LDS) usually occurs in the lower third of the leg with brawny edema above [9] the fibrosis and on the foot giving the typical appearance of an inverted champagne bottle with the neck being the area of lipodermatosclerosis and the edematous leg being the body of the bottle. Even though these areas of pigmentation are dark brown to black, there may be patches of depigmented macules called atrophie blanche, avascular and fibrotic in nature, that are thought to be forerunners to ulcer formation (Fig. 3.2) [9].

Clinically the changes include edema, dermatitis and eczema, hyper- or hypopigmentation (called atrophie blanche), and eventually tissue hypoxia leading to ulceration which is typically non-healing or recurrent [24].

Venous ulcers can be seen in patients with valvular incompetence at the superficial, deep, or perforating systems or a combination of two or even all three [25, 26], and in patients with ulcers, incompetence generally occurs at multiple locations [26]. Indeed some researchers studied closely the patterns of reflux and agree the incidence of multiple systems being involved in lower-limb venous ulcers was 64 % [27]. Furthermore, in 36 % patients with venous disease, one other etiological factor was a contributor to the chronic venous ulcer, and 96 % of these either had a previous history of a DVT or some condition that may have caused this pathology [28].

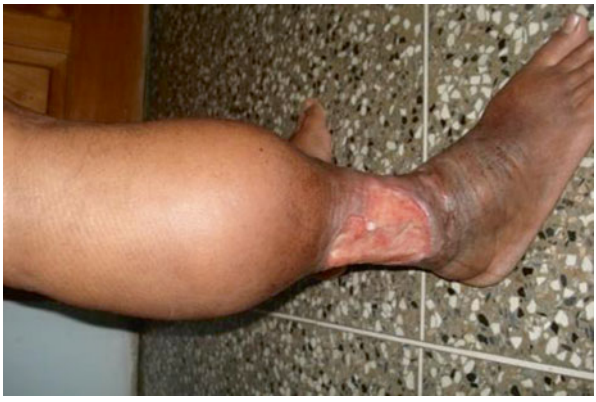

Fig. 3.2 Lipodermatosclerosis with ulceration

3.3 Arterial Ulcer (Figs. 3.3, 3.4, and 3.5)

Peripheral arterial disease is the only etiology identified in about 10 % of patients with leg ulcers [29]. Pure arterial ulceration is not as common as we may believe. One large study of 689 leg ulcers showed that only 15 limbs (2.2 %) were purely arterial in origin [2, 30] and another large study involving 1333 limbs with ulcers (1163 fully evaluated) indicated that 55 % were venous, 25 % were mixed, and 8.3 % were diabetic [3, 31], alluding to the fact that many clinicians do not separate leg ulcers into venous and arterial but venous, diabetic, and mixed origin. They believe that there is usually some other etiological factor present even if it is quiescent or subtle.

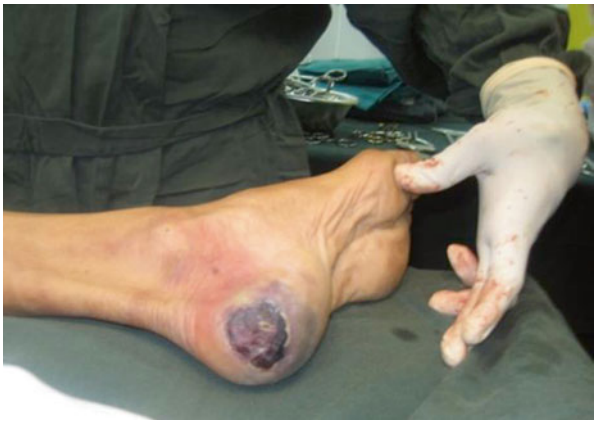

Fig. 3.3 Ischemic ulcer of the heel

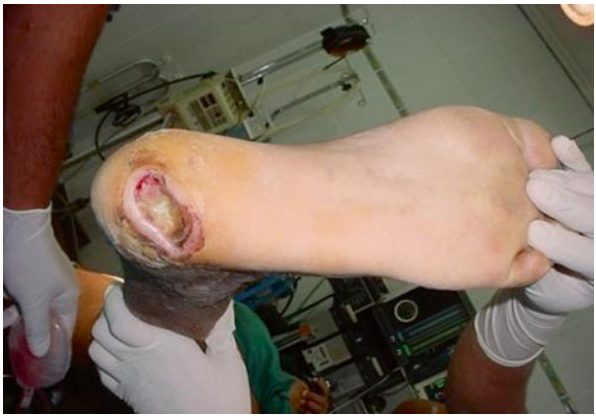

Fig. 3.4 Ischemic heel ulcer

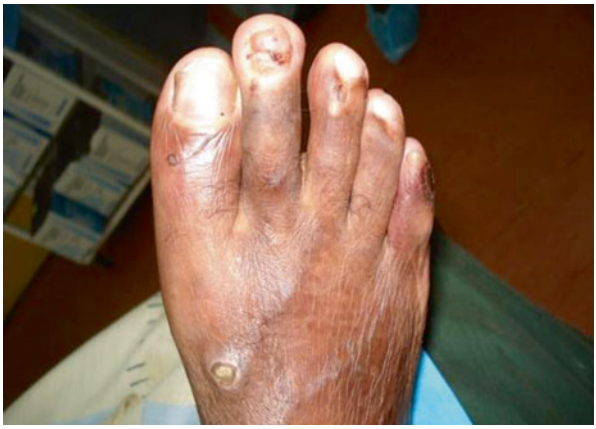

Fig. 3.5 Arterial ulcers on the dorsum and first three toes

Arterial ulcers of the leg tend to develop distally and are seen commonly on the toes and feet. They tend to be small and multiple and may occur in the areas commonly seen in venous disease or diabetes but are notorious for lying in unusual places such as the interdigital spaces, web-space areas, lateral dorsum, or plantar surface of the foot as well as the heel. They tend to be painful and they are usually dry and crusted and devoid of granulation tissue [5, 22].

Objective parameters to diagnose arterial insufficiency were considered to be ankle-brachial index (ABI) < 0.7 and a toe systolic pressure (TP) of <50 mm Hg [4, 32]. Arterial disease is seen primarily in patients with atherosclerosis whether the cause is uncontrolled hypertension, chronic smoking, or diabetes, or in patients with dyslipidemias.

Most arterial leg ulcers may not be included in the category of chronic critical limb ischemia; however, they are unlikely to heal with conservative measures. An ankle pressure of 110 mmHg was able to determine those who should proceed to revascularization [1, 29], and generally they can be treated by conservative means using local therapy [4, 32], but wound care must be supplemented by active wound debridement, percutaneous transluminal angioplasty (PTA), or infrainguinal arterial bypass [6, 33].

The natural history of ischemic limb ulceration has not been well understood [4, 32]. Some patients with arterial ulcers can heal well in time without undergoing revascularization procedures such as angioplasty or arterial bypasses. Use of pressure relief, debridement, moist wound care, negative pressure, application of a strict antibiotic policy (with repeated wound swabs or tissue culture) for control of infections or special chemical debriding or granulation-producing agents, dipteran larvae (flies), or hyperbaric oxygen therapy (HBOT) may assist in wound healing [4, 32].

Limb salvage can be achieved in chronic non-healing ulcers that are uncomplicated, but if the ankle-brachial index (ABI) is less than 0.5, the end result can be a major amputation [4]. Infrainguinal bypasses are likely to result in wounds healing even if the ulcer was located in the heel area [6, 33], and limb salvage rates of >85 % can be achieved once the graft remained patent but other factors are also relevant in

predicting healing. These included normal renal function, a palpable pedal pulse, a patent posterior tibial artery past the ankle joint, and the number of patent tibial arteries after completion of the bypass [6, 33]. Interestingly, the ABI, the presence of infection, diabetes, nor cardiovascular risks were unable to influence outcome of these ulcers [6, 33].

Therefore, most patients with an ulcer due to arterial insufficiency that is not complicated, even if appearing to be non-healing, may do so with local therapy. The patients with a low ABI and ankle and toe systolic pressure may attain limb salvage through percutaneous angioplasty or infrainguinal bypasses [29].

3.4 Mixed Arterial and Venous Ulcers

The mixture of venous and arterial disease is likely to be the second most common etiological factor leading to leg ulcers [31]. Combined arterial and venous insufficiency (CAVI) [34] accounted for the second largest group of patients with leg ulcers. In a study assessing 689 chronic leg ulcers, 14.5 % were of mixed origin as compared with those of a completely venous origin 72 % [30]. Elderly patients in this category may also have some degree of venous reflux giving rise to a "mixed" arteriovenous origin of the ulcers.

Clinically these patients can be difficult to diagnose due to the mixed symptoms and clinical signs with which they present. They may have some characteristics of arterial disease that may far overwhelm the venous picture such as a cold, dry dorsum of the foot, decreased pedal pulses, small ulcers on digits or dorsum of the foot, "hammer toes," with lipodermatosclerosis at the medial malleolar area leading an inexperienced clinician to think this may be a form of gangrene and ignore the venous component.

Alternately, a large medial malleolar ulcer typical of venous insufficiency may be accompanied by cutaneous gangrene of the covered toes or simply a dry withered foot with an absent dorsalis pedis pulse and loss of cutaneous hair on the lower leg but a good popliteal pulse. To the casual observer, this is venous disease, and the fact that the patient is diabetic or an ex-smoker of a pack a day prior to admission may be lost to an inexperienced medical officer.

Ulcers may develop anywhere on the foot or calf in mixed disease [34], and patients need the eye of an experienced clinician to properly assess and manage the patient. Patients with a previous history of a previous deep vein thrombosis (DVT) of the calf or thigh vessels complicate not only the diagnosis but subsequent treatment since these mixed ulcers are unlikely to heal [34].

In a large study of 689 limbs with chronic venous ulcers, 100 (14.5 %) were of mixed origin [30] and 56 had arterial revascularization via bypass procedures, 36 had venous surgery, 23 had local therapy (compression bandaging) whilst of 15 with pure arterial origin 13 had angioplasty (PTA) and the remaining 2 patients had dressings to the area [30]. This shows the multifactorial nature of the disease, the array of treatment options available, and therefore the treatment modalities adopted. Investigations always center on a careful clinical examination including bedside

ankle-brachial index (ABI), handheld Doppler investigation, color flow duplex scan, and either MR, CT, or conventional arteriography. Ankle pressures are crucial in determination of the pathway management should follow and are required even with respect to the venous component since it allows estimation for the degree of compression allowed in the patient.

The value of ankle pressure of below 110 mmHg identified those patients for revascularization [29], but an ankle pressure (AP) of > or = 80 mmHg predicts favorable outcome as well as a toe pressure of 30 mmHg [35]. In any case a practical bedside test such as the ankle-brachial index (ABI) of < 0.5 should alert clinicians to seek revascularization for these slowly healing ulcers [29].

3.5 Diabetic/Neuropathic/Neuroischemic (Figs. 3.6, 3.7, 3.8, 3.9, and 3.10)

Diabetes mellitus patients may have a whole host of pathologies, some of which have the greatest effect on the foot. Ulceration of the foot is the commonest major end point in diabetic complications. Diabetic neuropathy and peripheral arterial

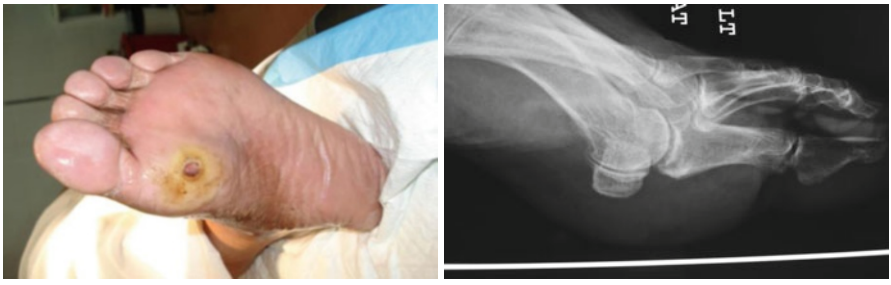

Fig. 3.6 Neuropathic ulcer with underlying sesamoid bone

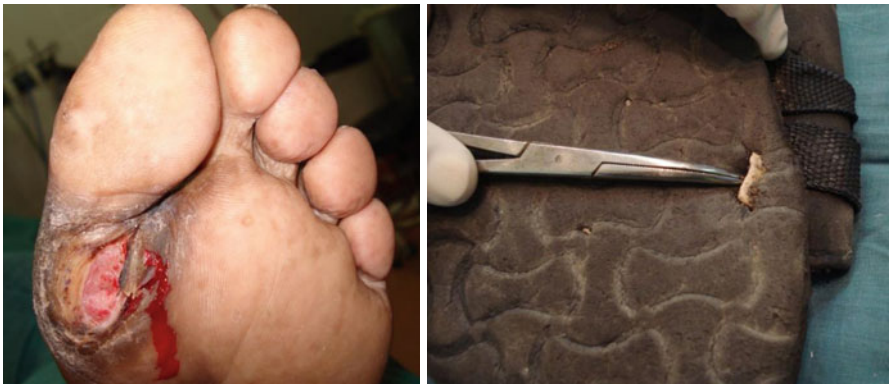

Fig. 3.7 Traumatic neuropathic ulcer from foreign body embedded in slipper

disease are the main players in foot ulceration alone or in tandem or with other factors such as mechanical issues (poor footwear, deformities with points of increased pressure), limited joint mobility, microvascular disease, and infections.

One study found foot ulceration in 7 % of diabetic patients over the age of 60 years; another study showed a 3 % history of ulceration in insulin-dependent diabetes patients (IDDM); patients aged 15–50 years are 45–60 % purely neuropathic, 10 % are purely ischemic, and 25–45 % are mixed.

Neuropathic ulcers are usually at the site of repeated trauma as in the area at the metatarsal heads where a high pressure exists or dorsal surface of the "hammer toes" or the distal-most portion of these hammer toes where there is flexion at the interphalangeal joint (IPJ) of these "clawed" toes. The foot is warm, well perfused, and pulse bounding. A foreign body may get lodged in the footwear, or a sharp object like a nail can penetrate the shoe or slipper. The presence of callus continues to impede ulcer healing since wounds heal from margins or edge, and epidermal cells from this area are prevented from so doing by position of the callus.

The pure ischemic ulcer is rare and most are neuroischemic occurring at the medial aspect of the first metatarsal head, the heel, and the digits. There is no callus present but there is a ring of hyperemia, with or without a necrotic center. Again ulcer formation is preceded by mild trauma and the tight or poorly fitting usually "under"-sized shoe in women and the hard boot in the industrial areas. Diabetic

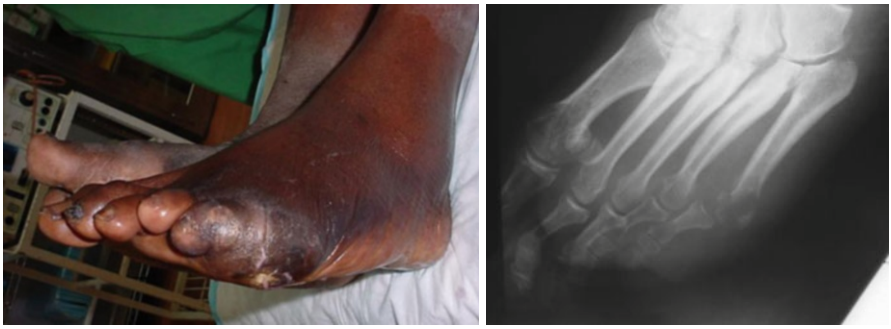

Fig. 3.8 Neuropathic ulcer opposite to the 5th metatarsal head with underlying bony destruction

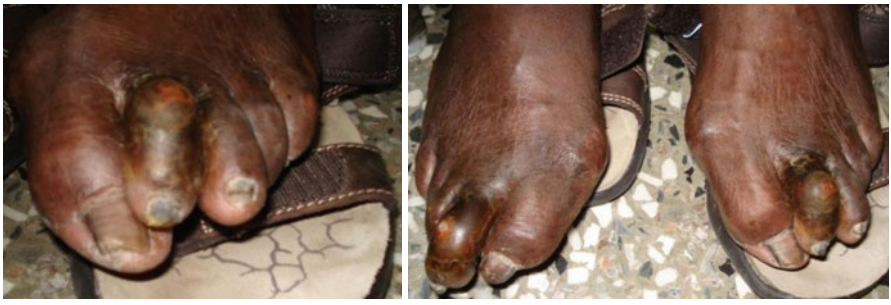

Fig. 3.9 Ulcers on the dorsum of hammer toes

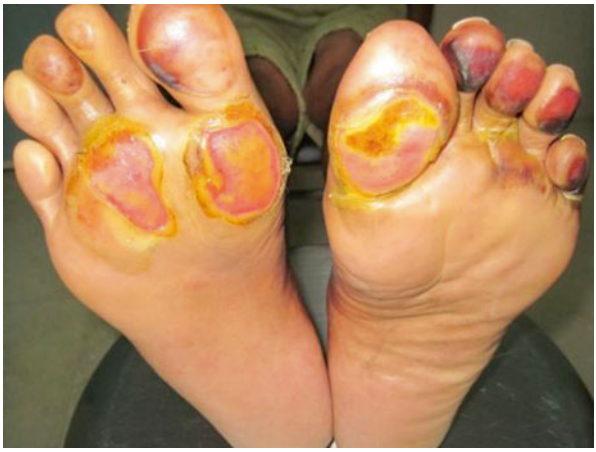

Fig. 3.10 Ulcers from neuropathic foot on hot surface

neuropathy affects approximately 30–50 % of patients. Diabetics then suffer from another source of ulceration, namely, those of a neuropathic origin which tends to be typically small, shallow, and painful and lies in relation to the digits and the plantar surface of the hallux at the metatarsal-phalangeal joint (MPJ). The ulcers in diabetics could be ischemic, neuropathic, or mixed neuroischemic. These account for the majority of ulcers seen in the practice of clinical surgery at the emergency room, clinic, or long-stay "sepsis ward." However, they are not by any means the only (etiology of) ulcers encountered in practice of surgery, and indeed there are more striking, chronic, and lethal forms of ulcers encountered on the legs and feet of patients.

3.6 Hematological Ulcers

Patients with hematological diseases such as sickle-cell anemia as well as β-thalassemia (genetic disorders of hemoglobin synthesis frequently present with leg ulcers, which tend to be painful and slow to heal [1–3, 36–38]. The incidence varies from 8 to 10 % of sickle-cell patients (with the homozygote SS disease) between ages of 10 to 50 years [36]. Leg ulcers did not occur in sickle beta plus thalassemia and sickle hemoglobin C disease. Low steady-state hemoglobin patients had a higher incidence of ulcer formation, and fetal hemoglobin seemed to have a protective effect on sickle-cell patients [36]. The pathophysiology of the ulcers is unclear, but there may be a relation to vaso-occlusive complications where decreased oxygen-carrying capacity of the abnormal hemoglobin has been suggested [39]. There were no ulcers in patients below age 10, and males were much more affected than female patients for reasons unknown to clinicians [36].

Even though the exact etiology remains unknown, another theory advanced is one related to the hemorheological changes (blood cell deformability, blood viscosity, and aggregation properties), and the hemolytic pathways leading to anemia may be responsible. The hematocrit-to-viscosity ratio (HCT/viscosity or HVR) appears

to give an idea of the blood oxygen transport system and is lower in the patients with leg ulcers [40].

This really indicates a lower hemoglobin level and a higher viscosity (and therefore probable hypercoagulability) and when taken together with decreased red cell deformability it probably explains why this group of sickle-cell patients had a higher prevalence of leg ulcers even though the viscosity and deformability characteristics seem to oppose each other [41]. Other malignant hematological disorders such as lymphomas and leukemias can present with leg ulcers [42]. Not only are traditional T-cell lymphoma skin lesions associated with multiple extremity ulcers [43] but patients with B-cell lymphomas (including post-transplant lymphoproliferative disorders as well as Epstein-Barr virus driven large B-cell lymphomas) can manifest themselves as well, since primary cutaneous B-cell lymphomas (PCBCL) are the second most common cause of primary cutaneous lymphomas [44].

3.7 Rheumatoid Arthritis Ulcers

Rheumatoid arthritis (RA) patients can present with extra-articular findings such as ulcerated rheumatic nodules, ischemic vasculitic lesions, pyoderma gangrenosum [1, 45], and gangrene [2, 46]. These are characteristic of the disease; however, rheumatoid arthritis patients have a more complex picture since chronic venous disease, peripheral arterial disease, and combined arteriovenous etiologies coexist [45]. Rheumatoid arthritis patients tend to develop gravitational leg ulcers and pressure ulcers on their legs and around their ankles that can be visualized as punched-out indolent ulcers that are slow to heal and can be quite painful [3, 47]. Due to the existence of dermal infarction, a necrotizing arteritis would be more likely the cause of these ulcers than the expected vasculitis [46].

3.8 Vasculitis-Associated Ulcers

Cutaneous vasculitis is an uncommon cause of ulceration in the lower limb [1]; sometimes these patients present with mild skin lesions like purpura, erythema, or severe infarction of the skin with ulceration. There may be an increased incidence of hypercoagulability with patients presenting with vasculitic ulcers [2] which may explain the larger-than-expected size. In Sjogren's syndrome characterized by dryness of the mucous membranes, xerostomia and xerophthalmia are present, but this uncommon chronic autoimmune disease may have leg ulcers that are painful and difficult to treat. Polyarteritis nodosa can occur with hematologic malignancies, characterized by palpable purpura, while small-vessel vasculitis causing leg ulcers can be drug induced as seen in some patients taking hydroxyurea therapy (for myeloproliferative disorders) [3]. They are painful ulcers occurring on the dorsum of the foot or lateral malleolar area that may disappear on cessation of hydroxyurea therapy.

3.9 Connective Tissue Disease: Ehlers-Danlos with Ulceration

Connective tissue disorders such as Ehlers-Danlos syndrome (type VIII) are very rare autosomal dominant diseases usually characterized with periodontic disease at a young age. Skin fragility, atrophic scars, and relatively thin skin are seen together with atrophic pretibial plaques and leg ulcers which is pyoderma gangrenosum, a rare inflammatory noninfective, nonneoplastic skin disorder with association to systemic disease like rheumatoid arteritis, inflammatory bowel disease, or hematologic malignancy [1]. There are enlarging necrotic ulcers with advancing zones of erythema.

3.10 Traumatic (Figs. 3.11, 3.12, 3.13, and 3.14)

Traumatic ulcers may arise in a number of scenarios and may be considered a complex wound. Such a wound is defined as a difficult wound or ulcer that challenges the skill of doctors and nurses. They usually are difficult to heal and may require more complex dressings such as vacuum-assisted closure and have a significant psychosocial impact on the patient and a major economic impact on healthcare systems. They usually require skin grafting and complex flaps and the help of a multidisciplinary team approach to achieve closure [48].

When we think of trauma, we think of road traffic accidents, penetrating injury related to violence such as gunshots and stabs, and work-related crush-type injury, impalement, and burns. These can all result in a non-healing chronic ulcer affecting the upper limb, lower limb, or elsewhere on the body.

We must be mindful that there is an iatrogenic component whereby ulceration may result after surgery to a limb and may be worse in cases such as

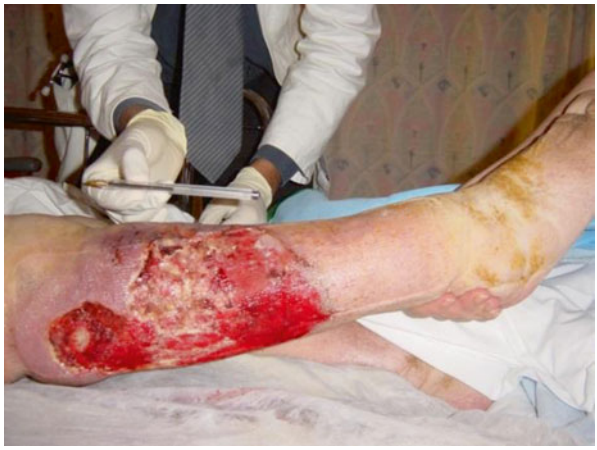

Fig. 3.11 Chronic ulceration from previous trauma to the lower limb

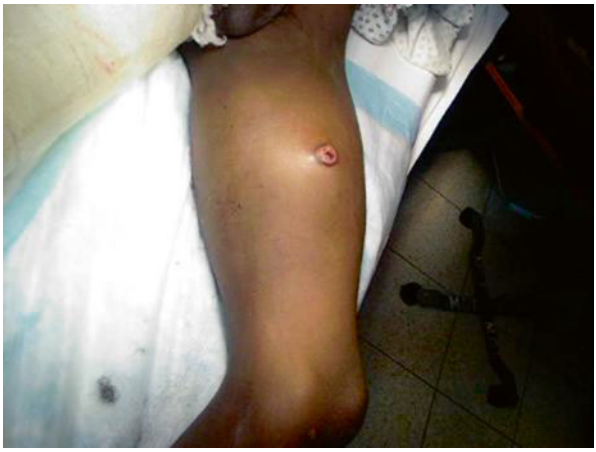

Fig. 3.12 Gunshot wound to the left thigh with false aneurysm formation and ulceration of entry wound with impending rupture

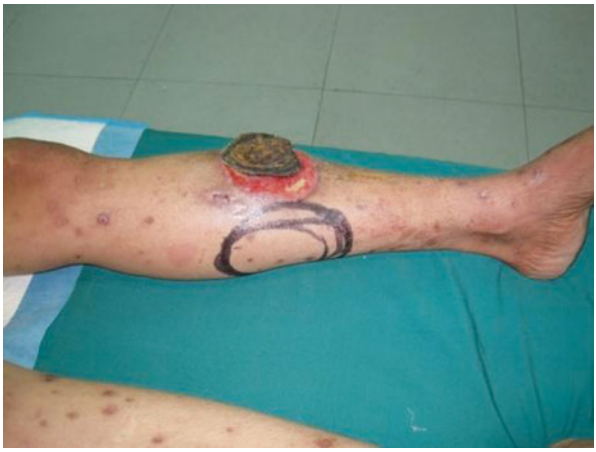

Fig. 3.13 Traumatic ulcer – not healing for 6 months

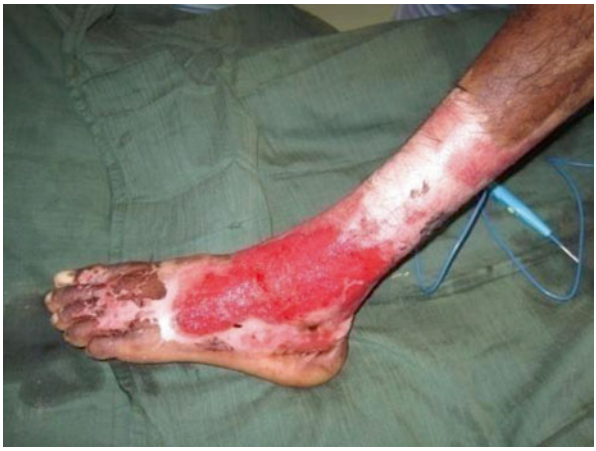

Fig. 3.14 Chemical burn ulcer

a degloving injury with a compound fracture as per Gustilo-Anderson classification [49]. After debridement and surgical reconstruction, many patients return years later with chronic ulceration of the lower limb which is difficult and slow to heal.

Clinically, the presentation is that of a chronic, non-healing ulcer usually around the distal leg area, ankle, anterior tibial region, gaiter area, or foot. They are usually deep and very painful. Therefore, it is essential to investigate and exclude vascular compromise in these cases and intervene along the lines of angioplasty or bypass surgery when required and surgical reconstruction using pedicled or free flaps as required [50]. Infection may be associated with slow healing, and one must always be mindful of MRSA, pseudomonas, and other atypical and hospital-acquired infections that are difficult to treat but contribute significantly to the pathological process.

3.11 Infective Ulcers

Infections may cause ulcers on the lower limb in a number of situations. The most common scenario is due to an infection in after trauma, a burn, the diabetic foot [51], or necrotizing fasciitis [52]. More rare situations occur in elephantiasis [53], lymphedema [54], and pathogenic bacteria as in tuberculosis [55], syphilis [56], and leprosy [57]. Syphilitic ulcers may occur elsewhere such as the mouth, tongue, and penis. Chronic osteomyelitis after a compound fracture may also lead to chronic painful non-healing ulcers and chronic discharging sinuses (Figs. 3.15, 3.16, 3.17, 3.18, 3.19, 3.20, 3.21, and 3.22) [58].

Chronic ulcers despite etiology may become infected with bacterial organisms. In a study conducted by Tascini et al. on 1295 patients, Gram-positive organisms were the most common isolate accounting for 52.6 % of cases. *Staphylococcus aureus* was the most common organism accounting for 29.9 % (MRSA was 22 % of *Staphylococcus aureus*) followed by *Enterococcus faecalis* (9.9 %), streptococci

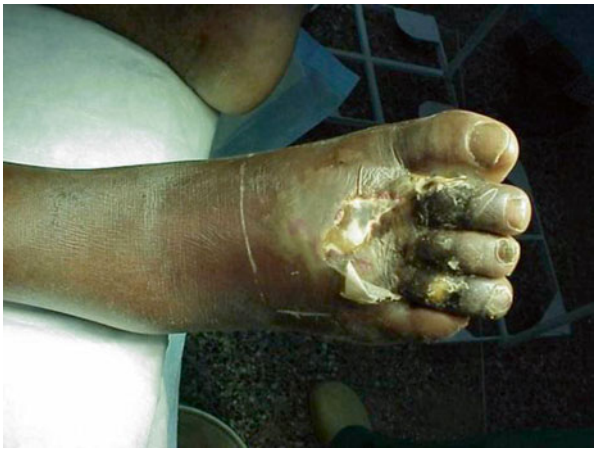

Fig. 3.15 Infected diabetic foot

(4.6 %), and *Pseudomonas aeruginosa* (10.3 %). Anaerobes were less than 1 %, and extended-spectrum beta-lactamase producers were *Escherichia coli* and *Proteus* species [52].

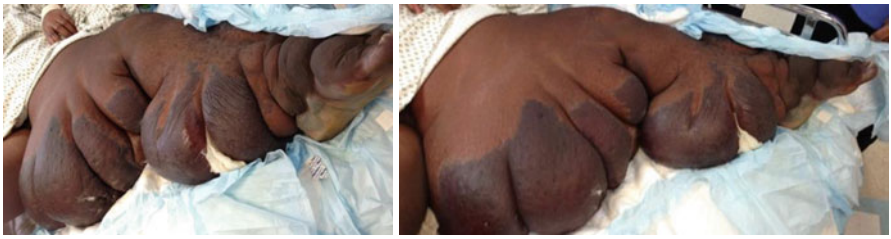

Fig. 3.16 Elephantiasis and lymphedema with superimposed skin necrosis and infection

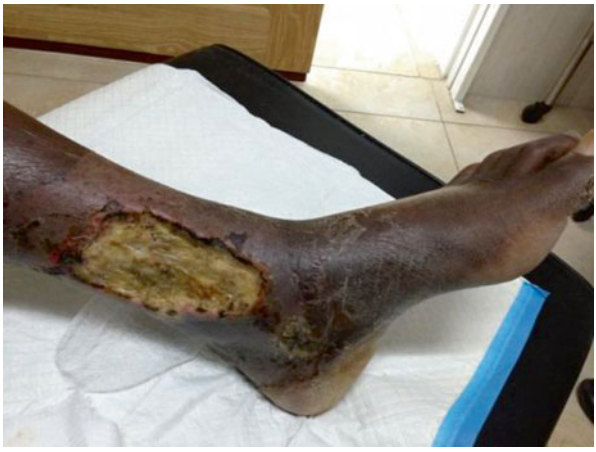

Fig. 3.17 Infected ulcer venous ulcer in the gaiter area

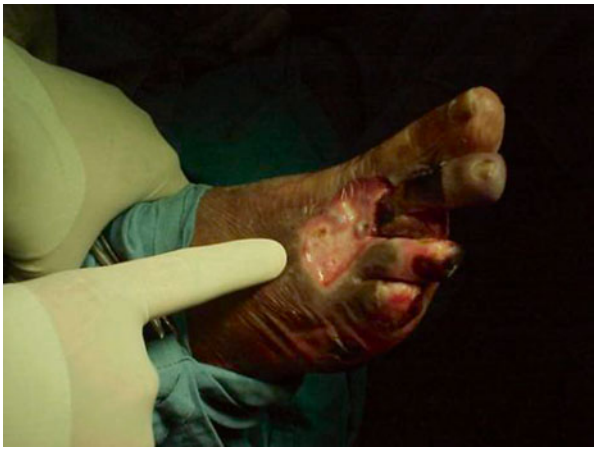

Fig. 3.18 Ischemic ulcers affecting the dorsum of the foot and digits with MRSA infection

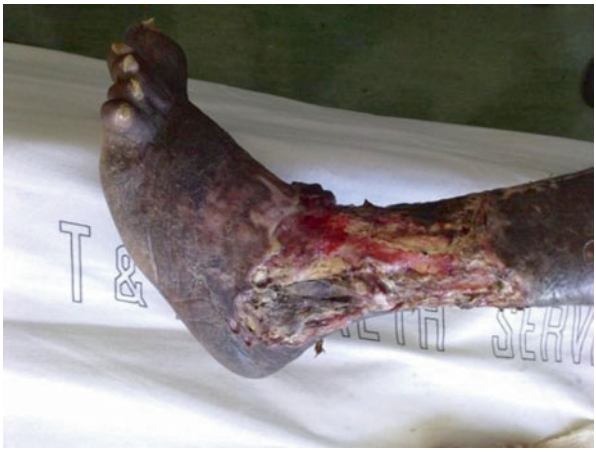

Fig. 3.19 Chronic mixed venous and arterial ulceration with superimposed infection with coliforms

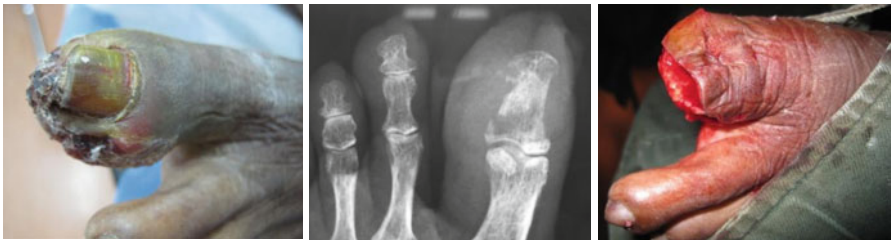

Fig. 3.20 Osteomyelitis with non-healing hallux ulceration. Though appearing ischemic, the blood supply is good

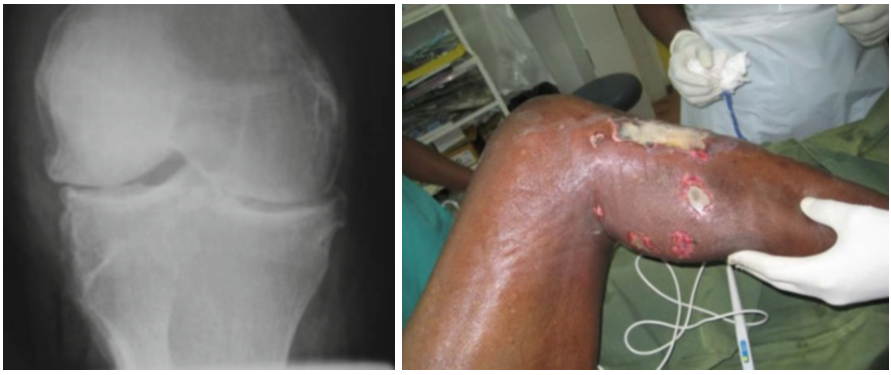

Fig. 3.21 Gas in subcutaneous tissue and necrotizing fasciitis

3.12 Malignancy

Malignant ulcers can be classified as primary and secondary. Primary malignant ulcers include those arising from the skin including basal cell carcinoma, squamous cell carcinoma (Fig. 3.23), and malignant melanoma. A study done by

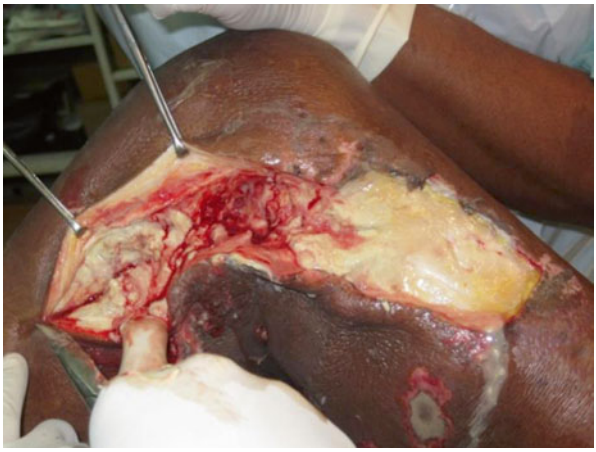

Fig. 3.22 Subcutaneous pus and fascial gangrene

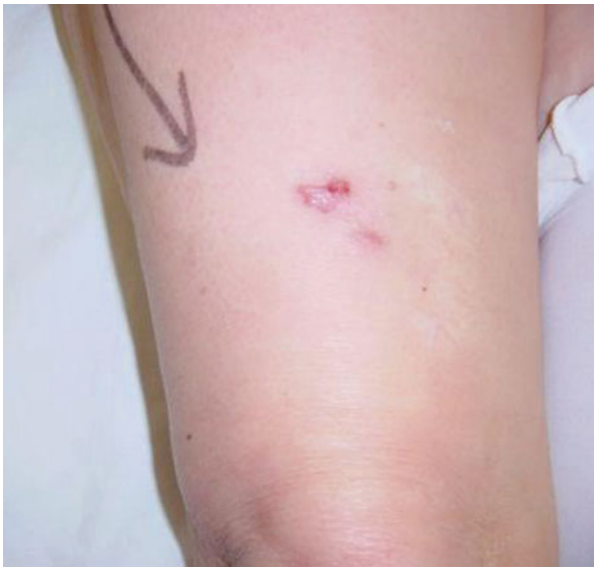

Fig. 3.23 Squamous cell carcinoma on the thigh with ulceration

Pilgrim et al. in 2014 details the epidemiology of skin malignancy and found basal cell carcinoma to be the most common and accounting for the majority of healthcare costs [59].

Ulcerating tumors may include liposarcomas and sarcomas from other tissues such as leiomyosarcomas of smooth muscle origin, rhabdomyosarcomas [60] of skeletal muscle origin, and advanced malignant bone tumors as may occur in the developing world setting (Figs. 3.24 and 3.25). These include osteosarcoma, chondrosarcoma, and chondrofibrosarcoma. A Marjolin's ulcer of a chronic venous ulcer may be considered a secondary malignancy.

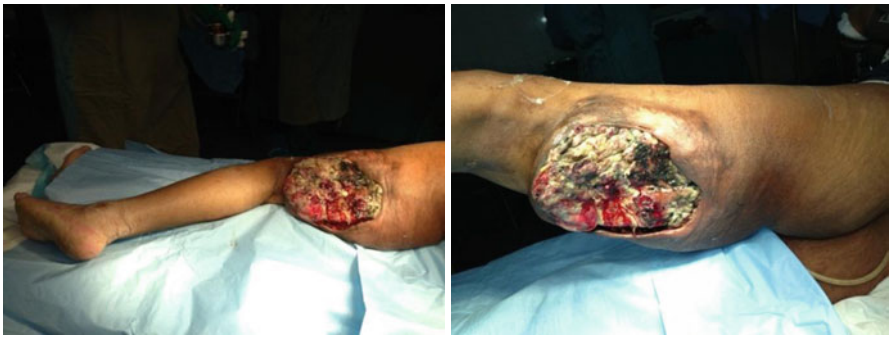

Fig. 3.24 Advanced rhabdomyosarcoma of the thigh with ulceration after radiation. The patient went on to have a hindquarter amputation

Fig. 3.25 Rhabdomyosarcoma of the proximal anterior compartment of the leg

3.13 Marjolin's Ulcer

Marjolin's ulcers are malignancies that arise in chronic venous ulcers, scars, burns, long-standing wounds, or sinuses [1]. A Marjolin's ulcer is a carcinoma that develops in chronic benign ulcers or scars (Fig. 3.26). The concept of or the term "Marjolin's ulcer" is generally representative of/refers to a long-term malignant complication of the scars resulting from burn. It was first described by the French Surgeon Jean-Nicolas Marjolin in 1828. It was originally associated with chronic osteomyelitis [2] but is seen in many different types of chronic wounds or in an area of chronically inflamed or scarred skin; it can occur in the quiescent scar overlying osteomyelitis [3].

Clinically they occur in middle-aged to older men, three times more commonly than women [4]. Any part of the body can be affected, but the extremities and scalp are the areas most commonly involved [5]. Usually involving the lower limb, they most often occur in the tibial region with typically increased bone destruction on

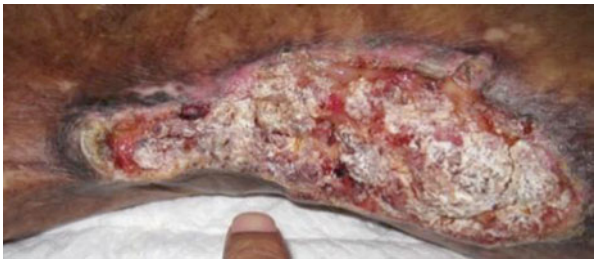

Fig. 3.26 Marjolin's ulcer in burn scar

radiographs. Earlier believed to be benign, these ulcers are sometimes called the skin malignancy of developing countries where a non-healing ulcer undergoes a malignant change over a period of a few decades and the patient only seeks advice of a physician for symptoms of increased pain, discharge with foul odor, and bleeding. The patient usually presenting with increased pain in a chronic fungating ulcer which has an unusually foul-smelling drainage, and occasional heavy bleeding for which they usually seek medical advice. A change in the size of the ulcer as evidenced by a fungating or exophytic growth or in its nature, such as "heaped-up" edges, is suspicious as well as persistent bleeding, recent or enlarging inguinal lympadenopthy [6] or an abnormal radiograph showing severe underlying bone destruction.

3.14 Calciphylaxis

Calciphylaxis is a syndrome of disseminated calcification (uremic gangrene syndrome) and is a rare and life-threatening condition occurring in 1 % of patients with chronic renal failure (CRF)/end-stage renal disease (ESRD) on dialysis each year with secondary hyperparathyroidism characterized by medial calcinosis of dermal arteriolar vessels leading to skin necrosis, ischemia, and then secondary infection. These hemodialysis patients suffer from various metabolic derangements and ectopic deposition of calcium in the skin, soft tissue, and vessel walls lead to abnormal condition of calcium and phosphate homeostasis (Fig. 3.27) [61].

The calcification of microvascular system and thrombosis and microvascular occlusion cause painful, violaceous lesions of the trunk and extremities. The lower extremities are predominantly involved in 90 % of patients that progress to subcutaneous tissue necrosis, non-healing ulcers, and gangrene skin lesions which become necrotic and can lead to non-healing ulcers. Secondary infection occurs with systemic sepsis and demise. The path physiology is not well understood, and although these patients have abnormal calcium-phosphate axis or elevated parathyroid hormone levels, these are not crucial to the eventual outcome.

Recently a functional protein C deficiency has been postulated to cause the hypercoagulable state which produces small-vessel thrombosis, skin ischemic necrosis, and then gangrene. By extension warfarin, a vitamin K antagonist, has been implicated in calciphylaxis. Rare cases not associated with ESRD include breast

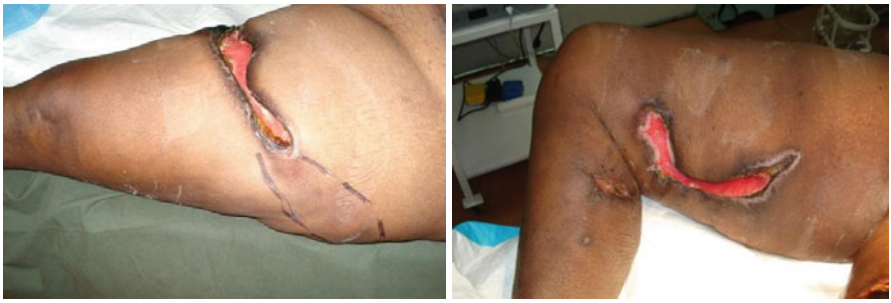

Fig. 3.27 Ulcers associated with calciphylaxis

carcinoma, hyperparathyroidism, alcoholic cardiomyopathy, and alcoholic cirrhosis. Indeed though calciphylaxis is characterized by spontaneous skin ulcers that progress to deep tissue necrosis, it can present in ESRD prior to dialysis and must be considered in a differential even if patient is not yet dialyzing. The lower extremity is the commonest location (90 %), and the trunk has been recorded in cardiac and alcoholic cardiomyopathy. The diagnosis lies in serologic and histopathologic findings and can only be healed by immunosuppressive therapy with modern wound therapy polyarteritis nodosa occurring with hematologic malignancies [62].

3.15 Bazin's Ulcer

Named after the French physician Pierre-Antoine-Ernest Bazin, the Bazin's ulcer, also known as erythema induratum or nodular vasculitis, is essentially panniculitis typically involving the calf region of adolescent and middle-aged females (Fig. 3.28). Usually occurring in the lower third of the posterior calf but can also involve the thigh and gluteal region, these ulcers commence as multiple painful nodules, sometimes red in color. The nodules eventually ulcerate leading to bluish irregular borders. Bazin's ulcers were initially thought to be directly related to tuberculous infection; however, the etiology is now multifactorial with the term Bazin's ulcer used when tuberculosis is the causative agent and Whitfield type for nontuberculosis etiology [63–65].

3.16 Martorell's Ulcer

First described by the Spanish cardiologist Fernando Martorell and also known as hypertensive ulcers, these are quite uncommon and associated with severe, uncontrolled diastolic hypertension. The ulcers commonly are located on the anterolateral aspect of the supramalleolar region as opposed to the typical gaiter region of venous ulcers. Less commonly, the region over the Achilles tendon can be affected. Despite the small inconspicuous size, they are characteristically exquisitely

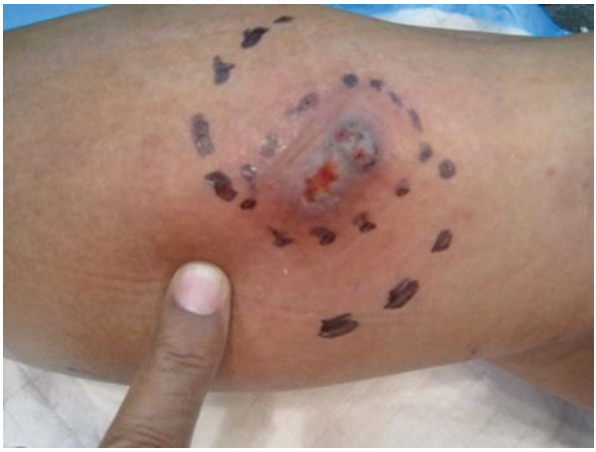

Fig. 3.28 Bazin's ulcer – nodular vasculitis

tender. Despite the pain, the easily palpable pulses differentiate the Martorell's ulcer from the more common arterial ulcer. The ulcer tends to be quite deep with tendon exposure and erythematous and irregular edges with a symmetrical distribution. Histology revealed arteriole hyalinization. Treatment is based on rigid hypertensive control with some success with oral anticoagulation and lumbar sympathectomy [66, 67].

Conclusion

There may be a variety of ulcerations in the lower extremity, but the common ones are venous, arterial, and diabetic ulcers. Other types of ulcer form a very small percentage. There should be a good approach to investigate these patients to make a proper diagnosis so that an appropriate treatment may be started. These ulcers may be very chronic and require a very good psychosocial support apart from the treatment of the ulcers.

References

1. Van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. J Vasc Surg. 2006;44(3):563–71.
2. Chadwick J, Mann WN. The medical works of Hippocrates. Oxford: Blackwell; 1950.
3. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology. 1997;48(1):67–696.
4. Mekkes JR1, Loots MA, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
5. Carpentier P1, Priollet P. Epidemiology of chronic venous insufficiency. Presse Med. 1994;23(5):197–201.
6. Carpentier PH. Epidemiology and physiopathology of chronic venous leg diseases. Rev Prat. 2000;50(11):1176–81.
7. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. Br Med J (Clin Res Ed). 1987;294(6584):1389–91.

8. Whiddon Lonnie L. The treatment of venous ulcers of the lower extremities. Proc (Bayl Univ Med Cent). 2007;20(4):363–6.
9. Alguire P, Mathes BM. Chronic venous insufficiency and venous ulceration. J Gen Intern Med. 1997;12:374–83.
10. Nelzen O, Bergqvist D, Lindhagen A. Leg ulcer etiology – a cross sectional population study. J Vasc Surg. 1991;14(4):557–64.
11. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. BMJ. 1982;285:1071–2.
12. Leach RD, Browse NL. Effect of venous hypertension on canine hind limb lymph. Br J Surg. 1985;72:275–8.
13. Browse NL, Gray L, Jarrett PEM, Morland M. Blood and vein-wall fibrinolytic activity in health and vascular disease. BMJ. 1977;1:478–81.
14. Wolfe JHN, Morland M, Browse NL. The fibrinolytic activity of varicose veins. Br J Surg. 1979;66:185–7.
15. Bollinger A, Isenring G, Franzeck UK. Lymphatic microangiopathy; a complication of severe chronic venous insufficiency. Lymphology. 1982;15:60–5.
16. Bollinger A, Pfister G, Hoffman U, et al. Fluorescence microlymphology in chronic venous incompetence. Int Angiol. 1989;8:23–6.
17. Bull RH, Gane JN, Evans JEC, Joseph AEA, Mortimer PS. Abnormal lymph drainage in patients with chronic venous leg ulcers. J Am Acad Dermatol. 1993;28:585–90.
18. Leu HJ. Morphology of chronic venous insufficiency – light and electron microscopic examinations. Vasa. 1991;20(4):330–42.
19. Partsch H. Hyperaemic hypoxia in venous ulceration. Br J Dermatol. 1983;109:249–50.
20. Partsch H. Investigations on the pathogenesis of venous leg ulcers. Acta Chir Scand Suppl. 1988;544:25–9.
21. Mani R, White JE, Barrett DF, Weaver PW. Tissue oxygenation, venous ulcers and fibrin cuffs. J R Soc Med. 1989;82(6):345–6.
22. Tam M, Moschella SL. Vascular skin ulcers of limbs. Cardiol Clin. 1991;9(3):555–63.
23. Bass A1, Chayen D, Weinmann EE, Ziss M. Lateral venous ulcer and short saphenous vein insufficiency. J Vasc Surg. 1997;25(4):654–7.
24. Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. J Am Acad Dermatol. 2001;44(3):401–21.
25. Shami SK, Sarin S, Cheatle TR, Scurr JH, Smith C. Venous ulcers and the superficial venous system. J Vasc Surg. 1993;17(3):487–90.
26. Hanrahan LM, Araki CT, Rodriguez AA, Kechejian GJ, LaMorte WW, Menzoian JO. Distribution of valvular incompetence in patients with venous stasis ulceration. J Vasc Surg. 1991;13(6):805–11.
27. Labropoulos N, Leon M, Geroulakos G, Volteas N, Chan P, Nicolaides AN. Venous hemodynamic abnormalities in patients with leg ulceration. Am J Surg. 1995;169:572–4.
28. Baker SR, Stacey MC, Jopp-McKay AG, Hoskin SE, Thompson PJ. Epidemiology of chronic venous ulcers. Br J Surg. 1991;78(7):864–7.
29. Hafner J1, Schaad I, Schneider E, Seifert B, Burg G, Cassina PC. Leg ulcers in peripheral arterial disease (arterial leg ulcers): impaired wound healing above the threshold of chronic critical limb ischemia. J Am Acad Dermatol. 2000;43(6):1001–8.
30. Adam DJ1, Naik J, Hartshorne T, Bello M, London NJ. The diagnosis and management of 689 chronic leg ulcers in a single-visit assessment clinic. Eur J Vasc Endovasc Surg. 2003;25(5):462–8.
31. Apollonio A, Antignani PL, Di Salvo M, Failla G, Guarnera G, Mosti G, Ricci E; SUV Study Group. A large Italian observational multicentre study on vascular ulcers of the lower limbs (Studio Ulcere Vascolari). Int Wound J. 2014. doi: 10.1111/iwj.12216.
32. Marston WA1, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, Keagy BA. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg. 2006;44(1):108–14.

33. Treiman GS1, Oderich GS, Ashrafi A, Schneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. J Vasc Surg. 2000;31(6):1110–8.
34. Treiman GS1, Copland S, McNamara RM, Yellin AE, Schneider PA, Treiman RL. Factors influencing ulcer healing in patients with combined arterial and venous insufficiency. J Vasc Surg. 2001;33(6):1158–64.
35. Wütschert R1, Bounameaux H. Predicting healing of arterial leg ulcers by means of segmental systolic pressure measurements. Vasa. 1998;27(4):224–8.
36. Koshy M1, Entsuah R, Koranda A, Kraus AP, Johnson R, Bellvue R, Flournoy-Gill Z, Levy P. Leg ulcers in patients with sickle cell disease. Blood. 1989;74(4):1403–8.
37. Matta BN1, Abbas O, Maakaron JE, Koussa S, Daderian RH, Taher AT. Leg ulcers in patients with β-thalassaemia intermedia: a single centre's experience. J Eur Acad Dermatol Venereol. 2014;28(9):1245–50. doi:10.1111/jdv.12211.
38. Ladizinski B1, Bazakas A, Mistry N, Alavi A, Sibbald RG, Salcido R. Sickle cell disease and leg ulcers. Adv Skin Wound Care. 2012;25(9):420–8.
39. Chung C1, Cackovic M, Kerstein MD. Leg ulcers in patients with sickle cell disease. Adv Wound Care. 1996;9(5):46–50.
40. Connes P, Lamarre Y, Hardy-Dessources MD, Lemonne N, Waltz X, Mougenel D, Mukisi-Mukaza M, Lalanne-Mistrih ML, Tarer V, Tressières B, Etienne-Julan M, Romana M. Decreased hematocrit-to-viscosity ratio and increased lactate dehydrogenase level in patients with sickle cell anemia and recurrent leg ulcers. PLoS One. 2013;8(11):e79680. doi:39.10.1371/journal.pone.0079680. eCollection 2013.
41. Connes P, Lamarre Y, Waltz X, Ballas SK, Lemonne N, Etienne-Julan M, Hue O, Hardy-Dessources MD, Romana M. Haemolysis and abnormal haemorheology in sickle cell anaemia. Br J Haematol. 2014;165(4):564–72. doi:10.1111/bjh.12786.
42. Helm KF, Su WP, Muller SA, Kurtin PJ. Malignant lymphoma and leukemia with prominent ulceration, clinicopathologic correlation of 33 cases. J Am Acad Dermatol. 1992;27(4):553–9.
43. Suga H, Sugaya M, Yamamoto M, Miyagaki T, Ohmatsu H, Hoashi T, Sato S. Peripheral T cell lymphoma, not otherwise specified, showing multiple ulcers on the extremities. Int J Dermatol. 2013;52(9):1147–9.
44. Kempf W, Kazakov DV, Mitteldorf C. Cutaneous lymphomas, an update. Part 2: B-cell lymphomas and related conditions. Am J Dermatopathol. 2014;36(3):197–210.
45. Hasegawa M1, Nagai Y, Sogabe Y, Hattori T, Inoue C, Okada E, Tago O, Ishikawa O. Clinical analysis of leg ulcers and gangrene in rheumatoid arthritis. J Dermatol. 2013;40(12):949–54. doi:10.1111/1346-8138.12359.
46. Seitz CS, Berens N, Bröcker EB, Trautmann A. Leg ulceration in rheumatoid arthritis – an underreported multicausal complication with considerable morbidity: analysis of thirty-six patients and review of the literature. Dermatology. 2010;220(3):268–73. doi:10.1159/000284583.
47. Nishikawa JA. Are leg ulcers in rheumatoid arthritis due to vasculitis? Eur J Rheumatol Inflamm. 1983;6(3):288–90.
48. Ferreira MC, Tuma Jr P, Carvalho VF, Kamamoto F. Complex wounds. Clinics (Sao Paulo). 2006;61(6):571–8.
49. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976;58(4):453–8.
50. Liu H, Wang L, Zhang Y, Yu Z, Liu Z, Li G, Zhao G, Hu K. Tissue transplantation with bone transmission for treating large defects of tibial bone and soft tissue. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2013;27(3):295–8.
51. Tascini C, Piaggesi A, Tagliaferri E, Iacopi E, Fondelli S, Tedeschi A, Rizzo L, Leonildi A, Menichetti F. Microbiology at first visit of moderate-to-severe diabetic foot infection with antimicrobial activity and a survey of quinolone monotherapy. Diabetes Res Clin Pract. 2011;94(1):133–9.

52. Khanna AK, Tiwary SK, Kumar P, Khanna R, Khanna A. A case series describing 118 patients with lower limb necrotizing fasciitis. Int J Low Extrem Wounds. 2009;8(2):112–6.
53. Davis JM, Crawford PS. Persistent leg ulcers in an obese patient with venous insufficiency and elephantiasis. J Wound Ostomy Continence Nurs. 2002;29(1):55–60.
54. Karnasula VM. Management of ulcers in lymphoedematous limbs. Indian J Plast Surg. 2012;45(2):261–5.
55. Baveja CP, Gumma VN, Jain M, Jha H. Foot ulcer caused by multidrug-resistant Mycobacterium tuberculosis in a diabetic patient. J Med Microbiol. 2010;59(Pt 10):1247–9.
56. Chao YC, Chen CH, Chen YK, Chou CT. A large ulcer and cutaneous small-vessel vasculitis associated with syphilis infection. Scand J Rheumatol. 2006;35(2):147–51.
57. Grauwin MY, Cartel JL, Lepers JP. How does one treat the osteitis and osteoarthritis of the extremities in older leprosy patients using granulated table sugar? Acta Leprol. 1999;11(4):147–52.
58. Cecilia-Matilla A, Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E, García-Álvarez Y, Beneit-Montesinos JV. Histopathologic characteristics of bone infection complicating foot ulcers in diabetic patients. J Am Podiatr Med Assoc. 2013;103(1):24–31.
59. Pilgrim W, Hayes R, Hanson DW, Zhang B, Boudreau B, Leonfellner S. Skin cancer (basal cell carcinoma, squamous cell carcinoma, and malignant melanoma): new cases, treatment practice, and health care costs in New Brunswick, Canada, 2002–2010. J Cutan Med Surg. 2014;18:1–12.
60. Wechsler RJ, Schilling JF. CT of the gluteal region. AJR Am J Roentgenol. 1985;144(1):185–90.
61. Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy. Kidney Int. 2002;61:2210–7.
62. Zhou Q, Neubauer J, Kern JS, Grotz W, Walz G, Huber TB. Calciphylaxis. Lancet. 2014;383(9922):1067.
63. Emohare O, Kowal-Vern A, Wiley D, Latenser BA. Vacuum-assisted closure use in calciphylaxis. J Burn Care Rehabil. 2004;25(2):161–4.
64. Sharon V, Goodarzi H, Chambers CJ, Fung MA, Armstrong AW. Erythema induratum of Bazin. Dermatol Online J. 2010;16(4):1.
65. Teramura K, Fujimoto N, Nakanishi G, Shigeta M, Tanaka T. Disseminated erythema induratum of Bazin. Eur J Dermatol. 2014;24(6):697–8.
66. Davison S, Lee E, Newton ED. Martorell's ulcer revisited. Wounds. 2003;15(6):208–12.
67. Duncan HJ, Faris IB. Martorell's hypertensive ischemic leg ulcers are secondary to an increase in the local vascular resistance. J Vasc Surg. 1985;2:581–4.

Healing of Leg Ulcers

4

M.G. Vashist

4.1 Introduction

An ulcer is defined as a break in the epithelial continuity. Most common chronic wounds in developed countries are leg ulcers [1]. All tissues in the body are capable of healing by one of two mechanisms: regeneration or repair. Regeneration is the perfect restoration of the preexisting tissue architecture in the absence of scar formation. It is replacement of damaged tissues by identical cells and is more limited than repair. In humans, complete regeneration occurs in a limited tissue compartments like bone and liver. The main healing mechanism is repair where damaged tissue is replaced by connective tissue which then forms a scar. Ulcer healing involves physiological changes by which the body replaces and restores function to damaged part. The healing process passes through different stages which are overlapping with each other. A brief haemostatic phase is followed by inflammatory phase which leads to fibroblastic activity with production of collagen and ground substance and new blood vessels. Finally epithelial cells migrate from the wound edges and reepithelisation takes place. This process of healing is influenced by a number of factors which may accelerate or delay the process of healing.

Acute ulcers are sometimes defined as those that follow the normal phases of healing; they are expected to show signs of healing in less than 4 weeks and include traumatic and postoperative wounds. The healing proceeds through an orderly reparative process to achieve sustained restoration of structure and function.

Ulcers that persist for longer than 4 weeks are termed as chronic ulcers and are often of complex poorly understood etiology. Chronic leg ulceration affects about 1

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% of the middle-aged and elderly population. The chronic ulcer however does not proceed to a restoration to complete functional integrity. It is stalled in the inflammatory phase owing to a variety of etiologies causing the ulcer and does not proceed to closure easily [2].

Following any injury or ulceration, the body tries to restore the integrity of the injured part. Several factors are known to influence the process of healing, but in acute phase, the healing proceeds through a set process of different stages which are overlapping and can be divided into four stages:

1. Hemostatic phase
2. Inflammatory phase
3. Proliferative phase
4. Remodeling or maturation phase

4.1.1 Hemostatic Phase

It is more pronounced in acute injuries where it leads to immediate clotting at the injured site to prevent the blood loss. There is vasoconstriction and thrombus formation to prevent blood loss. It is negligible in healing of an ulcer. The early phase, which begins immediately after skin injury, involves cascading molecular and cellular events that cause hemostasis and formation of an early, makeshift extracellular matrix that provides structural support for cellular attachment and subsequent cellular proliferation [3].

4.1.2 Inflammatory Phase

Platelets adhere to the damaged endothelial lining of the vessels releasing adenosine diphosphate (ADP), which causes thrombocytic aggregates to fill the wound. Then platelets release several cytokines from their alpha granules. These are platelet-derived growth factor (PDGF), platelet factor IV, and transforming growth factor beta (TGFB). Fibrin and fibronectin link together and form a plug that traps proteins and particles and prevents further blood loss. This fibrin-fibronectin plug is also the main structural support for the wound until collagen is deposited. Migratory cells use this plug as a matrix. The clot is eventually lysed and replaced with granulation tissue and then later with collagen. These attract inflammatory cells such as polymorphonuclear lymphocytes (PMN) and macrophages. Platelets and local injured tissue release vasoactive amines, such as histamine, serotonin, and prostaglandins, which increase vascular permeability, thereby aiding infiltration of these inflammatory cells. Macrophages remove devitalized tissue and microorganisms while regulating fibroblastic activity in the proliferative phase of the healing [1].

The cellular phase involves several types of cells cooperatively mounting an inflammatory response, synthesizing granulation tissue, and restoring the epithelial layer. Various components of the cellular phase occur in the following sequence:

Platelets, the most numerous cells soon after wounding, release such substances as ECM proteins and cytokines, including growth factors. Growth factors stimulate cells to speed their rate of division. Platelets also release other proinflammatory factors like serotonin, bradykinin, prostaglandins, prostacyclins, thromboxane, and histamine, which cause increasing cell proliferation and migration to the area and causing blood vessels to become dilated and porous.

4.1.2.1 Vasoconstriction and Vasodilatation

Immediately after a blood vessel is breached, ruptured cell membranes release inflammatory factors such as thromboxanes and prostaglandins that cause the vessel to spasm to prevent blood loss and collect inflammatory cells and factors in the area. This vasoconstriction lasts five to ten minutes and is followed by vasodilatation. Vasodilatation is caused by histamine released from platelets. This causes edema and migration of leukocytes to the injured site [4].

4.1.2.2 Polymorphonuclear Neutrophils

Within an hour of wounding, polymorphonuclear neutrophils (PMNs) arrive at the wound site and become the predominant cells for the first 2 days. Fibronectin, growth factors, and substances like kinins attract them to the wound. Neutrophils phagocytize debris and bacteria, kill bacteria by releasing free radicals, and cleanse the wound by secreting proteases that decompose damaged tissue. Neutrophils usually undergo apoptosis after completing their tasks and are engulfed and degraded by macrophages [5, 6].

4.1.2.3 Macrophages

Numbers of monocytes in the wound increase at about 2 days after the injury occurs. Once they are in the wound site, monocytes mature into macrophages. One of the macrophage's roles is to phagocytize other expended phagocytes, bacteria, and damaged tissue, and they also debride damaged tissue by releasing proteases [7, 8].

Macrophages function in regeneration and are essential for wound healing. They are stimulated by the low oxygen content of their surroundings to produce factors that induce and speed up angiogenesis, and they also stimulate cells that re-epithelialize the wound, create granulation tissue, and lay down a new extracellular matrix [9–12].

As inflammation decreases, numbers of neutrophils and macrophages are reduced at the wound site. If there is excessive devitalized tissue, or microbial biofilm is present in the ulcer, these factors may cause a prolonged inflammatory phase and prevent the ulcer from passing to the proliferation phase of healing. This can lead to formation of chronic ulcer [13].

4.1.3 Proliferative Phase

It lasts from the third day to the third week, consisting mainly of fibroblastic activity with the production of collagen and ground substance (glycosaminoglycans and proteoglycans), the growth of new blood vessels as capillary loops (angioneogenesis), and the re-epithelialization of the wound surface. Fibroblasts require vitamin C to produce collagen. The tissue formed in the early part of this phase is called granulation tissue. In the later part of this phase, there is an increase in the tensile strength of the wound due to increased collagen, which is at first deposited in the random fashion and consists of type III collagen.

About 2 or 3 days, fibroblasts begin to enter the wound site and proliferate, and angiogenesis occurs concurrently when endothelial cells migrate to the area of the wound. Because the activity of fibroblasts and epithelial cells requires oxygen and nutrients, angiogenesis is imperative for other stages in ulcer healing, like epidermal and fibroblast migration. The tissue in which angiogenesis has occurred typically looks red and erythematous due to the presence of capillaries [14, 15].

Stem cells of endothelial cells, originating from parts of uninjured blood vessels, develop pseudopodia and push through the ECM into the wound site to establish new blood vessels. Endothelial cells are attracted to the wound area by fibronectin found on the fibrin scab and chemotactically by angiogenic factors released by other cells, e.g., from macrophages and platelets when in a low-oxygen environment. Endothelial growth and proliferation is also directly stimulated by hypoxia and presence of lactic acid [16].

When macrophages and other growth factor-producing cells are no longer in a hypoxic, lactic acid-filled environment, they stop producing angiogenic factors. Thus, when tissue is adequately perfused, migration and proliferation of endothelial cells is reduced. Eventually blood vessels that are no longer needed die by apoptosis [16, 17].

4.1.3.1 Fibroplasia and Granulation Tissue Formation

Fibroblasts begin entering the wound site 2–5 days after wounding as the inflammatory phase is ending, and their numbers peak at 1–2 weeks post-wounding. By the end of the first week, fibroblasts are the main cells in the wound. Fibroplasia ends 2–4 weeks after wounding [4, 5].

In the first 2 or 3 days after injury, fibroblasts mainly migrate and proliferate, while later, they are the main cells that lay down the collagen matrix in the wound site [4]. Origins of these fibroblasts are thought to be from the adjacent uninjured cutaneous tissue (although new evidence suggests that some are derived from blood-borne, circulating adult stem cells/precursors) [18]. Initially fibroblasts utilize the fibrin cross-linking fibers (well formed by the end of the inflammatory phase) to migrate across the wound, subsequently adhering to fibronectin [16]. Fibroblasts then deposit ground substance into the wound bed, and later collagen, which they can adhere to for migration [19].

Granulation tissue functions as rudimentary tissue and begins to appear in the wound already during the inflammatory phase, 2–5 days post-wounding, and continues growing until the wound bed is covered. Granulation tissue consists of new blood vessels, fibroblasts, inflammatory cells, endothelial cells, myofibroblasts, and the components of a new, provisional extracellular matrix (ECM). The provisional ECM is different in composition from the ECM in normal tissue, and its components originate from fibroblasts [11]. Such components include fibronectin, collagen, glycosaminoglycans, elastin, glycoproteins, and proteoglycans [16]. Growth factors (PDGF, TGF-β) and fibronectin encourage proliferation, migration to the wound bed, and production of ECM molecules by fibroblasts. Fibroblasts also secrete growth factors that attract epithelial cells to the wound site. Hypoxia also contributes to fibroblast proliferation and excretion of growth factors, but severe hypoxia will inhibit their growth.

4.1.3.2 Collagen Deposition

Main strength of the wound is due to collagen, and it is deposited by fibroblasts. Before collagen is laid down, main strength of the wound is due to fibrin-fibronectin clot, which does not provide much resistance to traumatic injury. Also, cells involved in inflammation, angiogenesis, and connective tissue construction attach to, grow, and differentiate on the collagen matrix laid down by fibroblasts. Type III collagen and fibronectin are generally beginning to be produced in appreciable amounts at about 3 days. Their deposition peaks at 1–3 weeks. They are later replaced by the stronger type I collagen [11, 16, 20].

4.1.3.3 Epithelialization

The formation of granulation tissue into an open wound allows the re-epithelialization phase to take place, as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment. Basal keratinocytes from the wound edges and dermal appendages such as hair follicles, sweat glands, and sebaceous glands are the main cells responsible for the epithelialization phase of wound healing [21]. They advance in a sheet across the wound site and proliferate at its edges, ceasing movement when they meet in the middle. In healing that results in a scar, sweat glands, hair follicles, and nerves do not form [22, 23].

Epithelial cells climb over one another in order to migrate. This growing sheet of epithelial cells is often called the epithelial tongue. The first cells to attach to the basement membrane form the stratum basale. These basal cells continue to migrate across the wound bed, and epithelial cells above them slide along as well. The more quickly this migration occurs, the less scar will be formed. Fibrin, collagen, and fibronectin in the ECM may further signal cells to divide and migrate [8, 21, 24].

As keratinocytes migrate, they move over granulation tissue but underneath the scab (if one was formed), separating it from the underlying tissue. Epithelial cells have the ability to phagocytize debris such as dead tissue and bacterial matter that would otherwise obstruct their path. Because they must dissolve any scab that

forms, keratinocyte migration is best enhanced by a moist environment, since a dry one leads to formation of a bigger, tougher scab [21, 25].

The epithelial cells at the wound edges proliferate until the entire raw area is resurfaced. When the cells from either side meet in the middle, contact inhibition causes them to stop migrating and keratinocytes secrete the proteins that form the new basement membrane [24]. Cells reverse the morphological changes they underwent in order to begin migrating, and they reestablish desmosomes and hemidesmosomes and become anchored to basement membrane [26].

4.1.3.4 Contraction

Contraction is a key phase of healing with repair. If contraction continues for too long, it can lead to disfigurement and loss of function [27]. It is more in healing of deep ulcers. Contraction commences approximately a week after wounding, when fibroblasts have differentiated into myofibroblasts [28]. Myofibroblasts, which are similar to smooth muscle cells, are responsible for contraction. In full-thickness wounds, contraction peaks at 5–15 days post-wounding. Contraction can last for several weeks and continues even after the wound is completely re-epithelialized. Contraction usually does not occur symmetrically; rather most ulcers and wounds have an "axis of contraction" which allows for greater organization and alignment of cells with collagen [28].

As the actin in myofibroblasts contracts, the wound edges are pulled together. Fibroblasts lay down collagen to reinforce the wound as myofibroblasts contract. The contraction stage in proliferation ends as myofibroblasts stop contracting and commit apoptosis [27].

4.1.4 Remodeling Phase

It is characterized by maturation of collagen (type I replacing type III until a ratio of 4:1 is achieved) [1]. There is realignment of collagen fibers along the lines of tension, decreased wound vascularity, and wound contraction due to fibroblast and myofibroblast activity. When the levels of collagen production and degradation equalize, the maturation phase of tissue repair begins. Type III collagen, which is prevalent during proliferation, is replaced by type I collagen. Originally disorganized collagen fibers are rearranged, cross-linked, and aligned along tension lines, and tensile strength increases [24]. Gradually vascularity at the healing site decreases, and the scar loses its red appearance as blood vessels that are no longer needed are removed by apoptosis. If the phases of healing do not progress in a predictable and timely manner, it leads to the formation of a chronic ulcer such as a venous ulcer or pathological scarring such as a keloid scar [29, 30].

4.2 Basic Concept of Treatment of Chronic Ulcer

The basic treatment to promote healing of chronic ulcer includes cleaning and debridement of the ulcer if there is slough and presence of necrotic tissue and treatment of any infection. Treatment of biofilm of the ulcer which prevents healing, and

treatment of the cause of the ulcer depending on its etiology is equally important. A proper dressing should be done which does not damage the newly formed epithelial cells and at the same time promotes healing.

4.2.1 Cleaning the Ulcer

Meticulous skin care and cleansing of the ulcer are essential. Cleaning should be done first from the margin and then from the centre of the ulcer. Debridement is the removal of surface contamination and dead tissue which is essential for healing to start. Debridement may be surgical or medical using wet and dry dressings. Debridement converts the chronic ulcer into an acute ulcer so that it can progress through the normal stages of healing.

4.2.2 Treatment of Infection

In chronic ulcers, antibiotics are not necessary unless there is evidence of tissue infection like pain in the ulcer or redness in the surrounding skin. Patient may have fever and systemic symptoms if there is acute infection. Antibiotic should be as per sensitivity report to avoid resistance of the organism. Topical antibiotics can be used if there is evidence of infection. Their excessive use may result in increased antibiotic resistance and can cause local skin allergy.

4.2.3 Dressings

There is a wide range of specialized dressings available to assist ulcer healing. These are classified as nonabsorbent, absorbent, debriding, self-adhering, and others. Selection of dressing will depend on the site and type of ulcer, personal preference, and cost. Dressings are usually occlusive as ulcers heal better in a moist environment. If the ulcer is clean and dry, occlusive dressings are usually changed once or twice weekly because more frequent change of dressing removes healthy cells as well as debris. Contaminated ulcers discharging pus may require more frequent dressing changes. The principle of moist wound healing is a well-accepted concept for chronic wounds and ulcers. Maintaining a physiological moist environment helps in ulcer healing as it enables the undisturbed granulation and epithelialization in the ulcer. Moisture has various beneficial effects in the ulcer bed like the following:

- Nutrients, growth factors, and enzymes can easily spread across the wound.
- Moisture facilitates the proliferation of new cells.
- Epithelialization is much quicker than in dry ulcers.
- *Method of dressing*
  - Carefully rinse the ulcer and debride if necessary.
  - Dry the ulcer margins and peri-ulcer skin.

- Apply local antibiotic ointment (if evidence of infection) and the dressing and allow it to overlap the ulcer size by approximately 2 cm.
- Apply medical skin cream in the surrounding area as per requirement of skin.
- Finally apply the compression bandages or compression stockings as in venous ulcers.

4.2.4 Surgical Management of Ulcer

Surgery may be considered if the ulcer fails to heal with conservative measures, especially if it is very large or painful. First, the state of the venous and arterial systems should be assessed, infection eliminated, and underlying associated diseases such as diabetes, venous insufficiency, and arterial insufficiency treated. Nutritional deficiency and anemia must be corrected especially vitamin C, zinc, and adequate protein diet supplementation. Clean chronic ulcers may be treated by various types of skin graft. Meshed grafts are better than sheet grafts as they allow exudate to escape through the mesh. The bed of the ulcer needs to be carefully prepared. A shave procedure to remove surrounding lipodermatosclerosis may be required prior to applying the skin graft.

Various new products have also been used to accelerate the ulcer healing like: growth factors and cytokines, hyperbaric oxygen to increase tissue oxygen tension, skin graft substitutes (bioengineered skin), connective tissue matrix, expanded epidermis, epidermal stem cells, and V.A.C. (vacuum-assisted closure) device.

4.2.4.1 Vacuum-Assisted Closure (V.A.C.) Device

It is being frequently used to accelerate healing of chronic ulcers. Vacuum-assisted devices help in control of infection and prevent seroma formation. Negative pressure applied in the ulcer bed increases cell proliferation and promotes angiogenesis and vascularity. It promotes early healing by decreasing edema, by removing interstitial fluid, and by increasing blood flow [31].

4.2.4.2 Compression Therapy

Compression therapy is an important part of the management of venous leg ulcers and chronic swelling of the lower leg [32]. Compression results in healing of 40–70 % of chronic venous ulcers within 12 weeks. Compression therapy is achieved by using a graduated elastic compression stocking or a good quality crepe bandage that is wrapped from the toes or foot to the area below the knee. This externally created pressure on the leg helps to heal the ulcer by increasing the calf muscle pump action and reduce swelling in the leg. Compression is not used if the ABPI is below 0.8. Four-layer bandage has been shown to increase the healing of venous ulcers. Various stages of ulcer healing are shown in Figs. 4.1, 4.2, 4.3, and 4.4.

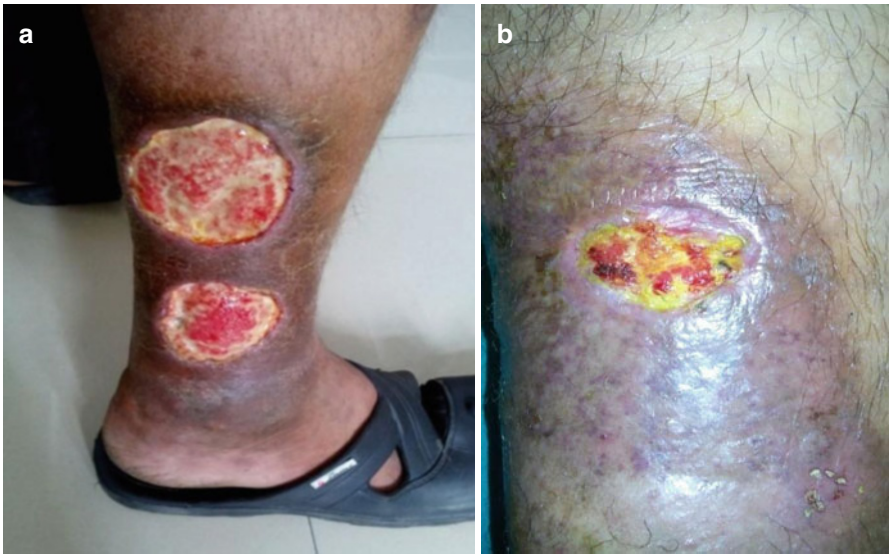

Fig. 4.1 (**a**, **b**) Unhealthy chronic ulcer showing slough at the base with patchy areas of granulation tissue in between

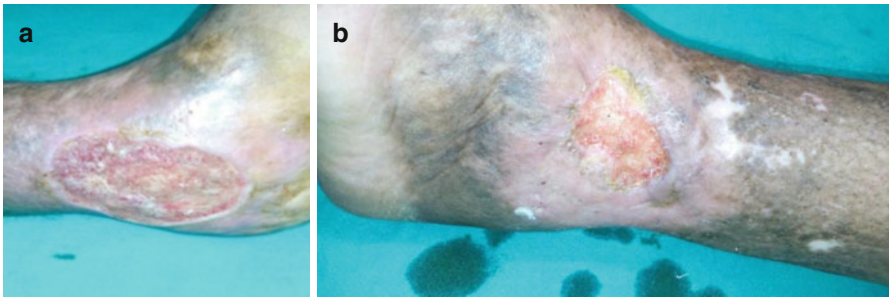

Fig. 4.2 (**a**, **b**) Chronic ulcers showing changes of lipodermatosclerosis in the surrounding skin

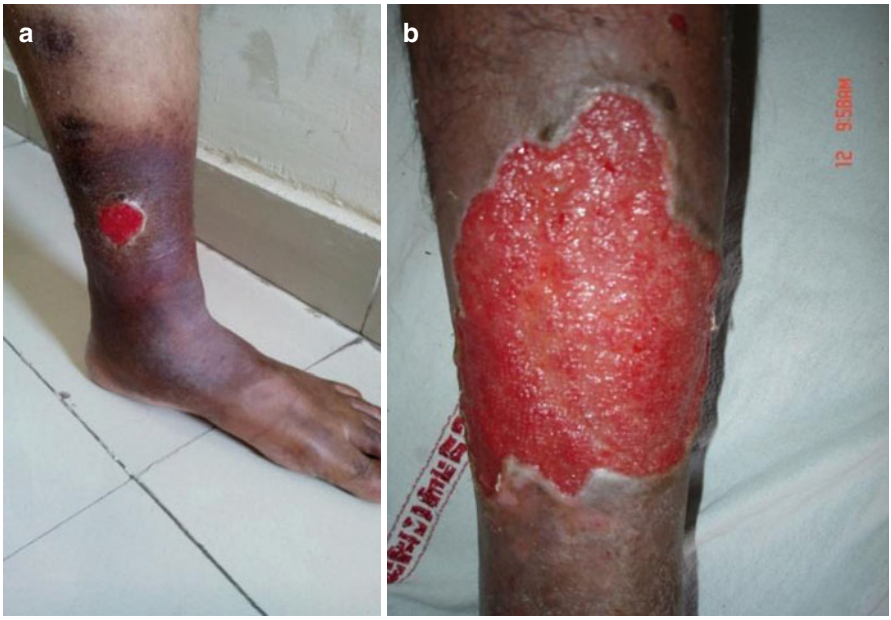

Fig. 4.3 (**a**, **b**) Chronic ulcer showing healthy granulation tissue ready for epithelialization

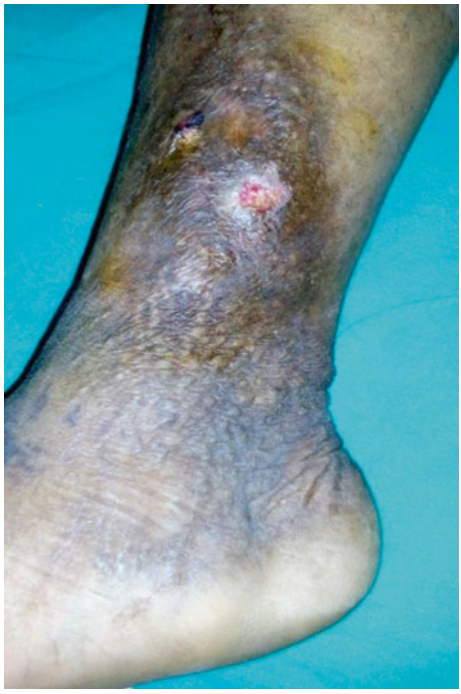

Fig. 4.4 Chronic ulcer in the contraction phase and showing epithelialization at the margins and changes of lipodermatosclerosis in the surrounding skin

References

1. Williams NS, Bulstrode CJK, O'Connell PR. Wound tissue repair and scars: in bailey and love's short practice of surgery. 26th ed. CRC Press, Taylor and Francis Group, LLC 6000 Broken Sound Parkway NW, Suite 300 Boca Raton. FL33487–2742; 2013. p. 24.
2. Rook A, Wilkinson DS, Ebling FJB, Champion RH, Burton JL, editors. Textbook of dermatology. 4th ed. Blackwell: Scientific Publications; 2001.
3. Nguyen DT, Orgill DP, Murphy GF. Chapter 4: The pathophysiologic basis for wound healing and cutaneous regeneration. In: Biomaterials for treating skin loss. Cambridge/Boca Raton: Woodhead Publishing (UK/Europe) & CRC Press (US); 2009. p. 25–57. (ISBN 978-1-4200-9989-8/ISBN 978-1-84569-363-3).
4. Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg. 1998;176(2A Suppl):26S–38. doi:10.1016/S0002-9610(98)00183-4.
5. De la Torre J, Sholar A. Wound healing: chronic wounds. Emedicine.com. 2006. Accessed 20 Jan 2008.
6. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol. 2005;15(11):599–607. doi:10.1016/j.tcb.2005.09.002.
7. Expert Reviews in Molecular Medicine. The phases of cutaneous wound healing. 5:1. Cambridge University Press; 2003. Accessed 20 Jan 2008.
8. Deodhar AK, Rana RE. Surgical physiology of wound healing: a review. J Postgrad Med. 1997;43(2):52–6.
9. Ovchinnikov, Dmitry A. Macrophages in the embryo and beyond: much more than just giant phagocytes. Institute for Molecular Bioscience and Cooperative Research Centre for Chronic Inflammatory Diseases (CRC-CID), University of Queensland, Brisbane, Queensland, Australia: researchgate.net. 2008 doi:10.1002/dvg.20417.
10. Newton PM, Watson JA, Wolowacz RG, Wood EJ. Macrophages restrain contraction of an in vitro wound healing model. Inflammation. 2004;28(4):207–14.
11. Mercandetti M, Cohen AJ. Wound healing: healing and repair. Emedicine.com. 2005. Accessed 20 Jan 2008.
12. Stashak TS, Farstvedt E, Othic A. Update on wound dressings: indications and best use. Clin Tech Equine Pract. 2004;3(2):148–63. doi:10.1053/j.ctep.2004.08.006.
13. Midwood KS, Williams LV, Schwarzbauer JE. Tissue repair and the dynamics of the extracellular matrix. Int J Biochem Cell Biol. 2004;36(6):1031–7. doi:10.1016/j.biocel.2003.12.003.
14. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005;366:1736–43.
15. Kuwahara RT, Rasberry R. Chemical peels. Emedicine.com. Accessed 15 Sept 2007.
16. Romo T, Pearson JM. Wound healing, skin. Emedicine.com. 2005. Accessed 27 Dec 2006.
17. Greenhalgh DG. The role of apoptosis in wound healing. Int J Biochem Cell Biol. 1998;30(9):1019–30. doi:10.1016/S1357-2725(98)00058-2.
18. Song G, Nguyen DT, Pietramaggiori G, Scherer S, Chen B, Zhan Q, Ogawa R, Yannas IV, et al. Use of the parabiotic model in studies of cutaneous wound healing to define the participation of circulating cells. Wound Repair Regen. 2010;18(4):426–32. doi:10.1111/j.1524-475X.2010.00595.x. PMC 2935287.
19. Rosenberg L, de la Torre J. Wound healing, growth factors. Emedicine.com. 2006. Accessed 20 Jan 2008.
20. Pollock RE, Brunicardi FC, Andersen DK, Billiar TR, David D, Hunter JG, Matthews JJ. The cellular, biochemical, and mechanical phases of wound healing. In: Schwartz's principles of surgery. 9th ed. McGraw-Hill Professional. ISBN 0-07-154769-X.2009.
21. DiPietro LA, Burns AL. Wound healing: methods and protocols. In: Methods in molecular medicine. Totowa, N.J.: Humana Press. Electronic book; 2003.
22. Fu XB, Sun TZ, Li XK, Sheng ZY. Morphological and distribution characteristics of sweat glands in hypertrophic scar and their possible effects on sweat gland regeneration. Chin Med J (Engl). 2005;118(3):186–91.
23. "BURN INJURIES". National trauma institute.org. Retrieved 18-03-08.

24. Lorenz HP, Longaker MT. Wounds: biology, pathology, and management. Stanford University Medical Center. 2003. Accessed 20 Jan 2008.
25. Larjava H, Koivisto L, Hakkinen L. Chapter 3: Keratinocyte interactions with fibronectin during wound healing. In: Heino J, Kahari VM, editors. Cell invasion, Medical intelligence unit, vol. 33. Georgetown, Tex., Austin: Tex Landes Bioscience, Inc. Electronic book; 2002.
26. Santoro MM, Gaudino G. Cellular and molecular facets of keratinocyte reepithelization during wound healing. Exp Cell Res. 2005;304(1):274–86. doi:10.1016/j.yexcr.2004.10.033.
27. Hinz B. Masters and servants of the force: the role of matrix adhesions in myofibroblast force perception and transmission. Eur J Cell Biol. 2006;85(3–4):175–81. doi:10.1016/j.ejcb.2005.09.004.
28. Eichler MJ, Carlson MA. Modeling dermal granulation tissue with the linear fibroblast-populated collagen matrix: a comparison with the round matrix model. J Dermatol Sci. 2006;41(2):97–108. doi:10.1016/j.jdermsci.2005.09.002.
29. O'Leary R, Wood EJ, Guillou PJ. Pathological scarring: strategic interventions. Eur J Surg. 2002;168(10):523–34.
30. Desmoulière A, Chaponnier C, Gabbiani G. Tissue repair, contraction, and the myofibroblast. Wound Repair Regen. 2005;13(1):7–12. doi:10.1111/j.1067-1927.2005.130102.x.
31. Argenta LC, Morykwas ML. Vacuum-assisted closure: a new method of wound control and treatment: clinical experience. Ann Plast Surg. 1997;38:563–77.
32. Nelson EA, Cullum N, Jones J. Venous leg ulcers. Clin Evid. 2006;15:2607–26.

Clinical Anatomy of Lower Extremity

5

Soumya Khanna and Ajay K. Khanna

5.1 Introduction

Ulcer is any breech in the continuity of the epithelium of the skin. The skin itself gets supply from artery, vein, and a nerve and any pathology of either of them results in ulcer.

Thus, ulcer can be broadly classified into the following:

1. If venous supply is hampered
   Venous ulcer (varicose ulcer): due to abnormal venous hypertension
   Ulcers from congenital arteriovenous fistula
2. If arterial supply is hampered
   Arterial ulcer: due to peripheral arterial disease and poor peripheral circulation
   Erythrocyanoid ulcer: due to abnormally small posterior tibial and peroneal arteries
   Gummatous ulcer: due to obliterative endarteritis, necrosis, and fibrosis. Occurs in tertiary syphilis
   Martorell's ulcer: sudden obliteration of end arterioles of the skin of region which is already having sparse arterial supply
   Diabetic ulcer: due to diabetic atherosclerosis
3. If nerve supply is hampered
   Trophic (neurogenic) ulcer
   Diabetic ulcer: due to diabetic neuropathy

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4. Infective: Infection can hamper either artery, venous, or nerve supply.
   Infective
   Meleny's
   Tropical
   Yaws
   Diabetic

Thus, this chapter basically focuses on the anatomy of veins, arteries, and nerves of lower limb and what all structures they supply and their significance.

5.2 Regions of Lower Limb [1]

Lower limb is divided into four regions:

1. Gluteal region/buttock: lies behind the pelvis, above the posterior compartment of thigh
2. Thigh: region above knee. It is further divided into three compartments:
   (i) Anterior or extensor
   (ii) Medial or adductor
   (iii) Posterior or flexor
3. Leg proper is also divided into three compartments:
   (i) Anterior or extensor
   (ii) Posterior or flexor
   (iii) Lateral or peroneal
4. Foot: has dorsum or upper surface and a sole or plantar surface

5.2.1 Gluteal Region and Hip Joint (Figs. 5.1 and 5.2)

The following structures emerge from the pelvis through greater sciatic foramen into the gluteal region:

1. Above the piriformis
   (i) Superior gluteal nerve
   (ii) Superior gluteal vessels
2. Below the piriformis
   (i) Inferior gluteal nerve and vessels
   (ii) Pudendal nerve and vessels
   (iii) Nerve to obturator internus
   (iv) Sciatic nerve
3. (v) Posterior femoral cutaneous nerve
4. (vi) Nerve to quadratus femoris

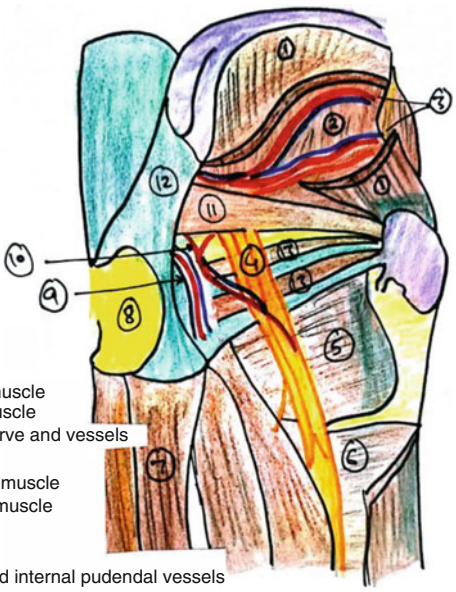


Fig. 5.1 Gluteal region

Superior gluteal nerve supplies both gluteus medius and minimus and ends in tensor fascia lata. It has no cutaneous distribution.

Superior gluteal artery gives superficial and deep branches. The superficial branch enters deep surface of gluteus maximus to supply the muscle and skin over it. The deep branch passes laterally between gluteus minimus and gluteus medius and further divides into upper and lower branch. The upper branch forms the anastomosis at the anterior superior iliac spine and lower supplies gluteus minimus and medius and forms the trochanteric anastomosis.

The *inferior gluteal nerve* passes below the piriformis to sink into deep surface of gluteus maximus.

The *inferior gluteal artery* supplies piriformis, obturator internus, and gluteus maximus.

The *pudendal nerve* (S2–S4) after emerging below the piriformis makes a forward turn around the back of sacrospinous ligament and ultimately leaves the buttock by passing through lesser sciatic foramen to pass through pudendal canal.

The *internal pudendal artery* follows a similar course to that of the nerve and lies lateral to the nerve. A companion vein lies on each side of the artery.

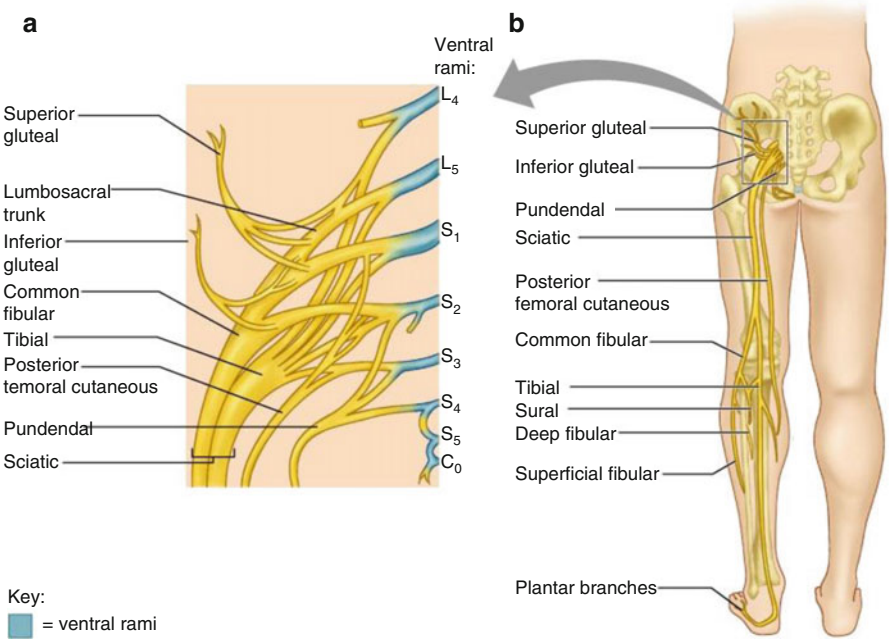


Fig. 5.2 Nervous anatomy of lower limb

The *nerve to obturator internus* (L5, S1, S2) lies lateral to internal pudendal artery and loops around base of ischial spine to finally supply obturator internus and superior gemellus.

The *sciatic nerve* (L4, L5, S1–S3) emerges from below piriformis muscle. It is typically 2 cm wide at its origin, thus being the thickest nerve in the body. It lies more laterally than the inferior gluteal and pudendal nerve and vessels. It passes upon the ischium over the posterior aspect of acetabulum. It comes in contact with ischial tuberosity at a point one third of the way from ischial tuberosity to the posterior superior iliac spine, its surface marking for entry of nerve into the gluteal region. It goes vertically downward going over the posterior surface of obturator internus and quadratus femoris and finally entering the hamstring compartment of the thigh, where it lies anterior to the long head of biceps femoris. In the upper part of the popliteal fossa, it divides into tibial and common peroneal in most of cases. Occasionally, there is a high division and the two components may leave the pelvis separately.

The *posterior femoral cutaneous nerve* (S1–S3) emerges below the piriformis, and during its course in the gluteal region, it lies on the sciatic nerve under cover of gluteus maximus. Below the buttock, the nerve goes vertically down as low as the mid calf. It lies below the fascia lata, superficial to hamstrings which separate it from sciatic nerve. It gives gluteal branches which curl around lower border of gluteus maximus to supply the skin over buttock convexity. The perineal branch supplies the posterior part of scrotum or labium majus.

It is noticeable that the segments of this nerve are also those of pelvic parasympathetic nerves which supply pelvic viscera. Pain from the pelvic disease is often referred over the supply of femoral cutaneous nerve and this pain should be distinguished from sciatica.

The *nerve to quadratus femoris* (L4, L5, S1) lies over the ischium anterior to the quadratus femoris. It gives an articular branch to the back of hip joint and supplies quadratus femoris and inferior gemellus.

5.2.2 Anterior Compartment of the Thigh [2]

5.2.2.1 Superficial Nerves

They are:

1. Ilioinguinal nerve
2. Femoral branch of genitofemoral nerve
3. Medial, intermediate, and lateral femoral cutaneous nerve
4. Cutaneous branches of obturator nerve

Ilioinguinal nerve is derived from first lumbar nerve. It supplies the skin of root of the penis, anterior one third of scrotum, and small area of thigh below medial end of inguinal ligament.

Genitofemoral nerve is derived from first and second lumbar nerves. But the femoral branch has fibers from L1 only. It supplies the skin over femoral triangle.

The medial femoral cutaneous nerve is a branch of femoral nerve (L2, L3). It supplies medial side of thigh.

The intermediate femoral cutaneous nerve (L2, L3), again a branch of femoral nerve after piercing the sartorius and fascia lata, supplies front of thigh.

The lateral femoral cutaneous nerve is a branch of lumbar plexus (L2, L3). It gains entry to the thigh by piercing the fascia lata and divides into anterior and posterior branches. The anterior branch supplies the anterolateral surface of the thigh, whereas the posterior branch supplies the skin on posterolateral aspect from the level of greater trochanter to the mid thigh. The nerve if compressed while passing through inguinal ligament causes pain and altered sensation in lateral side of thigh (meralgia paraesthetica). Sometimes, it may get compressed while passing through iliac fascia as well. The treatment of this condition requires division of inguinal ligament and freeing the nerve from any compression.

The cutaneous branches of obturator nerve (L2–L4) pass to the skin over the medial side of thigh.

Patellar plexus: It is a network of communicating twigs present in subcutaneous tissue over and around the patella and patellar ligament. It receives contribution from the terminal branches of medial and intermediate femoral cutaneous nerves, anterior branch of lateral femoral cutaneous nerve, and infrapatellar branch of saphenous nerve.

5.2.3 Superficial Arteries

There are four cutaneous branches of femoral artery:

I. Superficial circumflex iliac artery
II. Superficial epigastric artery
III. Superficial external pudendal artery
IV. Deep external pudendal artery

Superficial circumflex iliac artery passes up below the inguinal ligament to the anastomosis at anterior superior iliac spine.

Superficial epigastric artery crosses inguinal ligament and runs toward umbilicus.

Superficial external pudendal artery emerges from saphenous opening, passes in front of spermatic cord (round ligament), and goes to the penis and scrotum (labium majus).

Deep external pudendal artery pierces fascia lata and goes behind spermatic cord (round ligament) to supply the skin of scrotum (labium majus).

5.2.4 Superficial Veins (Fig. 5.3)

The *great saphenous vein* (GSV) being the longest vein in the body runs from foot to groin, beginning as upward continuation of the medial marginal vein of foot. This vein runs between superficial and deep fascia, and on ultrasound, it gives the appearance of Egyptian eye. It goes upward in front of medial malleolus, crosses lower fourth of medial surface of tibia obliquely, and runs behind the medial border of tibia toward the knee where it lies palm breadth behind medial border of patella. It curves forward around medial convexity of the thigh and ends by piercing deep fascia and passing through cribriform fascia, where it joins femoral vein. Normal diameter of GSV is 5–6 mm in thigh and 2–3 mm in calf. There are about 20 valves. Incompetence of these valves is a cause of varicosity of the vein. Four tributaries join great saphenous vein in the region of saphenous opening. They are superficial circumflex iliac, superficial epigastric, and superficial and deep external pudendal vein (Fig. 5.4) near the saphenofemoral opening. Superficial external pudendal artery crosses at the level of saphenofemoral junction (SFJ) but many a times, it passes behind the GSV. Saphenofemoral junction is 4 cm below and lateral to pubic tubercle. Apart from the tributaries near SFJ, there are other tributaries as anterior accessory and posterior accessory veins draining into GSV. GSV is in close proximity to saphenous nerve which is the largest branch of femoral nerve purely sensory in origin. This nerve is in close proximity to GSV in lower part and that is why it is likely to damage if stripping or endovenous procedure is done in the leg.

Short saphenous vein (SSV) arises from lateral side of foot and drains in popliteal fossa at variable positions. It usually penetrates the deep fascia in the mid calf and

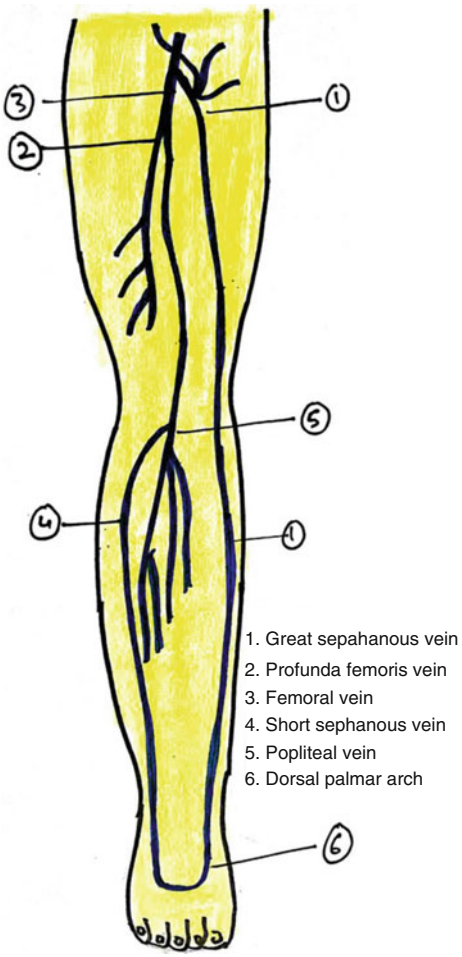


Fig. 5.3 Venous anatomy of lower limb

then, it runs between two heads of gastrocnemius to open in popliteal vein. Sural nerve is in relation with SSV and is likely to be damaged during surgery of SSV mainly in the lower part as it is in close proximity in that part. Sometimes, the vein of Giacomini which connects SSV with GSV is present and that may be the reason for recurrence of varicose veins after surgery or endothermal treatment.

There are numerous perforating (anastomotic) veins which connect great saphenous vein with deep veins of the calf. They are variable in position but the constant ones are the following [3]:

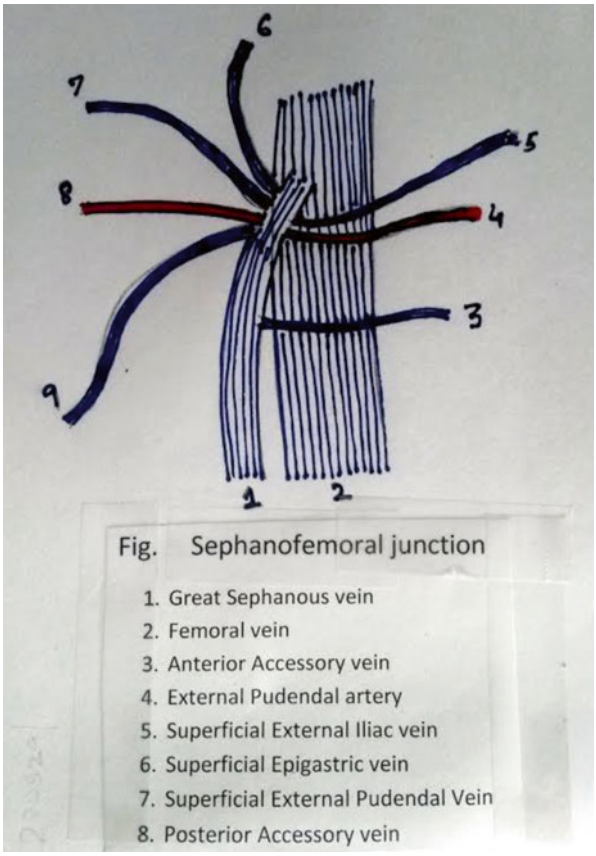


Fig. 5.4 Saphenofemoral junction

I. Just below the medial malleolus
II. 10 cm above the medial malleolus
III. Little below the middle of the leg
IV. Just distal to the knee
V. In lower thigh joining great saphenous vein or one of its tributaries to the femoral vein in adductor canal

The perforators in the leg may connect the *posterior arch vein* which joins the great saphenous vein below the knee. Also, some perforating veins join the venae comitantes of the posterior tibial artery, whereas others communicate with venous plexus of the soleus. The valves in the perforating veins are directed from superficial to deep and are found where the veins pierce the deep fascia and also where they communicate with the deep veins. The blood in the superficial system flows to the deep system of veins which is further pushed upward by the pumping action of the soleus and other calf muscles. If the valves in the perforators become incompetent, the flow becomes reversed resulting in varicose veins. Although deep venous

insufficiency is common and important, the anatomy of deep vein valves is poorly understood. A study was conducted to investigate the location, number, and consistency of venous valves in the femoral and popliteal veins in normal subjects. All studies were cadaveric and subjects ranged from stillborn fetuses to 103 years of age. Studies suggested that femoral veins contain between one and six valves, and popliteal veins contain between zero and four valves. Deep vein valves were consistently located in the common femoral vein (within 5 cm of the inguinal ligament), the femoral vein (within 3 cm of the deep femoral vein tributary), and the popliteal vein near the adductor hiatus. Valves are consistently located at specific locations in the deep veins of the leg, although there is often significant variability between subjects [4].

5.2.5 **Femoral Artery** (Figs. 5.5, 5.6, and 5.7)

The femoral artery enters the thigh at midinguinal point (point between anterior superior iliac spine and pubic symphysis) as a continuation of external iliac artery. Here, it lies over the psoas major. It is here where its pulsation can be felt and catheterization can be done. It emerges from the femoral sheath, goes downward, and enters adductor canal deep to sartorius.

It has four small branches below the inguinal ligament and just below the ending of femoral sheath gives off a large deep branch, the *profunda femoris*, the chief artery of the thigh.

The profunda femoris artery usually supplies all muscles of thigh. It arises from lateral side of femoral artery about 3–4 cm distal to the inguinal ligament and then curves down deep to it, passing between pectineus and adductor longus, whose upper border separates femoral and profunda arteries.

In addition to perforating arteries and muscular branches, it gives off large lateral and medial circumflex femoral artery.

The lateral circumflex femoral artery passes between branches of femoral nerve and divides into three branches beneath sartorius. The ascending branch runs up on the vastus lateralis. It gives a branch to the trochanteric anastomosis and passes on toward anterior superior iliac spine where it terminates by anastomosing with superficial and deep circumflex iliac and superior branch of superior gluteal artery. The transverse branch passes across vastus lateralis and spirals around the femur to form part of the cruciate anastomosis. The descending branch runs downward with nerve to vastus lateralis in a groove between anterior edges of vastus lateralis and vastus intermedius.

The medial circumflex femoral artery arises from medial side of profunda. It gives an ascending branch to the trochanteric anastomosis and a horizontal branch to the cruciate anastomosis.

The four perforating arteries pass backward, through adductor magnus, first pass above, second through, and third and fourth below adductor brevis. They supply hamstring and adductor muscles.

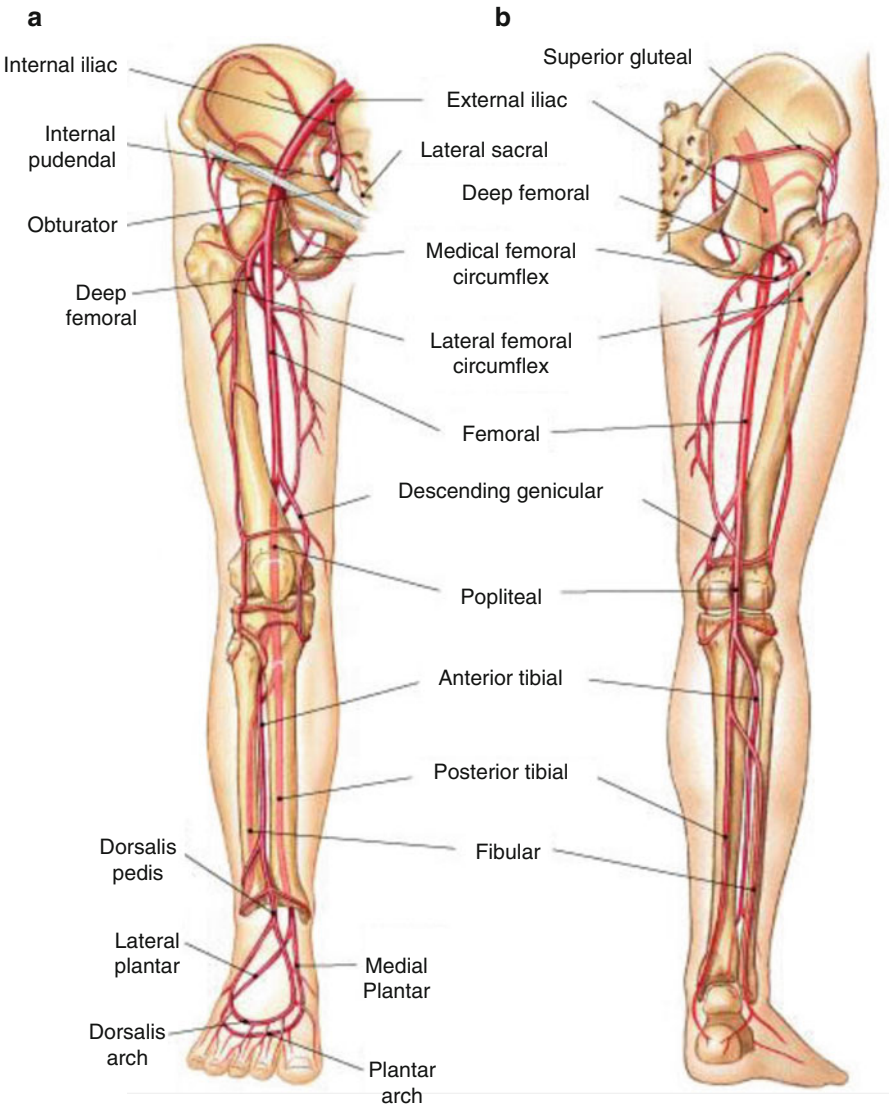


Fig. 5.5 Arterial anatomy of lower limb

5.2.6 Femoral Vein

It enters through the lower part of femoral triangle lying posterior to femoral artery. It goes upward through femoral triangle and comes to lie medial to femoral artery. A tributary corresponding to profunda femoris artery drains into it and just below the femoral sheath the great saphenous vein joins it. It bears 4 or 5 valves, the most constant ones being just above the junction with profunda and great saphenous vein.

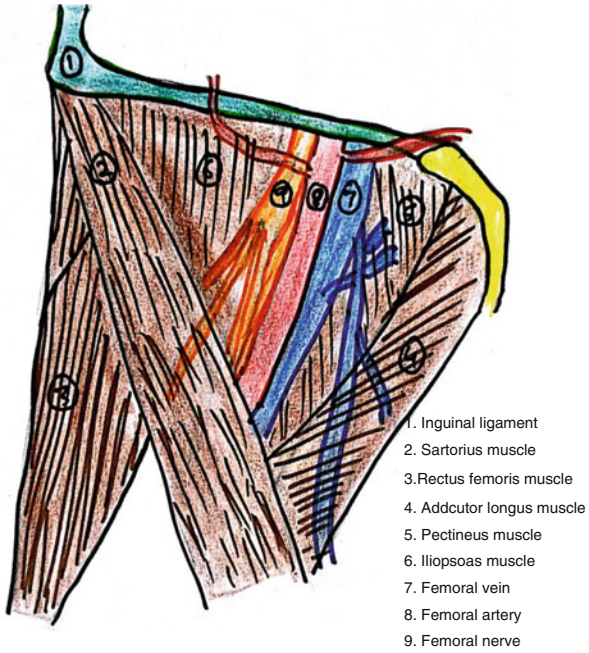


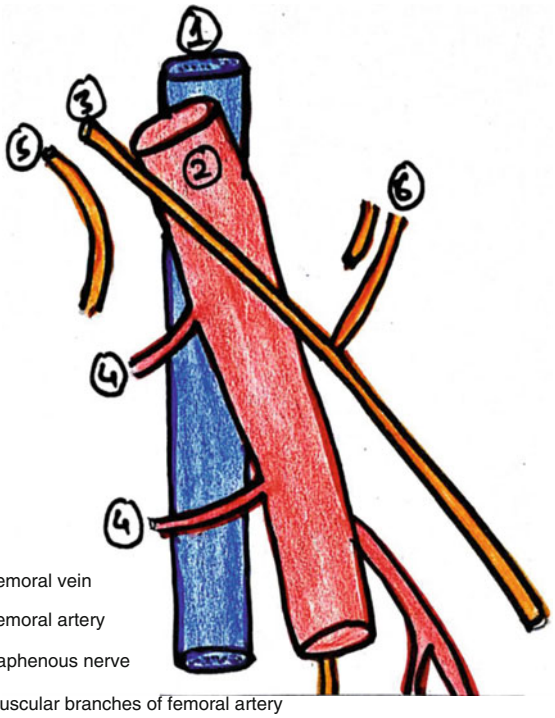
Fig. 5.6 Femoral triangle

The position of femoral vein in the living body is found by feeling the pulsations of the femoral artery and the femoral vein lies immediately medial to it [5]. More than 80 % of blood flow in the lower limb is through deep veins.

5.2.7 Femoral Nerve

It is the nerve of extensor compartment of the thigh. It is formed by posterior divisions of the anterior rami of the lumbar nerves 2, 3, and 4. It supplies iliacus in the abdomen. It lies between psoas and iliacus in iliac fossa. It enters the thigh by passing deep to the inguinal ligament. On entering the femoral triangle, it gives a branch to pectineus. After passing down the inguinal ligament, the femoral nerves divide into numerous branches:

I. Intermediate and medial femoral cutaneous nerves
II. Nerve to sartorius
III. Nerve to rectus femoris
IV. Nerve to vastus medialis
V. Nerve to vastus lateralis
VI. Nerve to vastus intermedius
VII. Saphenous nerve



1. Femoral vein
2. Femoral artery
3. Saphenous nerve
4. Muscular branches of femoral artery
5. Nerve to vastus medialis
6. Anterior and posterior division of obturator nerve

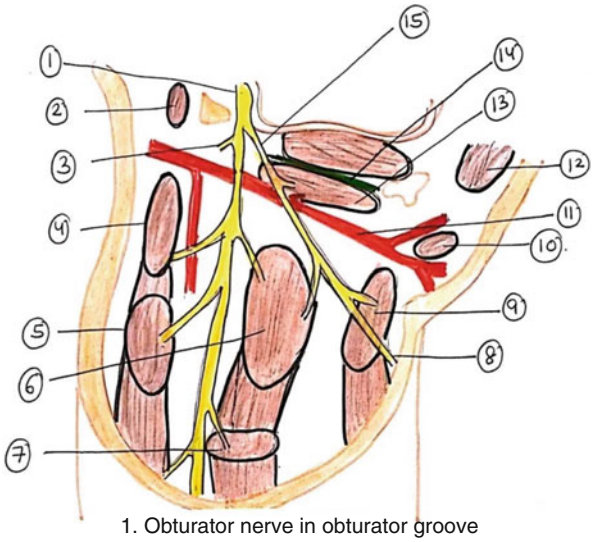
Fig. 5.7 Adductor canal

5.2.8 Medial Compartment of the Thigh

The artery of the compartment is the profunda femoris, assisted proximally by the obturator artery, and the nerve is the obturator nerve.

Obturator artery emerges from the obturator foramen along with the nerve and divides into anterior and posterior branches which anastomose with each other and the medial circumflex artery.

Obturator nerve (Fig. 5.8) divides in the obturator notch into anterior and posterior divisions. The anterior division passes above obturator externus and, after giving an articular branch to hip joint, descends in the thigh behind the adductor longus. After supplying adductor brevis and gracilis, it ends up in the subsartorial plexus, the branches of which supply the skin over medial side of thigh. The posterior division passes through obturator externus and also supply to it. It supplies the adductor magnus and gives a terminal branch which enters the popliteal fossa through the adductor hiatus and supplies capsule of knee joint.



1. Obturator nerve in obturator groove
2. Psoas major muscle
3. Branch to hip joint from anterior division
4. Pectineus
5. Adductor longus muscle
6. Adductor brevis muscle
7. Gracilis muscle
8. Branch to knee joint
9. Adductor magnus muscle
10. Quadratus femoris muscle
11. Medial circumflex femoral artery
12. Gluteus maximus muscle
13. Obturator externus muscle
14. Obturator membrane
15. Posterior division

Fig. 5.8 Course and distribution of obturator nerve

5.2.9 Posterior Compartment of the Thigh

It extends from buttock to the back of knee. The cutaneous nerve supply is by posterior femoral cutaneous nerve. The muscles of the back of the thigh are called hamstring muscles**.** They are semitendinosus, semimembranosus, long head of biceps femoris, and ischial head of adductor magnus.

The sciatic nerve travels between the long head of biceps femoris and adductor magnus to finally reach the superior angle of popliteal fossa. It is accompanied by a small companion artery which is a branch of inferior gluteal artery.

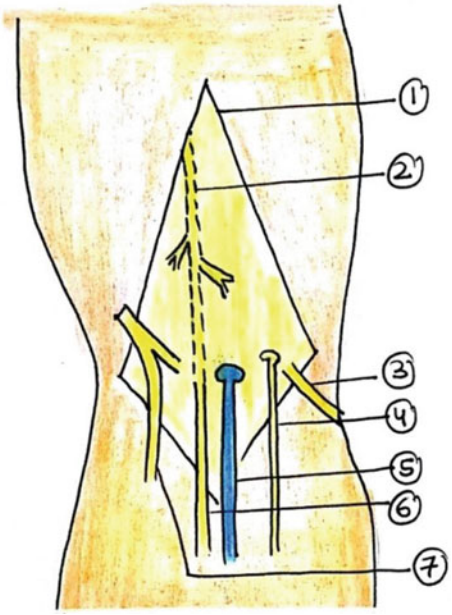
The arteries of the back of thigh are terminal parts of the branches of the profunda femoris artery, the main supply being the perforating branches of the profunda femoris. Other branches are the lateral circumflex femoral and medial circumflex femoral artery.

Anastomosis on the back of thigh is formed by branches of internal iliac, femoral, and popliteal arteries, thus from above downward:

I. The gluteal artery anastomose with each other and with circumflex femoral artery
II. The circumflex femoral artery anastomose with first perforating artery
III. The perforating artery anastomose with one another
IV. The fourth perforating artery anastomose with upper muscular branch of popliteal artery

5.3 Popliteal Fossa (Figs. 5.9 and 5.10)

Popliteal Fossa is a diamond-shaped space behind the knee bounded above by semimembranosus and semitendinosus (medially) and biceps femoris (laterally) and below by heads of gastrocnemius.



1. Outline of popliteal fossa
2. Posterior cutaneous nerve of thigh
3. Lateral cutaneous nerve of calf
4. Peroneal communicating nerve
5. Small sephanous vein
6. Posterior cutaneous nerve of thigh
7. Posterior division of medial cutaneous nerve of thigh

Fig. 5.9 Structures on roof of popliteal fossa

Fig. 5.10 Popliteal region

1. Popliteal artery
2. Popliteal vein
3. Tibial nerve
4. Common peroneal nerve

The popliteal vein and artery along with the tibial and common peroneal vein pass through the fossa. A group of popliteal lymph nodes lie alongside the popliteal vein. The common peroneal nerve goes downward and laterally, medial to biceps femoris, and disappears into the substance of peroneus longus to lie along the neck of fibula. Following are the branches of it:

I. Sural communicating nerve after piercing the roof of the fossa goes downward to join the sural nerve below the bellies of gastrocnemius.
II. The lateral cutaneous nerve of the calf pierces the roof of the fossa over the lateral head of gastrocnemius and gives cutaneous innervation for upper part of peroneal and extensor compartments of the leg.
III. The superior and inferior genicular nerves supply the capsule of knee joint and lateral ligament.

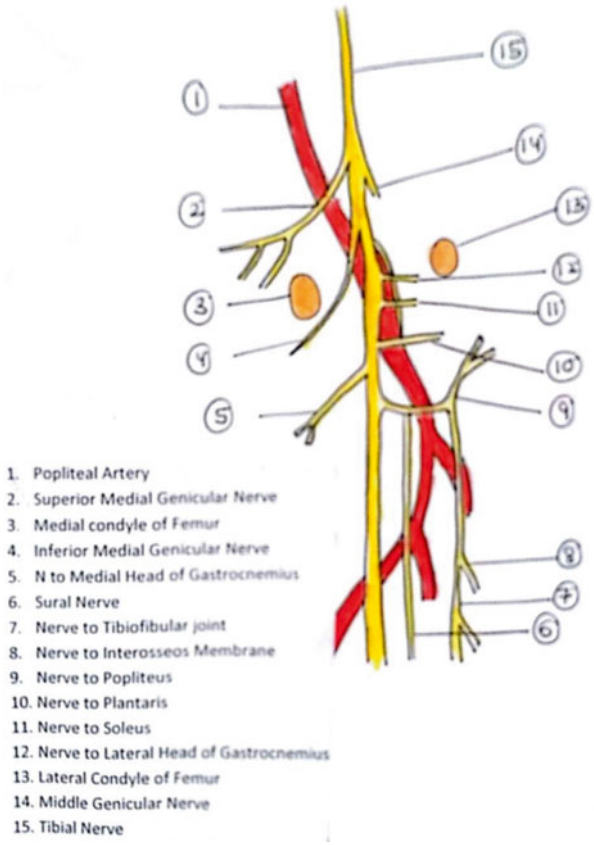


Fig. 5.11 Distribution of tibial nerve

IV. The recurrent genicular nerve, coming from the substance of peroneus longus, perforates tibialis anterior and supplies the capsules of the superior tibiofibular and knee joints.

The *common peroneal nerve* terminates by dividing in substance of peroneus longus into deep and superficial peroneal nerves.

The *tibial nerve* (Fig. 5.11) runs downward along the mid of the fossa and then disappears by going deep within the heads of gastrocnemius where it is accompanied by the popliteal vessels. It gives motor branches to plantaris, both heads of gastrocnemius, soleus, and popliteus. The last branch winds around the lower border of popliteus to enter its deep (tibial) surface. It has only one cutaneous branch, the sural nerve. Sural nerve goes vertically down between two heads of gastrocnemius and pierces the deep fascia in the middle of the calf where it replaces posterior cutaneous nerve of thigh. It is accompanied by the small saphenous vein and the vein usually lies medial to it. Its articular branches are three in number known as genicular nerves. They supply the medial ligament and the capsule of the knee joint, oblique popliteal ligament, and cruciate ligament.

5.3.1 Popliteal Artery

It extends from the opening in the adductor magnus to the fibrous arch in the soleus to the fibrous arch in the soleus. It enters the popliteal fossa medially and lies deep and medial to the sciatic nerve. As it goes downward, it lies lateral to the tibial nerve which is a continuation of sciatic nerve itself. Below the fibrous arch of soleus, it divides into anterior and posterior tibial artery which lies medial to the tibial nerve. In rare case, the popliteal artery divides way above proximal to popliteus and in this case, anterior tibial artery lies anterior to the muscle. The popliteal artery may get compressed by the medial head of gastrocnemius if the artery takes a variant course leading to a condition known as popliteal artery syndrome. It may also get compressed by an accessory slip of muscle. It gives muscular branches to the muscles in the popliteal fossa. The genicular arteries are five in number – upper, lower, middle, medial, and lateral. The middle genicular artery is accompanied by genicular branch of posterior division of obturator nerve.

5.3.2 Popliteal Vein

The popliteal vein holds a constant position and lies between nerve and artery throughout the course. It is formed by the union of the venae comitantes of the anterior and posterior tibial arteries. After passing through the adductor magnus hiatus it becomes the femoral vein.

5.3.3 Anterior Compartment of the Leg

Its cutaneous innervation is from the femoral nerve over the tibia and from the common peroneal nerve over the extensor compartment. The *saphenous nerve* gives off its infrapatellar branch, to supply the subcutaneous periosteum of the upper end of the tibia and the overlying skin, and then descends along with the great saphenous vein and both the structures pass in front of medial malleolus. It usually divides above the medial malleolus and the branches run in front of and behind the great saphenous vein. The main nerve (anterior branch) often extends on the medial side of the foot as far as the metatarsophalangeal joint. The lateral cutaneous nerve (branch of common peroneal nerve) supplies deep fascia and the skin over the upper parts of the extensor and peroneal compartments. The superficial peroneal nerve supplies the remaining surfaces.

The subcutaneous surface of the tibia has subcutaneous fat in direct contact with periosteum and also the deep fascia is blended with the periosteum over here.

Muscles of anterior compartment of leg are tibialis anterior, extensor hallucis longus, extensor digitorum longus, and peroneus tertius.

The main artery of the anterior compartment of the leg is the anterior tibial artery. In addition to it, perforating branch of peroneal artery supplies the region.

The *anterior tibial artery* is smaller terminal branch of popliteal artery. It begins on the back of the leg at the lower border of the popliteus and enters the anterior compartment through an opening in the upper part of the interosseous membrane. It then runs vertically downward to a point midway between two malleoli where it is named as *dorsalis pedis artery*.

Deep peroneal nerve is the nerve of anterior compartment of leg. It is one of the terminal branches of the common peroneal nerve. It begins on lateral side of neck of fibula. It enters the anterior compartment by piercing the anterior intermuscular septum. It then pierces extensor digitorum longus and comes to lie next to anterior tibial artery. The nerve ends on the dorsum of foot close to the ankle joint by dividing into lateral and medial terminal branches.

5.3.4 Dorsum of the Foot

The dorsum of the foot receives innervation from superficial peroneal nerve, assisted by deep peroneal, saphenous, and sural nerves. The large veins form a dorsal venous arch which receives most of its blood by marginal and interosseous tributaries from the sole of the foot. The *dorsal venous arch* finally drains from its medial and lateral ends into great and small saphenous veins, respectively.

The *superficial peroneal nerve* divides into medial and lateral branches which supply the skin of the dorsum of foot. The medial branch further divides to supply the medial side of the dorsum of great toe as well as the sides of the second cleft. On the other hand, lateral branch divides to supply third and fourth clefts. The sural nerve supplies lateral side of the foot and lateral side of little toe. The *deep peroneal nerve s*upplies the first cleft. The skin over the terminal phalanges is supplied by the medial and lateral plantar nerves. The medial side of the foot is supplied by the termination of the saphenous nerve.

The *anterior tibial artery* lying over the distal end of tibia midway between the malleoli continues forward as the *dorsalis pedis artery*. This travels to the first intermetatarsal space and passes down into the sole, where it joins the lateral plantar artery to complete the plantar arch. Its pulsation can be palpated lateral to the tendon of extensor hallucis longus on a line from the midpoint between two malleoli toward the first toe cleft on the underlying intermediate cuneiform and navicular bone. On occasions, the dorsalis pedis artery is replaced by an enlarged perforating peroneal artery in front of the lateral malleolus. It has three branches:

I. Lateral tarsal artery passes laterally beneath extensor digitorum brevis to supply that muscle and underlying tarsal bones.
II. Arcuate artery goes laterally beneath the tendons of extensor digitorum brevis over the bases of metatarsal bones which further branches to give dorsal metatarsal arteries to supply the lateral three clefts. Each metatarsal artery further divides to give perforating branches at the posterior and anterior end of its intermetatarsal space and these further communicate with the plantar arch and its metatarsal branches.
III. First dorsal metatarsal artery is given off before the dorsalis pedis artery enters the sole and it provides supply to the first cleft and the medial side of the dorsum of great toe.

5.3.5 Lateral Compartment of the Leg

It contains peroneus longus and brevis muscles and the superficial peroneal nerve. Its blood supply is derived from branches of the peroneal artery which pierce flexor hallucis longus and the posterior intermuscular septum. Its veins drain mostly into the small saphenous vein.

The *superficial peroneal (superficial fibular) nerve*, after supplying peroneus longus and brevis, pierces the deep fascia between the middle and lower third of the leg and gives off medial and lateral branches which further supply dorsum of the foot. It also supplies the skin of the anterolateral aspect of the lower leg.

5.3.6 Posterior Compartment of the Leg

The cutaneous innervation of the upper half of this region is by the termination of the posterior femoral cutaneous nerve. Below this level, the sural and sural communicating nerves, from tibial and common peroneal nerves, supply the back and lateral side of the calf and the saphenous nerve supplies the medial side.

The small saphenous vein lies with sural nerve behind the lateral malleolus and it drains the lateral side of the dorsal venous arch and the lateral margin of the foot. It ascends upward to run within and then beneath deep fascia for some distance to finally enter the popliteal vein. It communicates with the great saphenous vein by several channels.

The popliteal artery at the lower border of the popliteus gives off anterior and posterior tibial branches. The *posterior tibial artery* passes under the fibrous arch in the origin of soleus and runs over tibialis posterior. It ends below the flexor retinaculum by dividing into medial and lateral plantar arteries. Its pulsation can be palpated behind the medial malleolus, 2.5 cm in front of the medial border of the tendo calcaneus. An arteriovenous shunt with the great saphenous vein can be formed over here for hemodialysis. It gives off following branches:

I. The peroneal (fibular) artery runs in a fibrous canal formed between tibialis posterior and flexor hallucis longus, giving branches to the calf muscles and peroneus longus and brevis. It gives a nutrient artery to the fibula. It ends by dividing into a perforating branch, which can sometimes replace the dorsalis pedis artery and a lateral calcaneal branch.
II. The circumflex fibular artery contributes to the arterial anastomosis around the knee
III. Nutrient artery to the tibia.
IV. Muscular branches supply deep flexors and soleus.
V. Median calcaneal branch supplies medial side of heel.

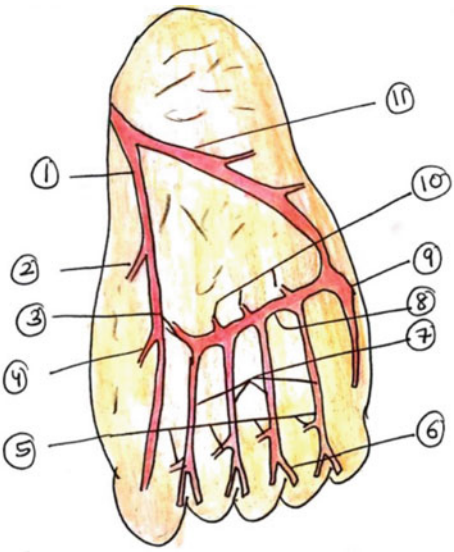
The *tibial nerve* can be surface marked from the middle of the popliteal fossa to midway between the medial malleolus and the tendo calcaneus. It is the nerve of the flexor compartment giving supply to soleus, flexor digitorum longus, flexor hallucis longus, and tibialis posterior. It gives medial calcaneal nerves which pierce the flexor retinaculum to supply the skin of the heel.

5.3.7 Sole of the Foot

Sole gets its cutaneous innervation from medial and lateral plantar nerves. The plantar digital nerves also supply the nail bed and the surrounding the skin.

The vessels and nerves are derived from the posterior tibial neurovascular bundle. Both the posterior tibial artery and tibial nerve divide, each into medial and lateral plantar branches, under cover of the flexor retinaculum. On the medial and lateral borders of the sole, the artery is more marginal than the nerve and accompanying the artery is a pair of venae comitantes. The plantar arteries and nerves lie between the first and second layers, inferior to the long tendons.

The *medial plantar artery* (Fig. 5.12) supplies the greater toe. It has no contribution in the formation of plantar arch. The *lateral plantar artery* forms the plantar arch. It runs an oblique course deep to the first layer of the sole, toward the base of the fifth metatarsal bone. It gives a superficial branch which accompanies superficial branch of the lateral plantar nerve but its main trunk accompanies the deep branch of the nerve to form the plantar arch. The *plantar arch* forms a convex loop, across the bases of the fourth, third, and second metatarsals



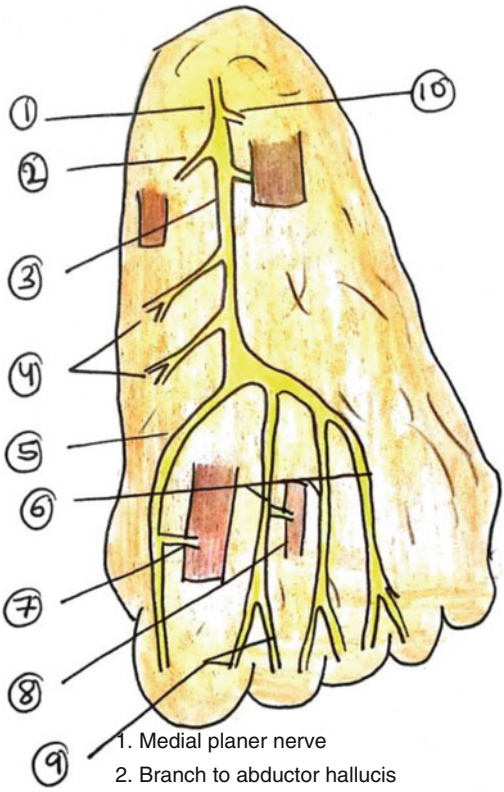
1. Medial plantar artery
2. Muscular branches
3. Dorsalis pedis artery
4. Cutaneous branches
5. Distal perforating arteries
6. Plantar digital artery
7. Plantar metatarsal artery
8. Plantar arch
9. Superficial branch
10. Proximal perforating artery
11. Lateral plantar artery and branches

Fig. 5.12 Medial and lateral plantar arteries

and is joined in the proximal part of the first intermetatarsal space by the dorsalis pedis artery. The plantar metatarsal arteries arise from the plantar arch which further bifurcates to supply the four webs and the digits. Perforating arteries from the plantar arch and its metatarsal arteries reinforce the dorsal metatarsal arteries.

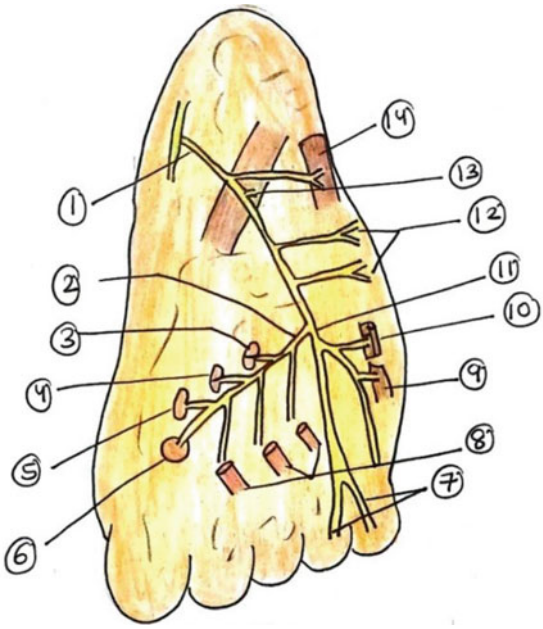
Most of the blood from the sole and from interosseous muscle drains to the veins accompanying perforating arteries which finally drain to the dorsal venous arch. The veins present in the plantar muscles acts as a "sole pump" which aids the "soleal pump" of the posterior compartment of the calf.

The *medial plantar nerve* (Fig. 5.13) gives off digital cutaneous branches to supply medial three and half toes. It gives muscular supply to abductor hallucis, flexor



1. Medial planer nerve
2. Branch to abductor hallucis
3. Branch to flexor digitorum brevis
4. Branch to skin of medial side of sole
5. Proper digital branch to great toe
6. Common plantar digital nerve
7. Branch to flexor haullicis brevis
8. Branch to first lumbrical
9. Proper plantar digital nerve
10. Lateral plantar nerve

Fig. 5.13 Medial plantar nerve



1. Lateral planer nerve
2. Deep branch
3. 3rd dorsal and 2nd plantar interossei
4. 2nd dorsal and 1st plantar interossei
5. 1st dorsal interossei
6. Adductor haullicis
7. Plantar digital nerves
8. Lumbricals
9. Flexor digital minimi brevis
10. 3rd plantar and 4th dorsal interossei
11. Superficial branch
12. Lateral part of skin of sole
13. Flexor digitorum accessories
14. Abductor digiti minimi

Fig. 5.14 Lateral plantar nerve

digitorum brevis, flexor hallucis brevis, and the first lumbrical. Its most lateral cutaneous branch communicates with the neighboring lateral plantar digital branch across the plantar surface of the fourth metatarsophalangeal joint. Pressure on the nerve over this region may lead to painful condition known as metatarsalgia.

The *lateral plantar nerve* (Fig. 5.14) like the artery runs an oblique course but lies medial to the lateral plantar artery. It supplies abductor digiti minimi and flexor accesorius. It gives cutaneous innervation to lateral side of the sole. It divides into superficial and deep branches near the base of the fifth metatarsal bone. The superficial branch supplies the fourth cleft and supplies the skin of the lateral side and distal dorsum of the little toe. It also gives supply to flexor digiti minimi brevis and

the two interossei of fourth space (third plantar and fourth dorsal). The deep branch supplies the remaining interossei, transverse head of adductor hallucis, and the three lateral lumbricals.

5.4 Applied Aspect

5.4.1 Applied Anatomy of Venous System of Lower Limb

Leg can be regarded as a tube consisting of veins running in the center. Muscles enclosed within a thick inelastic fascia form a powerful pump mechanism which on contraction forces blood from superficial to deep veins which then goes upward through deep veins. Thus, direction of flow being from superficial to deep and from below upward and any discrepancy in this pattern of flow lead to varicose veins.

Each limb has three anatomically and functionally distinguishable sets of veins:

1. Superficial
2. Deep
3. Perforating

Superficial: They are long and small saphenous veins. These have relatively thick muscular walls. These run in tunnels created by a condensation of superficial fascia.

Deep: They are tibial, popliteal, and femoral and their tributaries. These veins lie among and are supported by powerful muscles.

Perforating veins: These are the communication between superficial and deep veins. They show a predilection for intermuscular septa occurring on either side of sartorius, between vastus lateralis and the hamstrings, on either side of the peroneal group, and along anterior border of soleus. They are of two types:

- Indirect: Small superficial vessels penetrating deep fascia
- Direct: Long and small saphenous veins and smaller perforating veins

Varicose veins and ulcers: If incompetency occurs in the valves of perforating veins or at the termination of superficial veins, the defective veins become “high pressure leaks” through which high pressure of deep veins produced by muscular contraction is transmitted to superficial veins. As a result, superficial veins become dilated and gradual degeneration of their walls produces varicose veins and varicose ulcers.

With calf pump and peripheral heart in the upright position of the body, venous return of lower limb largely depends upon calf muscle contraction. For same reason, soleus is called peripheral heart.

Great saphenous vein is used for transfusion of blood/fluids in case of nonavailability or collapse of other veins. It lies in front of medial malleolus and posterior to saphenous nerve. Great saphenous vein is used for bypassing the blocked coronary

arteries. The vein is reversed so that valves do not block the passage of blood. Femoral vein is commonly used for intravenous infusion in infants and in patients with peripheral circulatory failure.

Anatomy of the veins may vary. A retrospective review of 404 bilateral (808 limbs) lower limb venograms obtained from medical patients participating in a thromboprophylaxis clinical trial and found to be free of thrombus was performed. Venograms were evaluated according to predetermined criteria for the presence of duplication of vessels and inter- and intraindividual variations in venous anatomy. Two vessels were seen in the popliteal fossa on 337 (42 %) of 808 venograms, and 41 (5 %) were true duplicated popliteal veins. There were 253 (31 %) duplicated superficial femoral veins (SFVs), with 12 (1.5 %) being complex duplicated systems. Of 265 duplicated SFVs, 138 (52 %) began in the midthigh region and 80 (30 %) in the adductor canal region. The duplicated vessel was medial to the main SFV in 122 (46 %), lateral in 131 (49 %), and both (i.e., triplications) in 12 (4.5 %). The length of the duplicated SFV ranged from 1 to 35 cm; 6–15 cm was the most common length in 162 (62 %) SFVs. There was no significant association between the incidence of anatomic variations and age or sex ($P > .1$). The presence of multiple vessels in one leg was strongly correlated with the probability of occurrence in the other leg ($P < .001$).Variations in lower limb venous anatomy are common and have important implications for the US diagnosis of deep vein thrombosis [6].

5.4.2 Applied Anatomy of Arteries of Lower Limb

Femoral artery pulsations can be felt at the midinguinal point against head of femur and the tendon of the psoas major. A bilateral absence or feebleness of the femoral pulse may occur due to coarctation of aorta. Stab wounds at the apex of femoral triangle may cut all large vessels of the lower limb, the arrangement backward being femoral artery and vein and profunda femoris artery and vein. Since femoral artery is quite superficial in the femoral triangle, it can be easily exposed for ligation or passing a cannula. Blood pressure in the lower limb is recorded from the popliteal artery. In coarctation of aorta, the popliteal pressure is lower than brachial pressure. When the popliteal artery is affected by atherosclerosis, grafts can be tried in the lower part of artery as it is usually patent.

The popliteal artery is one of the common arteries prone to aneurysm. Pulsations of the dorsalis pedis artery are easily felt between tendons of the extensor hallucis longus and the first tendon of the extensor digitorum longus. However, it is to be noted that dorsalis pedis artery is congenitally absent in about 14 % of subjects. Posterior tibial artery can be palpated against the calcaneum about 2 cm below and behind the medial malleolus. It is palpated in doubtful cases of intermittent claudication. Hamada et al. studied three-dimensional arteriography to analyze the arterial supply of the great and second toes of 100 cadaveric feet down to the microsurgical level for purpose of successful composite tissue transfers of these toes to the hand. The arterial blood supply of the great toe came principally from the first dorsal

metatarsal a. (78 %) and the first plantar metatarsal a. (22 %) and secondarily from the medial tarsal a. and the three terminal branches of the medial plantar a. For the second toe, the first dorsal metatarsal a. (78 %) and the first plantar metatarsal a. (22 %) supplied blood from the medial side, and the second dorsal metatarsal a. (78 %) and the second plantar metatarsal a. (22 %) supplied blood from the lateral side. Seven arterial patterns were found in the interdigital web space. The so-called general pattern was seen in the first web space in 65 % of the feet examined. In the second web space, it was found in 85 %. The first intermetatarsal space sometimes contained a large artery arising directly from the dorsalis pedis or first proximal perforating a. as well as the first dorsal and first plantar metatarsal arteries. In this space, arterial patterns were classified into 4 types and 9 subtypes based on the origins and proximal courses of these arteries. The so-called standard pattern was found in only 19 % of the feet, while an arterial pattern with a common proximal trunk on the plantar side for the first dorsal and first plantar metatarsal a. was found most frequently [7].

5.4.3 Applied Anatomy of Nerves of Lower Limb

As compared to the upper limb, the peripheral nerve injuries are much less in lower limb, the most common injured nerve being the common peroneal nerve.

Femoral nerve can be injured in the following ways:

I. Penetrating injuries of lower abdomen and thigh
II. Pelvic masses such as hematoma or neoplasm compressing it
III. Catheterization of femoral artery
IV. During laparoscopic repair of inguinal hernia

Complete lesion of femoral nerve presents with the following:

I. Extension of the knee by quadriceps that is lost
II. Weakness of hip flexion (due to rectus femoris)
III. Sensory loss over front of thigh
IV. Pain extending as far as the medial side of foot (saphenous branch)

Obturator nerve rarely gets injured as it is deeply situated, but it can get injured by obstetric procedures or involved in the pelvic disease, e.g., an ovarian tumor may cause pain in the medial side of the thigh. On sitting, the affected limb cannot be crossed over the other.

Sciatic nerve is injured by the following ways:

I. Misplaced gluteal injections
II. Pelvic disease
III. Severe trauma to the hip

Lesion of the sciatic nerve results in:

I. Paralysis of the hamstring muscles
II. Foot drop with ulceration
III. Sensory loss below knee sparing the medial side of the leg and upper part of the calf.

Sciatic nerve can be approached by exposure over the lower border of gluteus maximus, retracting semitendinosus and the long head of biceps medially.

Common peroneal nerve is injured by:

I. Direct trauma at the neck of fibula
II. Pressure by plaster casts over the neck of fibula

Lesion of common peroneal nerve results in;

I. Foot drop and ulceration
II. High stepping gait
III. Peroneus longus and brevis affected
IV. Sensory loss over lower lateral part of the leg and the dorsum of foot

The nerve can be approached by tracing it down from the lateral side of the popliteal fossa, where it lies medial to the biceps tendon.

Tibial nerve damage is uncommon. Lesion of it results in paralysis of the calf muscles and sensory loss over lower part of calf and sole. The lesion can be tested by asking the patient to stand on tiptoe. It can be approached in the middle of the popliteal fossa.

Saphenous nerve is prone to get injured in front of the medial malleolus during varicose vein surgery and when great saphenous vein is harvested for arterial bypass procedures. Sural nerve may be damaged in lower part when operating for Small sephanous vein varicosity.

Morton's neuroma is a neuroma formed on the branch of medial plantar nerve between 3rd and 4th metatarsal bones causing pain between 3rd and 4th metatarsals.

Peripheral nerve pathology can be detected on high-resolution MRI on the basis of primary or secondary findings. Primary findings of nerve pathology include alterations in signal, course, and caliber; secondary findings include skeletal muscle denervation. Although two-dimensional (2D) MRI sequences comprised of a combination of fluid-sensitive and non-fat-suppressed anatomical sequences can detect changes in nerve size, signal, course, and architecture, three-dimensional (3D) imaging can play an important role in the detection and characterization of nerve pathology including caliber changes at typical compression sites, anomalous course, and nerve discontinuity [8].

Conclusion

For a better understanding of the cause of ulceration, anatomy of the lower limb is helpful in knowing the cause, site, and type of pathology. It is essential to know which part of the lower limb is affected so that one can plan the treatment accordingly. The treatment of venous ulcer is compression therapy, but if the patient also has arterial diseases, then the compression is relatively contraindicated. When the treatment for varicose veins is carried out, one has to avoid injury to Sephanous nerve especially in leg and sural nerve in the lower part of calf.

References

1. Garg K, editor. B D Chaurasia's human anatomy. 5th ed. New Delhi: CBS Publishers and Distributor; 2010.
2. Standring S, editor. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. Philadelphia: Elsevier; 2005. p. 1452.
3. Dodd H, Cockett FB. The pathology and surgery of the veins of the lower limb. 2nd ed. Edinburgh: Churchill Livingstone; 1976. p. 160.
4. Moore HM, Gohel M, Davies AH. Number and location of venous valves within the popliteal and femoral veins: a review of the literature. J Anat. 2011;219(4):439–43.
5. Sinnatamby CS. Last's anatomy regional and applied. 11th ed. Boston: Churchill Livingstone Elsevier; 2009.
6. Quinlan DJ, Alikhan R, Gishen P, Sidhu PS. Variations in lower limb venous anatomy: implications for US diagnosis of deep vein thrombosis. Radiology. 2003;228(2):443–8.
7. Hamada N, Ikuta Y, Ikeda A. Arteries to the great and second toes based on three dimensional analysis of 100 cadaveric foot. Surg Radiol Anat. 1993;15(3):187–92.
8. Ahlawat S, Carrino JA. Three-dimensional imaging of lower limb neuropathies. Semin Musculoskelet Radiol. 2015;19(2):168–78.

Approach to a Case of Ulcer of Lower Extremity

6

Ajay Kumar Khanna

6.1 Introduction

Treatment of a wound of lower extremity is not a simple course, and one type of treatment does not fit for all patients. So the first step should be to find out the underlying pathology. There are several causes for the ulcers of the lower extremity. Basically they may be traumatic, inflammatory, neoplastic, or vascular causes and autoimmune causes. The common causes are venous, arterial, diabetic, and neuropathic ulcers. Other causes are shown in Table 6.1. The goal of treatment in any case of ulcer is to heal the wound, relieve the pain, regain a high quality of life, and prevent the recurrence. So treatment of chronic wound requires the multidisciplinary and comprehensive approach for salvage of the limb. This may require vascular physicians, vascular surgeons, cardiologist, podiatrist, endocrinologist, plastic surgeons, infectious disease specialist, dermatologist, oncologist, orthopedic surgeon, and rehabilitation personnel and dedicated nursing staff. It needs an individualized wound care protocols with the goal of special recovery. It may involve advanced technologies for diagnosis and treatment, topical wound care dressing and therapies, antibiotics, antiplatelet drugs, compression garments, intervention to improve circulation, and prosthetics. The patient's active participation in healing of wound is well appreciated in terms of keeping the wound clean and dry, changing the dressing as per need, taking prescribed medicines, healthy diet, regular exercises, and wearing compression stockings and shoes as prescribed. Basically the patients are advised to avoid smoking; take proper diet; control sugar, blood pressure, and cholesterol; and lose weight if overweight [1].

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Table 6.1 Other causes of limb ulcers

Physical or chemical injury	Pressure (decubitus), chemical (corrosive agents) following sclerotherapy, self-inflicted
Malignancy	Squamous cell carcinoma, basal cell carcinoma, melanoma, sarcoma, lymphoma, metastatic cancer
Drug induced	Steroid ulcers, halogens, ergotamine, methotrexate, hydroxyurea, paravasal injection of anticancer drugs as Adriamycin, mitomycin, vaccination ulcer following BCG
Skin diseases	Pyoderma gangrenosum, pseudoepitheliomatous hyperplasia, epithelioma, pemphigoid, panniculitis, periarteritis nodosa, erythema induratum, Behcet's disease, cutaneous discoid and systemic lupus erythematosus, scleroderma, lichen planus, keratosis actinica, contact dermatitis, fat necrosis
Autoimmune	Dermatitis, lupus, rheumatoid arthritis, vasculitis, Wegener's granulomatosis, allergic granulomatosis (Churg-Strauss), Henoch-Schonlein purpura,, erythema induratum Bazin, polyarteritis nodosa, Kawasaki disease
Metabolic	Diabetes mellitus, necrobiosis lipoidica, porphyria cutanea tarda, gout, calciphylaxis, calcinosis cutis, homocysteinuria, prolidase deficiency, hyperoxaluria
Hematologic disorders	Sickle cell anemia, thalassemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, thrombotic thrombocytopenic purpura, granulocytopenia, polycythemia, leukemia, multiple myeloma, cryofibrinogenemia, purpura, hyperglobulinemia
Clotting disorders	Factor V Leiden, lupus anticoagulant, antiphospholipid syndrome, factor XIII deficiency, antithrombin III deficiency, protein C or S deficiency
Infective causes	Tubercular, erysipelas, gas gangrene, anthrax, diphtheria, herpes, Madura, fungal, amoebiasis, leishmaniasis, leprosy

The ulcers usually present with wound which may or may not be painful associated with edema, burning, itching, and features of inflammation as red, brown discoloration, dry, and scaly skin. Most common ulcer in the leg is venous ulcer, diabetic ulcers, and arterial ulcers. Depending on the location of ulcer, appearance of ulcer, and who is affected can differentiate between the common ulceration of venous, arterial, and diabetic ulcers [2] (Figs. 6.1, 6.2, 6.3, 6.4, and 6.5).

Leg ulcer are caused by various medical conditions as poor circulation in atherosclerosis, venous insufficiency, diabetes, renal failure, hypertension, lymphoedema, vasculitis, hypercholestremia , smoking, pressure ulcers, malignancies, infections, and sometimes genetic.

For diagnosis of an ulcer, medical history is evaluated, then the ulcer is examined in detail, and various test like X-rays, Doppler, MRIs, CT scan, pus culture, and biopsy may be needed. The treatment of all ulcers begins with careful ulcer care and supportive treatment in form of antibiotics, antiplatelet drugs, etc. [3].

In examination of an ulcer, edge and floor of ulcer is most important. The edge of the ulcer can determine if it is a healing ulcer or it is a spreading ulcer or it is becoming chronic. Floor also tells about the healing of ulcer or if there is slough. The lymph node must be examined as it may suggest the inflammatory or neoplastic cause.

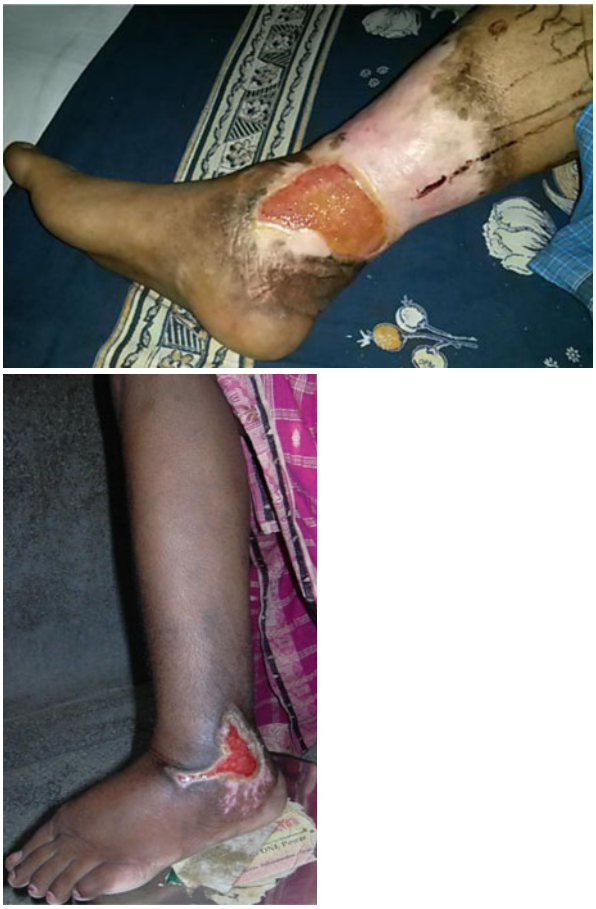

Fig. 6.1 Venous ulcer

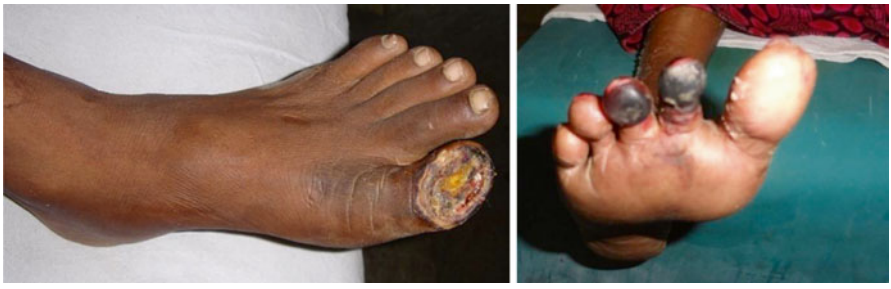

Fig. 6.2 Arterial ulcer

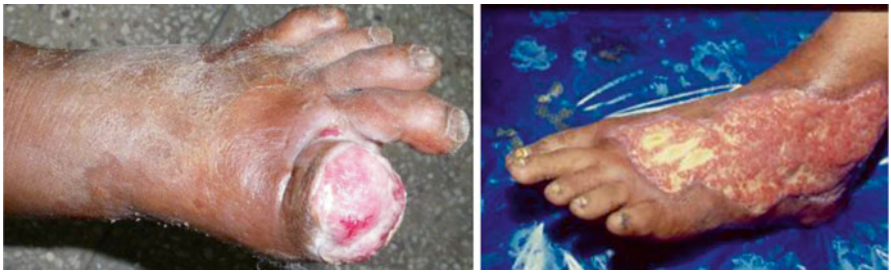

Fig. 6.3 Diabetic foot ulcer

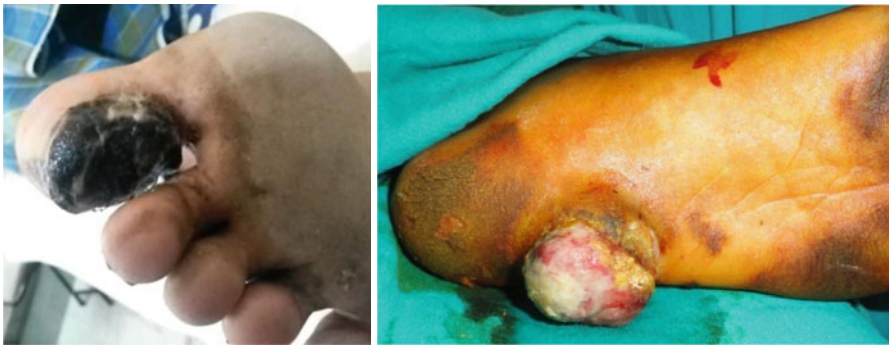

Fig. 6.4 Malignant ulcer

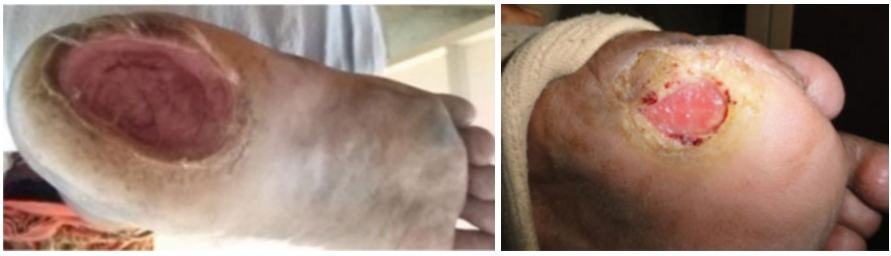

Fig. 6.5 Trophic ulcer

The ulcers may be classified as spreading ulcer, healing ulcer, or chronic or callous ulcer, and pathologically they can be classified as nonspecific ulcer, specific ulcers, and malignant ulcers. Further the ulcers can be classified as per the grading of involvement (Wagner's grading): Grade "0" preulcerative or healed ulcer, Grade "I" superficial ulcer, Grade "2" ulcer deeper to subcutaneous tissue exposing soft tissues or the bone, Grade "3" abscess formation underneath osteomyelitis, Grade "4" gangrene of part of tissues/limb/foot, and Grade "5" gangrene of entire one area/foot.

6.2 Thorough History

It is important to find out the cause of any lower extremity ulcer to provide the correct treatment. A thorough physical examination with proper history can give the basic pathological diagnosis in majority of cases, but few patients will require the various investigations to find out the cause. Always try to find out any comorbid illness as diabetes mellitus, hypertension, hypercholesterolemia, autoimmune disease, peripheral vascular disease, atherosclerosis, inflammatory bowel disease, and connective tissue disease must be investigated. Sometimes ulcers may be self-inflicted so a psychiatric evaluation should be done. Any history of deep vein thrombosis, recent surgery, prolonged bed rest, pregnancy, multiple spontaneous abortions, or genetic causes in form of thrombophilia may suggest the cause of ulceration. Patients with venous ulcers may give history of heaviness in limbs especially in the evening. Inquire about history of heavy smoking and drinking, patient's social and occupational situation as prolonged standing may lead to varicose veins, and subsequent skin ulceration. Patients with higher body mass index are likely to have more ulceration. Find out the history of numbness, paresthesias, burning, or loss of sensation in the feet which may suggest diabetic neuropathic ulcer. Prolonged and poorly controlled diabetes not only causes neuropathies but increases risks of leg infections and impairs wound healing. Also take the history of medications, such as hydroxyurea, which may lead to leg ulceration [4].

6.2.1 Examination

The physical examination must include the systemic examination, limb examination, skin examination, and ulcer examination. The systemic examination must evaluate the heart thoroughly as primary pathology may be in the heart. Also all the systems must be examined as respiratory, cardiac, neurological, abdomen, musculoskeletal examination.

6.2.2 Limb Examination

In the examination of the limb, especially palpate all the pulses up to dorsalis pedis, assess capillary filling time, and also look for signs of venous hypertension. These signs include varicose veins and pigmentation of the skin over the lower leg. The diameter of the limb at various levels must be measured including the normal side also. Mobility should also be assessed at all joints. Leg range of motion at the ankle/knee/hip should also be assessed to distinguish between pain from inflammation and pain from arterial insufficiency. One must examine the sensation of the foot along with motor power.

6.2.3 Skin Examination

Always examine the surrounding tissue. Venous disease may present with staining and pigmented spots especially around the ankle, brawny skin, lipodermatosclerosis, reticular or varicose veins, atrophic blanche (patchy areas of ischemia), telangiectasia, and stasis eczema. In venous ulcers, the surrounding skin may be erythematous with scaling, irregular shaggy borders, and crusting. On the other hand, patients with arterial disease have trophic changes of chronic ischemia, with pale skin which is often hairless, cool, and shiny. Nails may be thickened nail and architecture of the foot may be deformed.

6.2.4 Ulcer Examination

For having a firm diagnosis, location and pain are the key findings. Venous leg ulcers usually occur in the gaiter region of the lower leg, most often medially, and are superficial with poorly defined margins. The floor is usually red granulation tissue with moderate to high levels of exudate. Exudate levels vary depending on the ulcer size, the presence of leg edema, and the presence or absence of infection. Obese patients with coexisting lymphedema may have more edema and more exudates. Arterial ulcers can occur anywhere on the lower leg and less likely in the gaiter region. Many arterial/ischemic ulcers occur over a bony prominence and have a history of pressure related to the cause. Arterial ulcers have slough and devitalized tissue in the wound floor and less wound exudate. In patients with ulcers on the sole of the foot, the sole should be examined for signs of ascending infection, including proximal tenderness and appearance of pus on proximal compression of the sole. Surrounding calluses are typical of neuropathic ulcerations, and sinus track formation should be explored by probing the wounds. Neuropathic ulcers especially in diabetic patients and other neurological problems occur on the sole of the feet under the metatarsal heads, in the area with the most postural pressure exerted. The other types of ulcers may occur in any part of the lower extremity. The degree of discomfort or pain can give clue to the underlying condition. Arterial ulcers are particularly painful at night, can become severe, and are relieved by dependency and made worse by elevation, even to a horizontal position in bed. Venous ulcers are mildly painful, relieved with elevation, and often get relief from a gentle massaging of the surrounding skin. Ulcers with signs of inflammation with a purple border and extreme pain may be because of vasculitis or underlying connective tissue disorder. They often present with a rapid increase in size, severe pain, and necrotic tissue in the wound base. Lesions that present as blisters such as bullous pemphigoid are related to an autoimmune condition [5]. Table 6.2 shows the differential diagnosis of common ulcers.

6.3 Noninvasive Diagnosis

Many of the ulcers are diagnosed only by clinical examination, but it is advisable to combine with noninvasive or invasive assessment of the circulation to confirm the clinical impression.

Table 6.2 Differential diagnosis of common leg ulcers

Type	History	Usual location	Pain	Bleeding with manipulation	Lesion characteristics	Surrounding inflammation	Associated findings
Ischemic/ arterial	Smoking, intermittent claudication	Distal, on dorsum of the foot or toes, over bony prominences	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue, dry necrotic floor; round or punched-out with sharp demarcation	Absent	Trophic changes of chronic ischemia, pale, hair loss, atrophic skin, cool feet; absence of pulses, prolonged capillary refill (>4–5 s); ABI, 0.5; dependent rubor, elevation pallor
Venous	Varicose veins, DVT, trauma, surgery, multiple pregnancies; aching/ swelling worse at end of day, relieved with elevation	Lower third of the leg (gaiter area); between malleolus and lower calf, majority at medial malleolus	Mild; relieved by elevation	Venous ooze	Shallow, irregular/ shaggy shape; granulating base; flat or steep elevation margins; fibrinous material at ulcer bed with moderate to heavy exudates	Present	Lipodermatofibrosis/ lipodermatosclerosis, pigmentation, edema, atrophie blanche; telangiectasia; normal capillary refill time (3 s), normal ABI
Neurotrophic	Numbness, paresthesias, burning, loss sensation in the foot, DM	Under calluses or pressure points (e.g., plantar aspect of first or fifth metatarsophalangeal joint)	None	May be brisk	Punched-out, with deep sinus, variable depth partial thickness to severe involving tendon, fascia, joint capsule, or bone	Present	Demonstrable neuropathy, may be associated with underlying osteomyelitis

(continued)

Table 6.2 (continued)

Type	History	Usual location	Pain	Bleeding with manipulation	Lesion characteristics	Surrounding inflammation	Associated findings
Vasculitis	History of primary or secondary connective tissue disease	Pretibial and dorsum of foot but not always geographically limited	Extremely painful	Hemorrhagic vesicle	Multiple, punched-out, inflamed indurated base (pathergy phenomenon)	Present, surrounding skin shows reticulated vascular pattern	Fat necrosis/chronic panniculitis on pathology
Hypertensive (local infarct)	Normal pulses	Lateral malleoli	Severe	–	Black necrosis	Preset	Also called Martorell's ulcer; seen in patients with prolonged/ suboptimal controlled hypertension
Pyoderma Gangrenosum	Unknown pathogenesis	Develops in sites of previous trauma, around scars, donor sites used for grafting	Severe	Little or none	Ulceration with purulent base; well defined, bluish, undermined borders; surrounding erythema; deep necrotic ulcer	Noninfective ulcer, surrounding inflammation	Seen with inflammatory bowel disease, immunodeficient states, myeloma, leukemia, Behcet's syndrome

6.3.1 Ankle Brachial Pressure Index (ABPI)

ABPI testing is very important for the diagnosis of an ischemic ulcer. Brachial and ankle blood pressure determination is measured with the help of handheld Doppler measured after 10 min rest. The cuff is placed above the malleoli. The maximum cuff pressure at which the pulse can be heard with the probe is recorded and divided by the systolic blood pressure measured at the brachial artery. Normal ABPI value is 0.9–1.1 (average 1). ABPI values below 0.9 suggest peripheral arterial occlusive disease. If the vessels are calcified as in atherosclerosis and diabetes, ABPI can be inaccurate or invalid because the arteries may be hard to compress due to calcification. So usually pressure above 1.3 suggests calcified vessels and is an indication of diseased vessel. If the ABPI is 1.3 or more, then a toe pressure is measured as it is most often spared from calcification. ABI testing can be performed before and after exercise to uncover mild peripheral arterial atherosclerosis that presented with normal values at rest [6].

6.3.2 Duplex Ultrasound

Duplex ultrasound which combines B or M mode ultrasound with Doppler is an inexpensive, quick, and noninvasive method that screens and detects the various vascular diseases. It is regarded as the test of choice for diagnosis of venous reflux, thrombosis, arterial obstruction, and aneurysms. It differentiates between stenosis and occlusion and provides information for the plaque content and surface characteristics to aid and also guide treatment. It also helps to identify acute, chronic, and recurrent thrombosis as well as to demonstrate collateral pathways and the flow dynamics. It is also an excellent tool for differential diagnosis as tumors, cysts, hematoma, and other pathologies may be detected during the vascular examination. Furthermore, it is used for studying the effect of treatment, progression of disease, or developments of new pathology. So being the noninvasive test, Duplex ultrasound is the test of choice for any vascular pathology [7–9].

6.3.3 Plethysmography

Doppler ultrasound studies the flow of blood, while plethysmography measures the volume of blood. There are several types of plethysmography, such as air, photo, and strain gauge. It is used to detect and quantify arterial and venous disease. Depending on the device used, pressure and flow measurements, waveform patterns, volume changes, amount of reflux, degree of venous obstruction, and the efficiency of the calf muscle pump can be estimated. All these are important as the severity of the disease can be demonstrated to determine their impact on ulceration. Usually this test is not performed and is mainly used for academic purpose rather than clinical use. One can also measure ambulatory venous pressure especially in suspected venous ulcer cases.

6.3.4 Computer Tomography

Spiral CT angiography is an accurate modality to assess presence and extent of peripheral arterial disease. This test is usually performed if the intervention is required either endovascular or open surgery or hybrid techniques. CT angiography has become popular due to rapid technical developments in terms of shorter acquisition times, thinner slices, higher spatial resolution, and improvement of multidetector computed tomographic scanners which enable scanning of the whole vascular tree in a limited period with less amount of contrast. CT venography is also accurate to determine proximal venous obstruction, but as it is relatively static, one cannot evaluate reflux. CT can also detect aneurysms, AV fistulae, and any other pathology like neoplasms and can determine the extent of disease and involvement of surrounding structures.

6.3.5 Magnetic Resonance Imaging

Magnetic resonance arteriography (MRA) equivalent to CT angiography is a noninvasive method to visualize the peripheral vasculature, to detect hemodynamically significant stenosis, and to distinguish focal from long-segment occlusive disease. Advantage of its use is that it does not need any contrast, so the patients with deranged renal functions may undergo MRA. But the disadvantage is that it takes a much longer time to perform and also cannot be used in the patients on pacemakers and any other prosthesis. Further claustrophobia and the sounds produced during the procedure may not be palatable to the patients. MRA has the ability to define the pattern of the disease and help in planning for arterial access sites (retrograde or antegrade). More specifically, MRA has proven useful in detecting occult runoff channels, which can be used for distal bypass. Magnetic resonance venography has a great accuracy in detecting proximal vein obstruction and may differentiate acute from chronic thrombosis.

6.3.6 Phlebography

Phlebography is usually not done because of the availability of noninvasive tests as Duplex and relatively less invasive as CT or MRI, but it can identify the location and extent of blood clots and enables the condition of the deep leg veins to be assessed. It is especially useful when there is a strong suspicion of deep vein thrombosis, after noninvasive tests have failed to identify the disease. Phlebography can also be used to evaluate congenital vein problems and assess the function of the deep vein valves. Phlebography is a great method to demonstrate the extension of obstruction and all the collateral pathways. It can guide treatment and at the same time assess its effect. It is not used often, because it is painful, expensive, and time-consuming, exposes the patient to a fairly high dose of radiation, and can cause phlebitis, tissue damage, and the formation of deep vein thrombosis in a healthy leg. It is reserved for evaluating limbs that may need deep vein reconstruction or to open proximal vein obstruction.

6.3.7 Arteriography

Contrast arteriography was supposed as the gold standard for evaluation of arterial disease. But again as being the invasive procedure, it is less used until unless a therapeutic procedure is planned. It can be done usually by transfemoral route (Seldinger's technique), but in the higher blocks, direct lumbar puncture into aorta had been used in the past. It demonstrates the arterial tree in its entirety, to readily delineate the site of arterial stenosis and occlusion. It is indicated for select patients, who will undergo revascularization to reestablish perfusion. In addition to providing valuable anatomic information, pressure measurements across arterial stenosis can be obtained to gauge the hemodynamic severity of a lesion. More importantly, interventions can be done using balloons, stents, and other devices. In patients with vascular malformations, selective catheterization can be performed to obliterate the feeding vessels. There are several complications being an invasive technique, such as hematoma, pseudoaneurysm, arteriovenous fistula formation, embolism, dissection, and renal failure. As the amount of contrast used is high, so it can lead to renal failure. Further patient may go into anaphylaxis because of reaction to contrast.

6.3.8 Intravascular Ultrasound (IVUS)

Usually this technique is not available, but it can differentiate between the normal and abnormal vessel. It also determines plaque volume within the wall of the artery and the degree of stenosis. Small lesions like intimal flaps or tears are well visualized because of their high fibrous tissue content and the contrasting echoic properties of surrounding blood. Intramural thrombus appears as echogenic homogenous mass with varying image attenuation beyond the location. IVUS an also differentiate noncalcified vessels versus calcified because the latter appears as a bright image with dense acoustic shadowing because the ultrasound energy is reflected by calcified plaque. It is also used to identify proximal venous obstruction. It allows precise estimation of the stenosis and the diameter of the lumen so the correct balloons and stents are used in the best possible position.

6.3.9 Bacterial Culture

A quantitative bacterial culture is more specific and should be performed once wound infection is suspected. This is performed by curetting or biopsying the bed of the ulcer rather than just the superficial swab which usually is contaminated or has dead tissue. The quantitative biopsy is the current gold standard for assessing the quality and quantity of microbial pathogens within wound. Quantitative biopsies containing greater than 10^5 organisms per gram of tissue are considered significant. If osteomyelitis is suspected, representative cultures need to be obtained from the bone or deepest tissue layers [10].

6.3.10 Skin Biopsy

Skin biopsies is used in ulcers of indeterminate cause and suspected neoplastic pathology. A patient with long-standing ulceration like venous ulcers may change to malignancy as Marjolin's ulcer. Any wound that is suspected of a malignant process must be biopsied, especially if refractory to treatment for at least 3 months, and tissue sample must be taken from the wound bed and the edge including surrounding skin. One can perform the punch biopsy or an incision biopsy. Biopsy should be taken from the margins and not from the central part which may be necrotic. Usual neoplastic skin ulceration is squamous cell carcinoma in lower extremity, but one may get a basal cell carcinoma, melanoma, and the sarcomas rarely.

6.3.11 Documentation

All ulcers must be documented and one should note down all the dimensions of the ulcer. There are many ways to document and one should keep a serial order as per the date. The various types of rules, gauge piece, and camera documentation may be done. Sophisticated mobile softwares are available to carry out documentation.

Conclusion

Any ulcer in the leg present for more than six weeks is considered as chronic ulcer. Some say that this period may be only 6 weeks to 3 months. The commonest cause of chronic ulcer is venous followed by arterial, diabetic, and neuropathic. But a good number of cases may have etiology of different nature. A comprehensive history and examination of the patient, limb, and ulcer is required to determine etiology and to formulate an appropriate management plan, and it may require a battery of tests to reach to a final diagnosis. Management of patients with chronic ulcers has to be multidisciplinary, and it involves not only the physician but the nursing personnel who play a very important role, and the support of the family and the society is crucial. Educating patients and the family members on issues of correct foot care and the importance of seeking early medical advice cannot be overstated.

References

1. Agale SV. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. Ulcers. 2013;Article No. 413604.
2. Dean S. Leg ulcers and management. Aust Fam Physician. 2006;35:480–5.
3. London NJM, Donnelly R. ABC of arterial and venous disease. Ulcerated lower limb. Br Med J. 2000;320:1589–91.
4. Sardina D. Differentiating lower extremity ulcers. Wound Care Advisor. 2013;2:10.
5. van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. Br Med J. 2010;341(7782):1092–6.
6. Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. Br Med J. 2006;332(7537):347–50.

7. Collins L, Seraj S. Diagnosis and treatment of venous ulcers. Am Fam Physician. 2010;81(8):989–96.
8. Kahle B, Hermanns HJ, Gallenkemper G. Evidence-based treatment of chronic leg ulcers. Dtsch Arztebl Int. 2011;108:231–7.
9. Mekkes JR, Loots MAM, van der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
10. Casey G. Causes and management of leg and foot ulcers. Nurs Stand. 2004;18(45):57–8.

Investigations for Ulcer of the Lower Extremity

7

Satyendra K. Tiwary

7.1 Introduction

Ulceration of the lower limb in aging population with comorbidity associated has always been a challenge in philosophy of wound management. Acute ulcers have a predictable outcome with rapid progression or regression and outcome achieved within 3–4 weeks. The etiology of the lower limb ulcerations varies from different geographic regions in world. In Western societies, most chronic lower limb ulcers are due to vascular diseases, whereas in developing countries, trauma, infections, malignancies, and poorly controlled diabetes remain the most common causes of chronic lower limb ulceration [1–3]. The treatment of chronic lower limb ulcers requires multidisciplinary approach [4, 5]. Multifactorial etiology and interdisciplinary approach in management are key factors determining outcome [5].

7.2 Epidemiology

Chronic leg ulcer (CLU) also termed as chronic lower limb ulcer is a chronic wound of the leg that shows no tendency to heal after 3 months of appropriate treatment or is not still fully healed at 12 months [6]. Ulcers can be defined as wounds with full thickness depth and a slow healing tendency [7]. Investigations are aimed for correct diagnosis to avoid inappropriate treatment that may delay wound healing, cause deterioration of wound, or harm the patient to detect underlying cause and work up the needful intervention. Complete history and accurate assessment clinically are prerequisites before any investigations. Chronic leg ulcers affect 0.6–3 % of those aged over 60 years, increasing over to 5 % of those aged over 80 years [8].

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Principles and philosophy of investigations are governed by history and examination to detect cause, direct treatment, and predict prognosis. Both modalities, invasive and noninvasive, are essential according to assessment after history and examination. Almost 70 % of leg ulcers have a venous etiology; approximately 20–25 % are due to arterial insufficiency; and some of these have a mixed vascular etiology. The remaining causes include infection, malignancy, vasculitis, lymphedema, pyoderma gangrenosum, and other conditions [9].

Lower extremity ulcers are always assessed systematically with skin assessment, vascular assessment, ulcer assessment, and limb assessment with assessment of the patient as a whole for comorbidities and risk factors associated [10]. After complete history and physical examination, mostly diagnosis of lower limb ulcer is almost settled, but the role of investigations is always integral for etiology, treatment, follow-up, and prevention. In acute ulcers, investigations are directed toward the detection of risk factors and comorbidities, but isolation of microbes and antibiotic sensitivity are key investigations. In chronic ulcers, almost 95–98 % are caused by venous, arterial, or diabetic and other less common causes are to be detected mostly by invasive investigation with biopsy.

7.3 Investigations

Lower extremity ulcers are investigated after proper clinical history and examination. Both types of investigations, diagnostic and prognostic, are essential for proper management.

7.4 Diagnostic and Prognostic Investigations

First-line routine biochemical and hematological laboratory investigations included are essential as they are sometimes diagnostic but always of prognostic significance. Blood investigations like complete blood count, erythrocyte sedimentation rate, lipid profile, renal function tests, and liver function tests are prognostic, while blood sugar is diagnostic.

Screening tests for vasculitis are urine analysis for proteinuria, hematuria, cylindruria, antinuclear antibodies (ANA), rheumatoid factor (RA), complement C4, circulating immune complexes, paraproteins, immunoglobulin fractions, antineutrophil cytoplasmic antibodies, serological tests and cultures for underlying infections, and finally routine and immunohistopathology of skin biopsies [11]. These battery of tests have both diagnostic and prognostic significances.

Clotting disorders are screened by activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), factor V Leiden mutation, factor II (thrombin) mutation, antithrombin III, protein C and protein S, and lupus anticardiolipin [11].

For majority of ulcers falling in venous category, color Duplex ultrasound is the standard investigation serving diagnostic purpose by evaluating venous obstruction and assessing location and extent of reflux in venous obstruction. Plethysmography and venography are supplementary investigations for planning surgery. Plain X-ray, CT, and MRI are used in selective ulcers to rule out osteomyelitis and malignancy.

Microbe isolation by culture and sensitivity is very specific and always performed once there is a possibility of infection. Ulcer biopsy is done for final tissue diagnosis once there is a possibility of malignancy. Gene variant analysis in venous ulcer is evolving as a prognostic tool for healing and prevention of ulcer well in advance once high risk is detected.

7.5 Noninvasive and Invasive Investigations

Diagnostic tests are first line followed by prognostic tests. Based on history and clinical examination, selected tests should be performed according to requirement. In chronic ulcers almost up to 98 % are due to venous, arterial, or diabetic, so the primary and most important investigations in chronic ulcers are vascular assessment. ABPI and Duplex ultrasound are two key investigations in all cases of ischemic ulcers. If an ulcer is recurring, etiology is unclear, and all invasive and noninvasive studies have been preformed, a biopsy is essential to establish a diagnosis and to further understand the etiology of the disease. As always, management of chronic wounds can be improved by understanding the true etiology and therefore treating the underlying problem.

Assess the vascular supply to the site of ulceration so that the likelihood of satisfactory wound healing may be estimated. Several methods of determining the adequacy of the pedal circulation are available, e.g., ABI, Xenon-133 clearance, and transcutaneous oxygen tension.

A. *Ankle-brachial pressure index* (*ABI/ABPI*): (Figs. 7.1 and 7.2) Most basic and essential tool of noninvasive investigations is ankle-brachial pressure index (ABPI) for accurate assessment of arterial perfusion. Ischemic ulcers should always be assessed by ABI. It is done by using a handheld Doppler ultrasound and sphygmomanometer. The results are used to determine the likelihood of arterial insufficiency and can be used to guide the management plan. It should be done after 10 min of rest and cuff placed proximal to the malleoli. ABI values below 0.9 are considered as evidence of peripheral arterial occlusive disease [12].

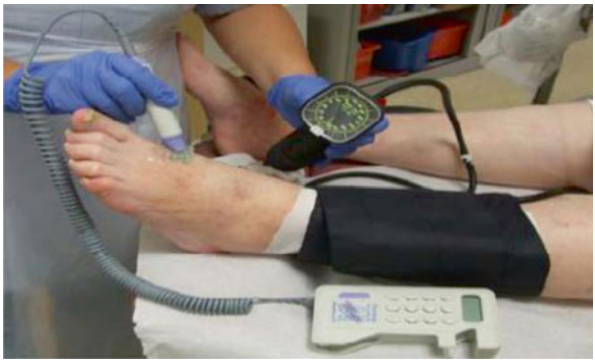

Fig. 7.1 Handheld Doppler for measurement of systolic pressure for ABPI

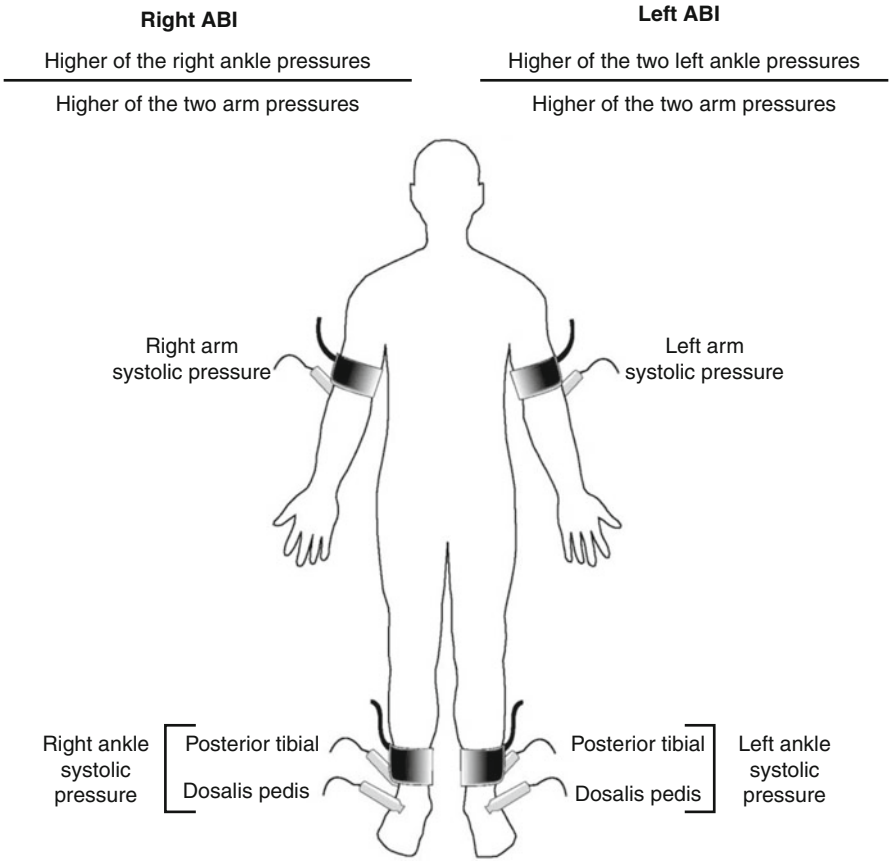

Fig. 7.2 ABPI

When Doppler tests indicate arterial insufficiency, arterial Duplex ultrasonography will (noninvasively) provide accurate anatomic and hemodynamic information on the site and extent of the arterial disease. When indicated, further detailed anatomic information for treatment planning can be obtained from magnetic resonance angiography, computer tomographic angiography, or digital subtraction angiography [12].

Ankle-brachial indices (ABIs) and toe digital pressures with pulse volume recordings can provide good clues to the perfusion of the foot. Findings are also predictive of wound healing, although they may be misleading in patients with diabetes and calcified noncompressible arteries. An ankle pressure greater than 55 mmHg suggests adequate leg perfusion. Research suggests that venous ulcers require a higher ABI for healing than arterial ulcers. The diagnosis of critical limb ischemia is supported by either an ankle systolic pressure of 50 mmHg or less or digital pressures less than 30 mmHg. Limitation of ABI is calcified atherosclerotic arteries mostly in diabetics giving higher false value of ABI due reduced compressibility caused by calcification.

B. *Xenon-133 clearance* to measure blood flow can help estimate the chance of wound healing. A rate of 2.6 mL/100 g is believed to be adequate for healing.
C. *Transcutaneous oxygen tension* may be measured; however, a wide discrepancy exists with the minimal level below which wound healing does not occur. Most agree that a pressure of 30–35 mmHg is sufficient for healing of more than 90 % of wounds.

7.5.1 Leg Ulcer Measurement Tools (LUMT)

Accurate and regular measurement of the wound is important to give an objective assessment of the effectiveness of the current management plan. The leg ulcer measurement tool (LUMT) is a validated tool that has been developed to quantify leg ulcer assessment and can be used to track change in wound status over time. Various methods have been used to document an ulcer of the lower extremity (Fig. 7.3). They can be broadly classified into the following:

(a) *Contact methods*
1. Ruler method
2. Graduated swab stick method
3. Alginate cast
4. Planimetry
5. Kundin gauge
6. Wound tracing

(b) *Noncontact methods*
1. Clinical photography
2. Stereophotogrammetry
3. Structured light techniques
4. Laser triangulation
5. Alfred/Medseed wound imaging system
6. Video image analysis
7. Magnetic resonance imaging

Fig. 7.3 Leg ulcer measurement tools

Role of ulcer measurement tools is to see progress of wound healing, and these are instrumental in monitoring of wound healing after different modes of interventions. Only limited role of ulcer measurement tools is well defined in experimental studies of chronic ulcers.

7.5.2 Doppler Duplex Scanning

Due to rapid, easy, and inexpensive assessment, Duplex ultrasound can be considered as a screening tool for detecting vascular pathology in chronic ulcers. Combination of ultrasound with Doppler detects the distribution and extent of vascular disease. It is regarded as the investigation of choice for the diagnosis of venous reflux, thrombosis, arterial obstruction, and aneurysms [13, 14]. Stenosis and occlusion can be clearly demonstrated and differentiated with adequate information about surface characteristics and plaque content to direct the treatment plan according to etiology and anatomical delineation of pathology of the vascular segment affected. In chronic cases or during follow-up, collateral pathways and flow dynamics are demonstrated leading to the identification of acute, chronic, or recurrent thrombosis. Duplex scan is an excellent tool to differentiate tumors, cysts, hematoma, clots, thrombus, and foreign body in vascular tree. Considering its excellent sensitivity and availability, it is integral in the diagnosis and follow-up with effect on treatment, progression of disease, or developments of new pathology. Duplex is superior in the detection of venous reflux with a sensitivity greater than 75 %, compared to approximately 40 % for descending venography. Neglen and Raju suggest that combining Duplex scanning with air plethysmography helps differentiate severe venous disease from mild venous disease [15].

7.5.3 Plethysmography

Considering the surgical options in chronic ulcers, plethysmography is used to detect and quantify arterial and venous diseases [16, 17]. Several types of plethysmography have been evolved such as air, photo, and strain gauge. Depending on the device used, pressure and flow measurements, waveform patterns, volume changes, amount of reflux, degree of venous obstruction, and the efficiency of calf muscle pumps can be calculated. All these parameters are important as the severity of the disease can be demonstrated to determine the impact of ulceration. So, these are good tests to assess treatment and progression of the disease. Venous pressure data are important in determining the need for surgical bypass or valve replacement. Quantitative data on venous obstruction, calf muscle pump ejection fraction, and reflux are provided by air plethysmography, whereas venous pressure studies assess the physiological importance of anatomic obstruction because the collaterals may or may not provide adequate compensation for an obstructed pathway. Dual significance with both diagnostic and prognostic efficacies is associated with plethysmography, but its use is limited mostly to academic and research purpose.

7.5.4 Computed Tomography (CT Arteriography and CT Venography) (Figs. 7.4 and 7.5)

In chronic ulcer, spiral CT angiography (CTA) is an accurate modality to assess the presence and extent of peripheral arterial disease (PAD). This investigation is done only if the active intervention is required to salvage the limb and improve the quality of life by reducing rate of limb loss and persistent pain. Modes of interventions are either endovascular, open surgery, or hybrid techniques. CT angiography has become popular due to rapid technical developments in terms of shorter acquisition times, thinner slices, higher spatial resolution, and improvement of multidetector computed tomographic scanners that enable the scanning of the whole vascular tree in a limited period with limited contrast [18]. CT venography (CTV) is also accurate to determine proximal venous obstruction, but as it is relatively static, one cannot evaluate reflux. CT can also detect aneurysms, AV fistulae, and any other pathologies like neoplasms and can determine the extent of disease and involvement of surrounding structures. Both CT arteriography and CT venography are considered as excellent tools for differential diagnosis to detect vascular lesion in chronic ulcers [19].

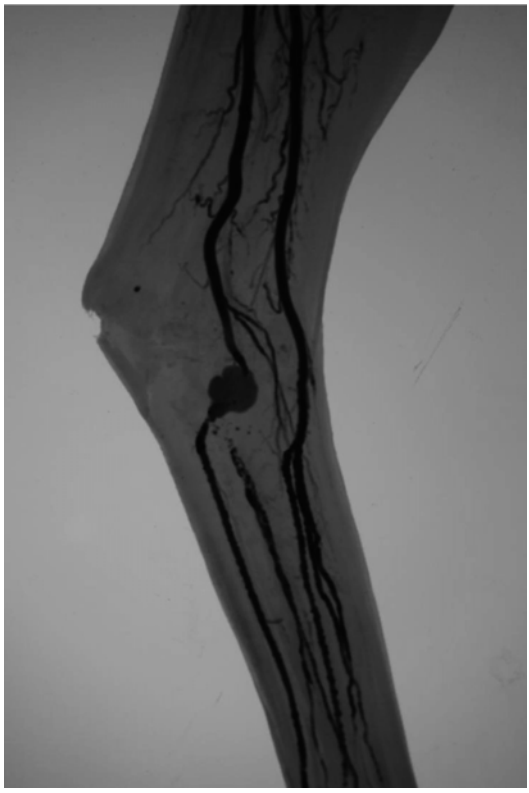

Fig. 7.4 CT angiography showing popliteal artery aneurysm. Patient presented with ulceration of foot

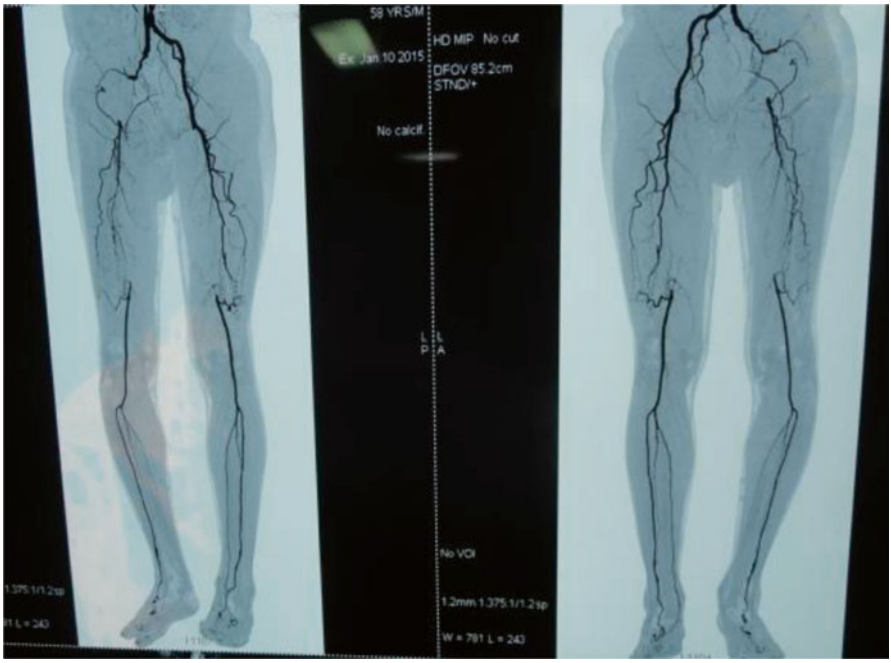

Fig. 7.5 CT angio showing bilateral femoral block at variable levels

7.5.4.1 Magnetic Resonance Imaging (MR Arteriography and MR Venography)

Despite limited availability and skilled interpretation of findings, magnetic resonance arteriography (MRA) equivalent to CT angiography is a noninvasive method to visualize the peripheral vasculature, to detect hemodynamically significant stenosis, and to distinguish focal from long-segment occlusive disease [20]. Advantage of its use is that it does not need any contrast, so the patients with deranged renal functions may undergo MRA. But the disadvantage is that it takes a much longer time to perform and also cannot be used in the patients on pacemakers and any other prosthesis. Further claustrophobia and the sounds produced during the procedure may not be palatable to the patients. MRA has the ability to define the pattern of the disease and help in planning for arterial access sites (retrograde or antegrade). More specifically, MRA has proven useful in detecting occult runoff channels, which can be used for distal bypass [21]. Ulcerations should be bright on T2-weighted imaging, with peripheral enhancement of the ulcer base. Magnetic resonance venography has a great accuracy in detecting proximal vein obstruction and may differentiate acute from chronic thrombosis [22]. Drawback of MRV is failure to demonstrate venous reflux. MRA and MRV can be easily compared to CTA and CTV for excellency in differential diagnosis tool for vascular lesions.

Magnetic resonance angiography (MRA) can also be useful when evaluating lower extremity disease. Yucel et al. found that MRA was 94 % accurate in

evaluating lower extremity vessels when compared to conventional angiography or surgery [23] Owen and coworkers found that MRA detected all runoff vessels when compared to conventional angiography and, in fact, was more sensitive than conventional arteriography for visualizing both runoff vessels and arterial stenosis [24].

7.5.4.2 Phlebography/Venography

Phlebography is usually not done because of the availability of noninvasive tests such as Duplex and relatively less invasive such as CT or MRI, but it can identify the location and extent of blood clots and enables the condition of the deep leg veins to be assessed. It is especially useful when there is a strong suspicion of deep vein thrombosis, after noninvasive tests have failed to identify the disease. Ascending venography also may be considered to obtain detailed anatomic information. This study can reveal axial channel patency, perforator incompetence, obstruction, and the presence of deep venous thrombosis. Phlebography can also be used to evaluate congenital vein problems and assess the function of the deep vein valves. Phlebography is a great method to demonstrate the extension of obstruction and all the collateral pathways. It can guide treatment and at the same time assess its effect. It is not used often, because it is painful, expensive, and time-consuming, exposes the patient to a fairly high dose of radiation, and can cause phlebitis, tissue damage, and the formation of deep vein thrombosis in a healthy leg. It is reserved for evaluating limbs that may need deep vein reconstruction or to open proximal vein obstruction [25].

7.5.4.3 Percutaneous Arteriography

It is integral to do angiography when visualization of the vessels of the lower extremities is desired. A femoral runoff study is the study of choice. It reveals the filling of leg vessels down to the ankle. The plantar arch also may be visualized if the location of the wound is distal enough to warrant it. This study is invaluable to both the plastic surgeon when providing coverage and to the vascular surgeon if revascularization is also performed.

Contrast arteriography is the gold standard for the evaluation of arterial disease. But again as being the invasive procedure, it is less used until unless a therapeutic procedure is planned. It can be done usually by transfemoral route (Seldinger's technique), but in the higher blocks, direct lumbar puncture into the aorta had been used in the past. It demonstrates the arterial tree in its entirety, to readily delineate the site of arterial stenosis and occlusion. It is indicated for select patients, who will undergo revascularization to reestablish perfusion. In addition to providing valuable anatomic information, pressure measurements across the arterial stenosis can be obtained to gauge the hemodynamic severity of a lesion. More importantly, interventions can be done using balloons, stents, and other devices. In patients with vascular malformations, selective catheterization can be performed to obliterate the feeding vessels. Limited use of arteriography in clinical practice due to catastrophic complications is occurring sometimes. There are several complications being an invasive technique, such as hematoma, pseudoaneurysm, arteriovenous fistula formation, embolism, dissection, and renal failure. As the amount of contrast used is

high, it can lead to renal failure. Further patient may go into anaphylaxis because of reaction to the contrast [26].

7.5.4.4 Intravascular Ultrasound (IVUS)

This technique is not available commonly, but it can differentiate between the normal and abnormal vessel. It also determines plaque volume within the wall of the artery and the degree of stenosis. Small lesions like intimal flaps or tears are well visualized because of their high fibrous tissue content and the contrasting echoic properties of surrounding blood. Intramural thrombus appears as echogenic homogenous mass with varying image attenuation beyond the location. IVUS can also differentiate noncalcified vessels versus calcified because the latter appear as a bright image with dense acoustic shadowing because the ultrasound energy is reflected by calcified plaque [27, 28]. It is also used to identify proximal venous obstruction. It allows precise estimation of the stenosis and the diameter of the lumen so the correct balloons and stents are used in the best possible position.

7.5.4.5 Skin Biopsy/Ulcer Biopsy

Although an invasive investigation, biopsy of the ulcer including normal adjoining skin is the final armamentarium in diagnosing doubtful, suspicious, or indeterminate causes of chronic ulcers. In acute ulcers biopsy has limited role and usually not recommended. Most common use of skin biopsies is in ulcers of indeterminate cause and suspected neoplastic pathology. Chronic ulcer of long durations of many years like venous ulcers may change to malignancy [29]. Marjolin's ulcer is an example of a malignant transformation of long-standing ulcers.

Ulcer biopsy is important in making a correct diagnosis and to rule out malignancy as these ulcers are prone to malignant transformation [29]. This requires taking a deep wedge of tissue from the ulcer edge and can usually be performed under local anesthesia [30]. Chronic ulcers are sometimes biopsied for experimental protocols to obtain information regarding the wound bed or the wound edge to grow cells in vitro from nonhealing wound. Chronic wounds do not worsen overall after a biopsy of the wound edge and wound bed is performed. In the majority of the patients, the biopsy site heals up to the original wound edge. The biological underpinning for this occurrence is unclear. There is a paucity of studies investigating the effects of biopsies on the healing of chronic wounds. However, recent research on the molecular pathogenesis of nonhealing wounds has shown that there are phenotypic differences in the cells populating the wound edge and the surrounding skin. Keratinocytes at the edge of the wound show deregulation in cell differentiation and cell migration, resulting in a hyperproliferative epidermal edge that fails to reepithelialize the wound bed. However, cells in the periwound area retain the capacity to differentiate, migrate, and respond appropriately to wound healing signals. In other studies, phenotypic changes have been found between dermal fibroblasts cultured from chronic versus acute wounds. Dermal fibroblasts cultured from the edge of chronic wounds have decreased responsiveness to transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor in terms of collagen production and proliferation. The mechanism for decreased responsiveness to TGF-β1 may be the result of downregulation of TGF-β type II

receptor expression and under phosphorylation of key signaling proteins, such as Smad2/Smad3 and p48/44 MAPK. The expression of a downstream TGF-β inducible protein, βig-H3, has been found to be decreased in chronic wound fibroblasts and in the dermis of chronic nonhealing wounds. Thus, taking a biopsy of the wound edge may remove part of the nonhealing edge and abnormal cell populations and thus produce an acute injury capable of resetting the healing process. This sequence of events may lead to healing in a more timely manner.

There are no studies that focused primarily on the safety of performing wound biopsies in chronic wounds. However, several practice guidelines have been recommended performing wound biopsies for histological diagnosis or microbiologic testing in wounds that have not improved within 2–6 weeks of appropriate management. The Food and Drug Administration (FDA) recommends performing biopsies of the wound, when needed clinically, as an objective tool to exclude neoplastic, immune-mediated, or primary infectious disease. In addition, they suggest performing wound biopsies to diagnose wound infections and to guide treatment. In the future, we may use this information to guide us when to best perform wound biopsies. One might recommend that diagnostic or experimental biopsies be performed several weeks after resolution of the infection.

Wound healing rates at 3 and 4 weeks have been used as predictors of ultimate wound closure. A recent study published on healing rates of both venous and diabetic ulcers determined that a healing rate of 1.5 mm/week was predictive of wound closure at 12 weeks. The biopsy site heals up to the original wound edge. It is quite possible that, once stabilized (standard therapy with a run-in period), chronic wounds reach a size that corresponds to the underlying pathophysiological defects and are, therefore, as large as they can be, based on those intrinsic abnormalities. Certainly, more studies with a larger sample size and a more homogenous patient population are needed. However, the data presented in this report are consistent with our long clinical experience that biopsies are a safe procedure in patients with otherwise impaired healing. These findings should prove useful for clinicians and investigators.

Usually neoplastic skin ulceration is squamous cell carcinoma in the lower extremity, but one may get a basal cell carcinoma, melanoma, and the sarcomas rarely.

7.6 Microbial Isolation

A quantitative bacterial culture is more specific and should be performed once wound infection is suspected [31]. This is performed by curetting or biopsying the bed of the ulcer. The quantitative biopsy is the current gold standard for assessing the quality and quantity of microbial pathogens within the wound [31, 32]. Quantitative biopsies containing greater than 10^5 organisms per gram of tissue are considered significant, and systemic antibiotic therapy should be considered. If osteomyelitis is suspected, representative cultures need to be obtained from the bone or deepest tissue layers [8]. Chronic wounds contain complex polymicrobial communities of sessile organisms that have been underappreciated because the

limitations of standard culture techniques increased bacterial diversity with an average of 17 genera in each wound. Data from microbial community profiling of chronic wounds were compared with published sequenced analyses of bacteria from normal skin. Increased proportions of anaerobes, Gram-negative rods, and Gram-positive cocci were found in chronic wounds. In addition, chronic wounds had significantly lower populations of *Propionibacterium* compared with normal skin. Using epifluorescence microscopy, wound bacteria were visualized in highly organized thick confluent biofilms or as scattered individual bacterial cells. Fluorescent in situ hybridization allowed for the visualization of *Staphylococcus aureus* cells in a wound sample. Quorum-sensing molecules were measured by bioassay to evaluate signaling patterns among bacteria in the wounds. A range of autoinducer-2 activities was detected in the wound samples. Collectively, these data provide new insights into the identity, organization, and behavior of bacteria in chronic wounds. Such information may provide important clues to effective future strategies in wound healing.

7.7 Gene Variant Analysis

The clinical application of gene variant analysis and evaluation in patients with venous leg ulcers implies that the high-risk minority of patients could be identified in advance by means of a simple blood test that would act as a genetic screening device. Utility of gene variant analysis is to prevent chronic ulcers by modifications of lifestyle and minimize morbidity in high-risk populations [33].

Conclusion

Majority of the ulcers may be diagnosed clinically by thorough history and examination, but investigations are needed for unusual cases. Baseline investigations must be available for all cases, and in special type of cases, specific investigations are needed. Majority of the chronic ulcers are vascular in origin, so Duplex ultrasound is the choice of investigation in almost all type of chronic leg ulcers. In long-standing cases where the ulcer is not responding to the treatment, a biopsy must be performed. The biopsy should be performed from the margins of the ulcer and not from the center which may show only necrotic material. The ulcers respond best if correctly diagnosed.

References

1. Barclay KL, Granby T, Elton PJ. The prevalence of leg ulcers in Hospitals. Hosp Med. 1998;59(11):8.
2. London NJ, Donnely R. ABC of arterial and venous disease Ulcerated lower limb. Br Med J. 2000;320:1589–91.
3. Cleverland TJ, Gaines P. Stenting in peripheral vascular disease. Hosp Med. 1999;60:630–2.
4. Ruckley CV. Caring for patients with chronic leg ulcer. BMJ. 1998;316:407–8.
5. Rahman IA, Fadeyi A. Epidemiology, etiology, and treatment of chronic leg ulcer: experience with sixty patients. Ann Afr Med. 2010;9(1):1–4.

6. Kahle B, Hermanns HJ, Gallenkemper G. Evidence based treatment of chronic leg ulcers. Dtsch Arztebl Int. 2011;108(14):231–7.
7. van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. BMJ. 2010;341(7782):1092–6.
8. Rayner R, Carville J, Keaton J, Prentice J, Santamaria XN. Leg ulcers: atypical presentations and associated comorbidities. Wound Practice Res. 2009;17(4):168–85.
9. Moloney M, Grace P. Understanding the underlying causes of chronic leg ulceration. J Wound Care. 2004;13:215–8.
10. Dean S. Leg ulcers: causes and management. Aust Fam Physician. 2008;36(7):480–4.
11. Mekkes JR, Loots MM, van der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
12. Lazarides MK, Giannoukas AD. The role of hemodynamic measurements in the managements in the management of venous and ischemic ulcers. Int J Lower Extrem Wounds. 2007;6:254–61.
13. Androulakis AE, Giannoukas AD, Labropoulos N, Katsamouris A, Nicolaides AN. The impact of duplex scanning on vascular practice. Int Angiol. 1996;15:283–90.
14. Mansour M, Labropoulos N. Vascular diagnosis. Philadelphia: Elsevier Saunders; 2005.
15. Neglén P, Raju S. A rational approach to detection of significant reflux with duplex Doppler scanning and air plethysmography. J Vasc Surg. 1993;17(3):590–5.
16. Needham T. Physiological testing of lower extremity arterial disease: segmental pressure, plethysmography, and velocity waveforms. In: Mansour M, Labropoulos N, editors. Vascular diagnosis. Philadelphia: Elsevier Saunders; 2005. p. 215–22.
17. Labropoulos N, Leon L, editors. Evaluation of chronic venous disease. In: Vascular diagnosis. Philadelphia: Elsevier Saunders; 2005. p. 447–62.
18. Met R, Bipat S, Legemate DA, Reekers JA, Koelemy MJ. Diagnostic performance of computed tomography angiography in peripheral arterial diseases; a systemic review and meta-analysis. JAMA. 2009;301:415–24.
19. Uhl JF, Gillot C. Embryology and three dimensional anatomy of the superficial venous system of the lower limbs. Phlebology. 2007;22:194–206.
20. Poschenrieder F, Hamer OW, Herold T, et al. Diagnostic accuracy of intraarterial and i.v. MR angiography for the detection of stenoses of the infrainguinal arteries. AJR Am J Roentgenol. 2009;192:117–21.
21. Morasch M, Collins J. The current role of MRA in planning interventions for lower extremity ischemia. In: Mansour M, Labropoulos N, editors. Vascular diagnosis. Philadelphia: Elsevier Saunders; 2005. p. 293–306.
22. Froelich JB, Prince MR, Greenfield LJ, Downing LJ, Shah NL, Wakefield TW. "Bull's -eye" sign on gadolinium enhanced magnetic resonance venography determines thrombus presence and age: a preliminary study. J Vasc Surg. 1997;26:809–16.
23. Yucel EK, Dumoulin CL, Waltman AC. MR angiography of lower-extremity arterial disease: preliminary experience. J Magn Reson Imaging. 1992;2(3):303–9.
24. Owen RS, Carpenter JP, Baum RA, et al. Magnetic resonance imaging of angiographically occult runoff vessels in peripheral arterial occlusive disease. N Engl J Med. 1992;326(24):1577–81.
25. Masuda EM, Kistner RL. Long term results of venous valve reconstruction: a four to twenty one year follow up. J Vasc Surg. 1994;19:391–403.
26. Ayerdi J, Hodgson K. Principles of arteriography. In: Rutherford R, editor. Vascular surgery. 6th ed. Philadelphia: Elsevier Saunders; 2005. p. 281–99.
27. Buckly CJ, Arko FR, Lee S, et al. Intravascular ultrasound scanning improves long-term patency of iliac lesions treated with balloon angioplasty and primary stenting. J Vasc Surg. 2002;35:316–23.
28. Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical and hemodynamic result. J Vasc Surg. 2007;46:979–90.
29. Agale SV, Kulkarni DR, Valand AG, Zode RR, Grover S. Marjolin's ulcer—a diagnostic dilemma. J Assoc Physicians India. 2009;57(8):593–4.

30. Ghauri SK, Nyamekye IK. Leg ulceration: the importance of treating the underlying pathophysiology. Phlebology. 2010;25(supplement 1):42–51.
31. Siddiqui AR, Bernstein JM. Chronic wound infection: facts and controversies. Clin Dermatol. 2010;28(5):519–26.
32. Han A, Zenilman JM, Melendez JH, et al. The importance of a multi-faceted approach to characterizing the microbial flora of chronic wounds. Wound Repair Regen. 2011;19(5):532–41.
33. Singh AV, Subhashree L, Milani P, Gemmati D, Zamboni P. Interplay of iron metallobiology, metalloproteinases, and FXIII, and role of their gene variants in venous leg ulcer. Int J Low Extrem Wounds. 2010;9(4):166–79.

Microbiology of Ulcer

8

Gopal Nath and Gopal Kumar

8.1 Introduction

The primary function of normal, intact skin is to control microbial populations that reside on the skin surface and to prevent underlying tissue from becoming colonized and invaded by potential pathogens. Ulcer causes break in continuity of skin and makes a path for entry of pathogen. Infections of the lower extremity ulcers are a major source of morbidity and important cause of amputation and sometimes mortality in patients particularly with neuropathy and diabetes. Not all ulcers are infected. Evaluation of infection should involve a thorough examination of the extremity for clinical signs of infection along with appropriate laboratory and imaging studies. The organisms implicated are often *Staphylococcus aureus* (often MRSA in diabetic patients) and Group B *streptococci* in limb-threatening infection. Chronic infected wounds often have multidrug-resistant pathogens, especially after exposure to health care procedures and use of multiple antibiotics. The presence of a foot ulcer should heighten the index of suspicion for associated infection.

8.2 Microbiology

8.2.1 The Normal Microbiota

The skin and mucus membranes of human beings always harbor a diverse number of microorganisms that can be broadly divided into two major groups:

The *resident flora* which consists of relatively fixed types of microorganisms regularly found in a given area at a given age, and if disturbed anyhow, it

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reestablishes itself. The *transient flora* consists of nonpathogenic or potentially pathogenic microorganisms that inhabit the skin or mucous membranes for hours to weeks; these are derived from the environment, do not produce any disease, and are not able to establish permanently on the surface. Members of the transient flora are generally of little significance so long as the normal resident flora remains intact. However, transient microorganisms may colonize, may proliferate, and may produce disease if the resident flora is disturbed.

It is likely that the culturable microorganisms in the laboratory represent only a fraction of those that are part of the normal resident or transient microbial flora of the area. When a range of polymerase chain reaction is used to amplify bacterial 16SrDNA, many previously unidentified bacteria can be detected. The number of species that make up the normal micro biota has been shown to be much greater than is recognized. Thus, the understanding and identification of normal micro biota is still in transition.

The microorganisms that are constantly present on the body surfaces are commensals, and their presence in that particular area depends upon many factors such as temperature, moisture, as well as the presence of certain nutrients and inhibitory factors. On mucous membrane and the skin, the resident flora may prevent colonization by pathogens and possible disease through bacterial interference which may involve competition for nutrients, mutual inhibition by metabolic or toxic products, and mutual inhibition by antibiotics or bacteriocins.

8.3 Role of Host and Environment

The most important factor in limiting the infection is the host resistance. Suppression of the normal microbiota creates a partial local gap that tends to be filled by organisms from the environment or from other parts of the body. Such organisms behave as opportunists and often become pathogens when conditions favor.

On the other hand, members of the normal micro biota may themselves produce disease under certain circumstances. These organisms get adapted to the noninvasive mode of life defined by the limitations of the surrounding environment. If forcefully removed from the restrictions of that environment and introduced into the bloodstream or tissues, these organisms may become pathogenic. The surrounding environment causes constant exposure of skin with different microbes, and so the skin is apt to contain transient microbiota. The constant and well-defined resident flora is modified in different anatomic areas by secretions, habitual wearing of clothing, or proximity to mucous membranes.

8.4 Role of Microbes in Infection

Most acute and chronic wound infections involve mixed population of both aerobic and anaerobic microorganisms. The predominant resident microorganisms of the skin are aerobic and anaerobic diphtheroid bacilli (e.g., *Corynebacterium,*

Propionibacterium); nonhemolytic aerobic and anaerobic staphylococci (*S. epidermidis* and other coagulase-negative staphylococci, occasionally *S. aureus* and *Peptostreptococcus* species); Gram-positive, aerobic, spore-forming bacilli that are ubiquitous in air, water, and soil; alpha hemolytic *Streptococci* (viridians streptococci) and Enterococci, and Gram-negative coliform bacilli and *Acinetobacter*. Fungi and yeast are often present in skin folds; acid-fast nonpathogenic mycobacteria occur in areas rich in sebaceous secretions (genitalia, external ear). The number of superficial microorganisms may be diminished by vigorous daily scrubbing with soap containing hexachlorophene or other disinfectants, but the flora is rapidly replenished from sebaceous and sweat glands.

Anaerobic and aerobic bacteria often join to form synergistic infections (gangrene, necrotizing fasciitis, and cellulitis) of the skin and soft tissue. These bacteria are frequently part of normal microbial flora. So mixture of microorganisms is usually involved in many skin lesions.

8.5 The Role of Biofilm in Infected Ulcer

Most chronic ulcers are colonized by bacteria in the form of a biofilm, which is difficult to treat [1]. Although the adverse effect of bacteria on wound healing has long been noted, biofilm, which does not always give rise to an overt phenotype or infectious picture, has been underappreciated. Indeed, a nonhealing wound is one of the more common presentations of biofilm.

Biofilm consists of a sessile community of multiple bacterial species enclosed by a protective carbohydrate-rich polymeric matrix that is resistant to antimicrobial and immune cell penetration [2]. Most wounds are in fact colonized by bacteria that set up in the form of biofilm. Unfortunately biofilm is exceedingly tenacious and readily accumulates after debridement. Thus, proper dressing care consists of dressings that both treat the wound and minimize biofilm accumulation.

Bacteria whether free floating or incorporated within a biofilm are extremely detrimental to wound healing, particularly when they reach the level of critical colonization [3].

8.6 Bioload of Ulcer Wound

Wounds may be classified as contaminated, colonized, critically colonized, or infected [4]. This classification is useful to understand relation between the bacteria and the patient (or host) and define the level of bioburden (i.e., the cost exacted by bacteria from the resources of the wound and the patient). All wounds are contaminated to some degree either by skin flora or by environmental pathogens.

It is likely that this level of bacterial contamination stimulates wound repair mechanisms by upregulating the inflammatory response. When the contaminating bacteria begin to proliferate, the wound is said to be colonized; however, when the

wound provokes an inflammatory reaction by the proliferating bacteria, the wound is said to be infected. It is important to keep in mind both host inflammatory reactions contribute to failure in wound healing as bacteria themselves do [5].

Microbiological factors such as the population density, the types of microorganisms present, and the microbial interactions and host factors such as the efficacy of the immune response and the condition of the tissue are all critical and must be considered collectively as factors predisposing to infection.

Antimicrobial treatment of clinically infected and/or nonhealing polymicrobial wounds should cover a variety of potentially synergistic aerobic or facultative and anaerobic microorganisms and should not simply target specific pathogens (e.g., *S. aureus and P. aeruginosa*).

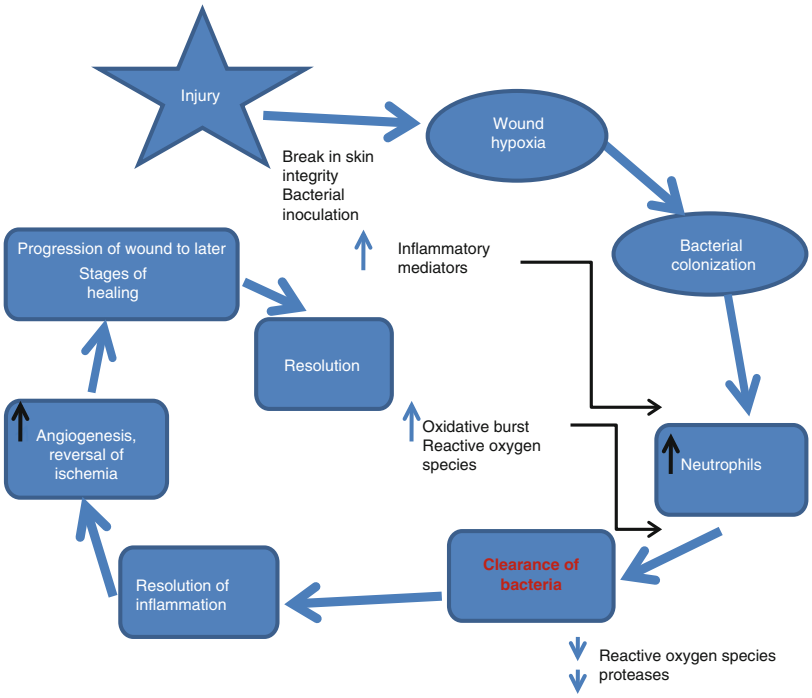
Judicious use of antibiotics, adequate debridement, and proper dressing choices can decrease bacterial numbers and reduce the competition for resources occurring in wounds contaminated by bacteria [3].

8.7 Vicious Cycle of Wound Healing

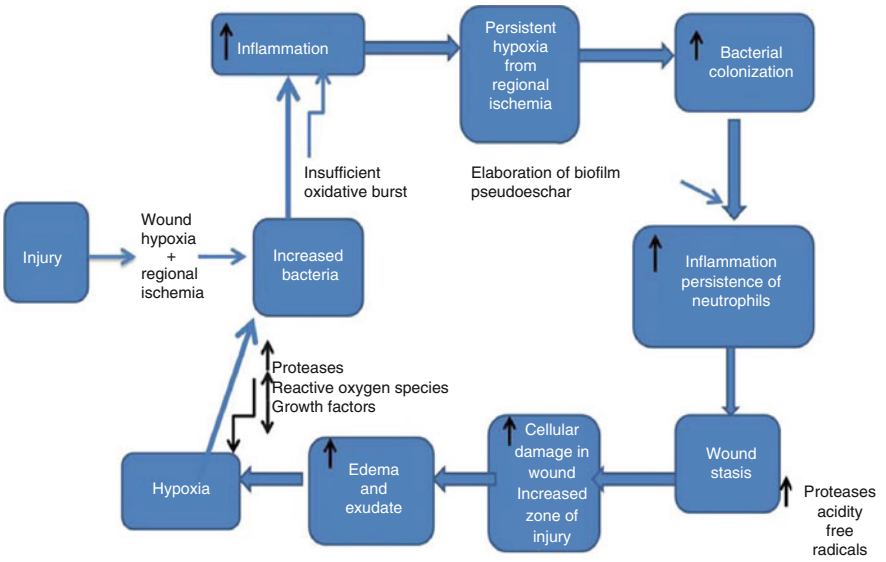
Schematic representation depicts interplay between bacterial levels, oxidative stress, and parameters of healing in a wound:

Lower extremity ulcers, *ACS Surgery* [42]

A. Typical self-limiting inflammatory response in a healthy healing wound:



B. Impaired healing of wound:



8.8 Infective Causes of Ulcer

8.8.1 Infectious Causes of Limb Ulcers

Ulceration in the lower extremity may be due to infectious agents. Diverse groups of microbes including bacteria, viruses, parasites, and fungi have been implicated [41].

Disease	Causative agent
Erysipelas (bullosa)	*Streptococcus pyogenes*
Fasciitis necroticans	*Streptococcus hemolyticus*
Ulcerating pyoderma	*Staphylococcus aureus*
Ecthyma gangrenosum	*Pseudomonas spp.*
Gas gangrene	*Clostridium spp.*
Septic embolism	*Meningococcus* and others
Anthrax	*Bacillus anthracis*
Diphtheria	*Corynebacterium diphtheriae*
Osteomyelitis	Several microorganisms specially *Staphylococcus aureus*
Herpes, CMV	HSV, CMV
Lues maligna (malignant syphilis)	*Treponema pallidum*
Tularemia	*Francisella tularensis*
Tropical ulcer	*Bacteroides, Borrelia vincentii,* and other bacteria
Maduromycosis (eumycetoma/ mycetoma)	*Nocardia brasiliensis, Exophiala jeanselmei*
Chromoblastomycosis, coccidioidomycosis, sporotrichosis, granuloma	Several bacteria; *Coccidioides immitis* or *Coccidioides posadasii*; *Sporothrix schenckii*; dermatophytes of the genera Trichophyton and Microsporum

Disease	Causative agent
Histoplasmosis	*Histoplasma capsulatum*
Buruli ulcer	*Mycobacterium ulcerans*
Bacillary angiomatosis	*Bartonella henselae* or *Bartonella quintana*
Ulcerating cutaneous tuberculosis	*Mycobacterium tuberculosis*
Amebiasis	*Entamoeba histolytica, Acanthamoeba*
Leishmaniasis	*Leishmania donovani* complex, *Leishmania mexicana* complex, *Leishmania tropica*; Leishmania major; *Leishmania aethiopica*
Leprosy	*Mycobacterium leprae and Mycobacterium lepromatosis*

CMV cytomegalovirus, *HSV* herpes simplex virus

8.9 Infected Ulcers

Some microorganisms can cause tissue necrosis, such as the notorious Group A β-hemolytic *Streptococcus pyogenes.* These bacteria have been implicated into a range of severe clinical symptoms varying from erysipelas, ecthyma, and fasciitis necroticans to deep cellulitis, sepsis, and multiorgan failure.

Almost all chronic wounds are secondarily contaminated with bacteria, but in most cases, with the exception of few, they are not of pathogenetic importance. Wound swab cultures are often routinely performed, but give only information about the bacterial flora in the superficial layers. The decision to prescribe systemic antibiotics should be based on the combination of culture results and clinical criteria, such as signs of infection (fever, erythema, calor).

Acquired immune deficiency due to human immunodeficiency virus (HIV) infection reintroduced ulcerative conditions that were thought to be eradicated, such as tertiary lues and ulcerating tuberculosis, and may be associated with atypical, large ulcers caused by herpes simplex or cytomegalovirus. In addition, bacillary angiomatosis, caused by *Rochalimaea* species, and *Histoplasma capsulatum* must be included in the differential diagnosis of ulcerations occurring in HIV disease [6, 7]. Increased world travel has brought tropical ulcerating infections to Western countries, especially leishmaniasis, but also atypical mycobacteria, ulcus tropicum [8], and deep mycotic infections.

Tuberculous cutaneous ulcer might occur in erythema induratum or Bazin's disease, situated usually on the back of the calves [9].

Ulcer by amoeba: Ulceration of the skin of the lower limbs by amoebae, which could be the result of superinfections of skin wounds due to scratching with dirty nails.

Tropical ulcer: These are necrotic painful lesions that result from a mixed bacterial infection. They are common in hot humid tropical or subtropical areas, where they occur on the lower legs or feet of children and young adults.

8.9.1 Other Infective Causes of Ulcer

Cutaneous tuberculosis
Syphilis

Parasitic infection
Fungal infection

8.10 Infected Diabetic Foot Ulcers

In most cases, diabetic foot infections are polymicrobial, and deep tissue culture after debridement is essential for identifying the true pathogens. Diabetic foot infections are frequently associated with *S. aureus, epidermidis, Streptococcus spp., P. aeruginosa, Enterococcus spp.,* and coliform bacteria [10].

8.10.1 Infection Status of Chronic Wounds

Chronic leg ulcers are defined as those that show no tendency to heal after 3 months of appropriate treatment or are still not fully healed at 12 months.

The interaction between ulcer and bacteria can be stratified into four levels: contamination, colonization, critical colonization, and infection [11], while contamination and colonization by microbes are not believed to inhibit healing, the line between colonization and infection can be difficult to define.

The term "critical colonization" has been used to describe the stage at which bacteria begin to adversely affect wound healing [11]. Moreover, the underlying pathogenesis of chronic wounds may result in wounds of different etiologies being differently affected by bacteria [12–14].

Chronic wounds by their very nature may not always display the classic symptoms of infection (pain, erythema, edema, heat, and purulence), and it has been suggested that an expanded list, including signs specific to secondary wounds (such as serous exudate plus concurrent inflammation, delayed healing, color of granulation tissue, foul odor, and wound breakdown) be employed to identify infection [15].

Microbiologically, a critical bacterial load, synergic relationships between bacterial species, and the presence of specific pathogens have all been proposed as indicators of infection. The presence of microbes per se is not indicative of wound infection.

8.10.2 Microbial Load and Healing of Wound

The possibility that a critical microbial load might directly affect the healing outcome in both acute and chronic wounds has been considered for several decades, with a direct relationship first being demonstrated by Bendy et al. [16] in 1964. Since then, work carried out by Robson [17] and others has led to the widely held opinion that nonhealing is associated with a bacterial load of more than 10^5 bacteria per gram of tissue.

The concept of bacterial synergy which recognizes the importance of interspecies interactions has been purported to occur in chronic wounds through studies such as that by Bowler and Davies [18]. They found the growth and pigmentation of

some Gram-negative anaerobes to be enhanced by some facultative bacteria through the provision of an essential, unidentified growth factor. Furthermore, they found significantly greater numbers of anaerobes in infected ulcers compared with noninfected ones.

With regard to specific pathogens, beta-hemolytic *streptococci* [17, 19] *S. aureus* [12], Enterobacteriaceae [12], and *Pseudomonas* species [12, 20] have all been implicated as having potentially adverse effects on wound healing. The impact of these species may vary in different settings, for example, over 60 % of arterial and diabetic ulcers colonized with *S. aureus* develop an infection compared with only 20 % of venous ulcers similarly colonized [12].

In summary, microorganisms are identified in the deep tissue of all chronic wounds, yet the role they play and the impact of specific species on wound longevity are not clear. The distinction between infected and colonized wounds has to be considered on a clinical basis and not by microbiological analysis only due to the universal colonization of chronic wounds [21]. Microbial analysis can be of benefit when considered in concert with clinical observations to confirm causative organisms and their sensitivities [22] and so enable refinement of antibiotic regimens [21].

8.10.3 Microbiology, Antibiotic Usage, and Resistance in Leg Ulcers

The microflora of leg and foot ulcers is usually polymicrobial, and recent studies using molecular techniques have emphasized the complex ecology of these wounds [23, 24]. Using conventional techniques, the mean number of bacterial species per ulcer has been found to range from 1.6 up to 4.4 [25–28]. Hansson et al. [29] observed that 86 % of ulcers with no clinical signs of infection contained more than one bacterial species.

Staphylococcus aureus and coagulase-negative *Staphylococcus* have been the predominant organisms isolated. *S. aureus* has been reported in frequencies varying from 43 % of infected leg ulcers to 88 % of noninfected leg ulcers [29], whereas *Staphylococcus epidermidis* has been reported in 14 % of venous ulcer specimens [30] and 20.6 % of diabetic foot ulcers (DFUs) [27]. *Pseudomonas aeruginosa* is another frequently identified organism and has been found in 7–33 % of ulcers [12, 26, 29]. A number of other aerobic species have also been reported, including *Escherichia coli* [18, 27, 29–31], *Enterobacter cloacae*, *Klebsiella* species, *Streptococcus* species, *Enterococcus* species [28, 29] and *Proteus* species [31]. This is by no means an exhaustive list, but is illustrative of the range of aerobic bacteria that exist in chronic wounds.

In addition to aerobes, anaerobic organisms are frequently identified in wounds, albeit with considerable variation. Trengove et al. [20] found obligate anaerobes in one-quarter of chronic leg ulcer samples, while Ge et al. [31] found they constituted only 6 % of DFU wound isolates.

However, a focused study by Bowler and Davies [18] found anaerobes in 73 % of noninfected leg ulcers and 82 % of infected leg ulcers. The most common isolates found in both the infected and noninfected leg ulcers were Peptostreptococcus species and pigmented and nonpigmented *Prevotella/Porphyromonas* species [18].

Finegoldia magna (previously classified as *Peptostreptococcus magnus*) was found by Hansson et al. [29] to be present in 19.6 % and *Peptoniphilus asaccharolyticus* in 9.8 % of noninfected venous leg ulcers. Kontiainen and Rinne [28] found that clinical swabs sent for analysis, presumably from infected or assumed infected wounds, yielded obligate anaerobic rods (mainly *Bacteroides* species) from 12 % of ulcers and anaerobic cocci (*Peptostreptococcus)* from 8 %. Ge et al. [31] found *Bacteroides, Peptostreptococcus,* and *Prevotella* species to be the most frequently isolated obligate anaerobes in mild or moderately infected DFUs. The continuity of the microbial profile of chronic wounds over time is unclear from the limited literature that has examined this issue. Hansson et al. [29] considered the microflora of chronic wounds to be a relatively stable entity having found that 90 % of ulcers that were followed for 4 months, or until healing, contained at least one resident organism that was isolated from all monthly swabs. Furthermore, Gilchrist and Reed [32] considered chronic wounds to have stable microbial populations, following the observation that once a species was present, it generally remained so under hydrocolloid dressings, with the exception of the transient appearance of *P. aeruginosa*. However, closer examination of their data shows that 85 % of wounds acquired new aerobes and 45 % new anaerobes over the 8 week of study period. Trengove et al. [20] logged the occurrence of new bacterial groups appearing in wounds after initial swabs had been taken. They found at least one new bacterial group present in subsequent swabs in 82 % of patients and thus concluded that the microbial populations of chronic wounds alter over time.

Each of these studies suggests that although there may be a degree of stability for some microbial populations, the chronic wound appears to be a dynamic environment. However, there are to date no definitive studies of bacterial succession within chronic wounds, the influence of antibiotics on this succession, or of the interactions between bacterial succession and healing.

8.11 Lab Diagnosis of Infected Ulcers

8.11.1 The Role of Microbiology in Diagnosis

The diagnosis of infected ulcer is made clinically and supported by microbiology lab reports. Finding purulent drainage (pus) or two or more signs or symptoms of inflammation, e.g., erythema, induration, swelling, pain, tenderness, or warmth, is indicative of infection.

Elevated concentration of C-reactive protein and procalcitonin can help distinguish mild or moderately infected ulcer wound from those that are uninfected [33].

Serologic tests for syphilis or polymerase chain reaction for mycobacterium DNA may be performed on specimens from an ulcer suspected of being of mycobacterial origin (e.g., erythema induratum of Bazin: Mycobacterial panniculitis with subsequent ulceration usually involving the calves). Cryoglobulins may be associated with hepatitis C and leg ulceration.

8.12 Culture

For culture, specimens should be obtained after the surface of the wound has been washed thoroughly by sterile saline and followed by debridement of superficial exudates. Specimens must be obtained by scraping the ulcer base or the deep portion of the wound edge with a sterile curette. A curettage, or tissue scraping with a scalpel, from the base of a debrided ulcer provides more accurate results than does the wound swab (Fig. 8.1).

Culture of open foot and leg ulcers cannot be used reliably to establish the presence of infection. These ulcers whether infected or not will contain multiple commensal or colonizing bacteria, some of which have the potential to become invasive pathogens.

Culturing specimens from a chronic wound that is healing at an expected rate and does not display any signs or symptoms of infection are unnecessary. Because all wounds are contaminated and colonized, a culture simply confirms the presence of microorganisms without providing any information as to whether they are having a detrimental effect on the host.

However, bacterial swabs can provide information on the predominant flora within a nonprogressing, deteriorating, or heavily exudating wound. Microbiological tests also can screen for multiresistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).

The soft tissue specimens should be promptly sent to the laboratory and processed for aerobic and anaerobic bacteria.

Following incubation under aerobic or anaerobic conditions for 24–48 h, qualitative and semiquantitative assessments of the cultures are normally made. A minimally inflamed but deep ulceration may be associated with underlying osteomyelitis [34] (Fig. 8.2).

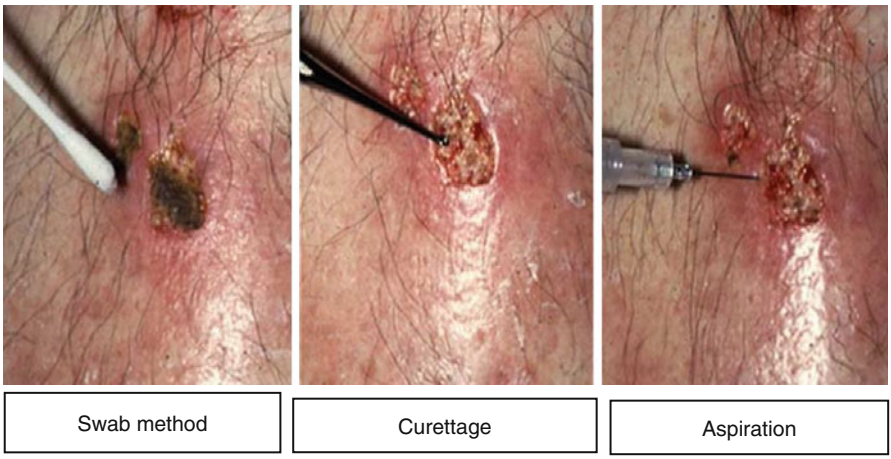


Fig. 8.1 Collection of specimen from ulcer

Fig. 8.2 McIntosh and Field's anaerobic jar

8.12.1 Picture of Common Isolates (Figs. 8.3–8.5)

Fig. 8.3 *Staphylococcus aureus* colonies on blood agar

Fig. 8.4 *Pseudomonas colonies* on nutrient agar

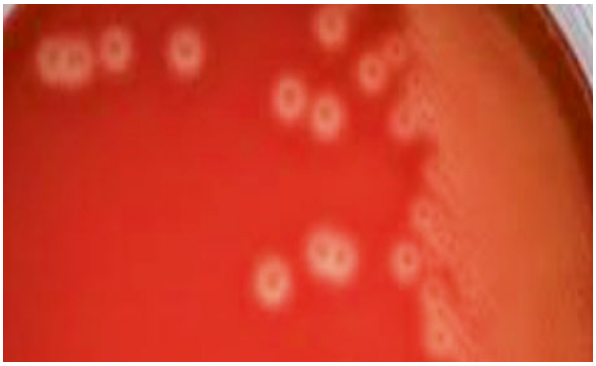


Fig. 8.5 Beta-hemolytic colonies of *Streptococcus pyogenes*

8.13 Gram Stain

The degree of inflammatory response is measured by the presence and quantity of neutrophils per high power field in the Gram stain of the swab contents before inoculating the specimen on growth media.

In case of cutaneous anthrax, a Gram stain smear of the lesion shows the typical, large Gram-positive rods (1–1.5 × 4–10 μm). The bacterium is noticeably larger than most other pathogens. An alternative to Gram stain is polychrome methylene blue (M'Fadyean's stain).

8.13.1 Which Culture Technique Should Be Used?

Quantitative sampling (tissue biopsy) has merits, and a strong association exists between the number of organisms in a wound and the ability of the wound to heal. Once bacterial load reaches 10^6 CFU/g of tissue, wound healing is usually impaired [35]. However, these findings need to be viewed in perspective. At least 20 % of wounds colonized with more than 10^5 CFU/g of tissue will still heal [36], and normal skin flora present in high quantities appears to enhance wound healing [37]. On the other hand, some microorganisms (e.g., beta-hemolytic Streptococci, *Mycobacterium tuberculosis, Treponema pallidum, Corynebacterium diphtheriae, Bacillus anthracis, Francisella spp.,* and *Brucella spp.*) can be detrimental in small numbers. Thus, quantitative microbiology does not necessarily provide an unambiguous diagnosis of infection (Figs. 8.3, 8.4, 8.5, 8.6, 8.7, and 8.8).

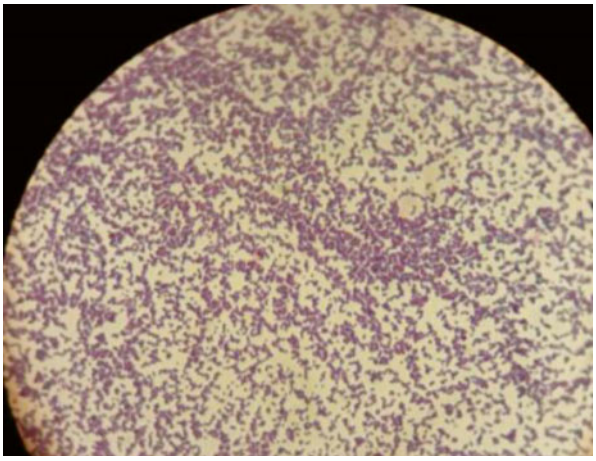


Fig. 8.6 Gram-positive cocci in clusters (*Staphylococcus aureus*)

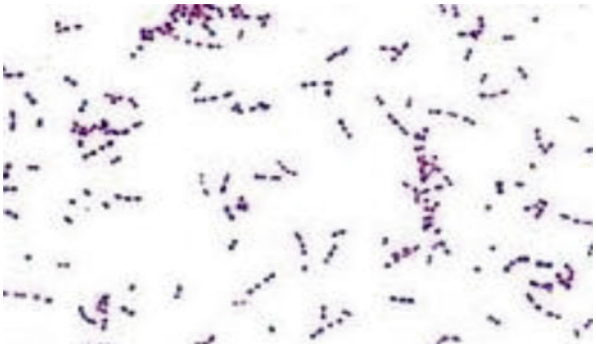


Fig. 8.7 Gram-positive cocci in short chain (*Streptococcus pyogenes*)

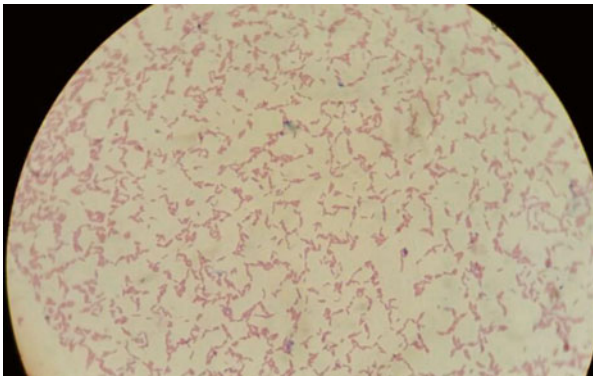


Fig. 8.8 Gram-negative bacilli (pseudomonas) on Gram stain

Qualitative aspects are at least as important as overall bacterial load, and evidence is growing that microbiology obtained by a swab may adequately correlate with qualitative findings obtained through tissue biopsy.

In a study on diabetic foot infections, Wheat et al. [38] showed that the results obtained with swabs are similar to those obtained with tissue biopsy.

Sapico et al. [39] found similar results in a study on chronic pressure ulcers, demonstrating a 75 % concordance between swab and biopsy results. Ehrenkranz et al. [40] demonstrated that an irrigation-aspiration technique could produce similar results to qualitative biopsy.

8.13.2 Procedure for Taking a Swab

In most cases, wounds should not be cultured if no evidence of infection or impaired healing is noted unless screening is being performed for colonization of multiresistant organisms. The wound bed must first be cleaned with saline and superficially debrided so the cultures from the superficial wound compartment more closely resemble those in the deep wound compartment.

Alginate or rayon-tipped swabs are sometimes preferred in the belief that the fatty acids contained in cotton swabs might inhibit growth in certain bacteria. However, the organisms commonly encountered in infection are likely to withstand the environment of a cotton swab (Fig. 8.9).

Pre-moistening a swab (Fig. 8.10) in the transport media is useful if the surface of the wound is dry but is not necessary if the wound is already moist. The swab should be taken from the surface of the granulation tissue wound. The tip of the swab should be rolled on its side for one full rotation over the part of the wound granulation tissue with the most obvious signs of infection, avoiding slough and surface purulent discharge.

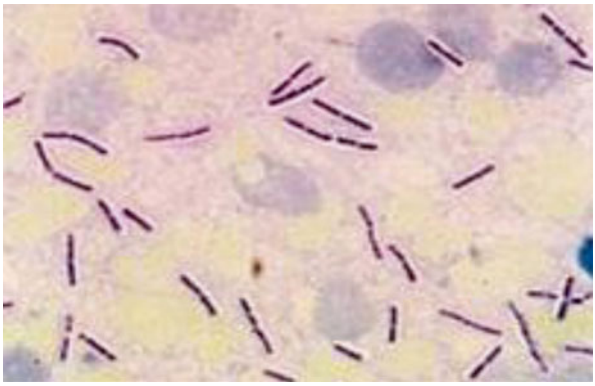


Fig. 8.9 *Bacillus anthracis* as large Gram-positive rod

Fig. 8.10 Sterile disposable cotton swab stick

A zigzag pattern can be used for wounds larger than 5 cm^2. This technique is likely to increase the yield. If pus or discrete abscesses are collected locally, the fluid should be aspirated into a syringe using a needle. The fluid is an ideal specimen for culture.

Cultures, while essential in the assessment of the microbiology of leg/foot infections, do not in isolation establish the presence of infection.

References

1. Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis. 2004;17:91.
2. Ghannoum M, O'Toole GA. Microbial biofilms. Washington, DC: ASM Press; 2004.
3. Robson MC, Munnari RJ, Smith PD, et al. Maintenance of wound bacterial balance. Am J Surg. 1999;178:399.
4. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003;11 Suppl 1:S1.

5. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol. 2007;127:514.
6. Carrascosa JM, Ribera M, Bielsa I, et al. Bacillary angiomatosis presenting as a malleolar ulcer. Arch Dermatol. 1995;131:963–4.
7. Laochumroonvorapong P, DiCostanzo DP, Wu H, et al. Disseminated Histoplasmosis presenting as pyoderma gangrenosum-like lesions in a patient with acquired immunodeficiency syndrome. Int J Dermatol. 2001;40:518–21.
8. Robinson DC, Adriaans B, Hay RJ, Yesudian P. The clinical and epidemiologic features of tropical ulcer (tropical phagedenic ulcer). Int J Dermatol. 1988;27:49–53.
9. Champion RH, Burton JL, Burns DA, et al. Rook, Wilkinson and Ebling's textbook of dermatology. 6th ed. Oxford: Blackwell Scientific; 1998. p. 2257–75.
10. Bowler P, Duerden B, Armstrong D. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev. 2001;14(2):244–69.
11. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003;11:1–28.
12. Schmidt K, Debus ES, Jeßberger S, et al. Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous, and the arterial ulcer? Vasa. 2000;29:62–70.
13. Olivencia JA. Pathophysiology of venous ulcers: surgical implications, review and update. Dermatol Surg. 1999;25:880–5.
14. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet. 2003;361:1545–51.
15. Gardner SE, Frantz RA, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. Wound Repair Regen. 2000;9:178–86.
16. Bendy RH, Nuccio PA, Wolfe E, et al. Relationship of quantitative wound bacterial counts to healing of decubiti. Effect of topical gentamicin. Antimicrob Agents Chemother. 1964;4:147–55.
17. Robson MC. Wound infection: a failure of wound healing caused by an imbalance of bacteria. Surg Clin North Am. 1997;77:637–50.
18. Bowler PG, Davies BJ. The microbiology of infected and noninfected leg ulcers. Int J Dermatol. 1999;38:573–8.
19. Schraibman IG. The significance of beta-haemolytic streptococci in chronic leg ulcers. Ann R Coll Surg Engl. 1990;72:123–4.
20. Trengove NJ, Stacey MC, McGechie DF, et al. Qualitative bacteriology and leg ulcer healing. J Wound Care. 1996;5:277–80.
21. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. FEMS Immunol Med Microbiol. 1999;26:267–76.
22. Kingsley A. A proactive approach to wound infection. Nurs Stand. 2001;15:50–8.
23. Davies CE. The comprehensive analysis of the Microbial community of clinically non-infected chronic venous leg Review ulcers. PhD thesis. Department of Oral Surgery, Medicine and Pathology, University of Wales College of Medicine, Cardiff, UK; 2003.
24. Davies CE, Hill KE, Wilson MJ, et al. Use of 16S Ribosomal DNA PCR and denaturing gradient gel electrophoresis for analysis of the micro floras of healing and nonhealing chronic venous leg ulcers. J Clin Microbiol. 2004;42:3549–57.
25. Tentolouris N, Jude EB, Smirnof I, et al. Methicillin resistant Staphylococcus aureus: an increasing problem in a diabetic foot clinic. Diabet Med. 1999;16:767–71.
26. Bowler PG, Davies BJ. The microbiology of acute and chronic wounds. Wounds. 1999;11:72–8.
27. Urbancic-Rovan V, Gubina M. Infection in superficial diabetic foot ulcers. Clin Infect Dis. 1997;25:S184–5.
28. Kontiainen S, Rinne E. Bacteria in ulcera crurum. Acta Derm Venereol. 1988;68:240–4.
29. Hansson C, Hoborn J, Moller A, et al. The microbial flora in venous leg ulcers without clinical signs of infection. Acta Derm Venereol. 1995;75:24–30.
30. Brook I, Frazier EH. Aerobic and anaerobic microbiology of chronic venous ulcers. Int J Dermatol. 1998;37:426–8.

31. Ge Y, MacDonald D, Hait H, et al. Microbiological profile of infected diabetic foot ulcers. Diabet Med. 2002;19:1032–5.
32. Gilchrist B, Reed C. The bacteriology of chronic venous ulcers treated with occlusive hydrocolloid dressings. Br J Dermatol. 1989;121:337–44.
33. Jeandrot A, Richard JL, Combescure C, et al. Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected from non-infected diabetic foot ulcers: a pilot study. Diabetologia. 2008;51:347–52.
34. Newman LG, Waller J, Palestro CJ, et al. Unsuspected osteomyelitis in diabetic foot ulcers: diagnosis and monitoring by leukocyte scanning with indium and 111 oxyquinoline. JAMA. 1991;266:1246–51.
35. Dow G. Infection in chronic wounds. In: Krasner DL, Rodeheaver GT, Sibbald RG, editors. Chronic wound care: a clinical source book for healthcare professionals. 3rd ed. Wayne: HMP Communications; 2001. p. 343–56.
36. Robson M, Duke W, Krizek T. Rapid bacterial screening in the treatment of civilian wounds. J Surg Res. 1973;14:420–30.
37. Tenorio A, Jindrak K, Weiner M, et al. Accelerated healing in infected wounds. Surg Gynecol Obstet. 1976;142:537–43.
38. Wheat LJ, Allen SD, Henry M, et al. Diabetic foot infections: bacteriologic analysis. Arch Intern Med. 1986;146:1935–40.
39. Sapico FL, Ginunas VJ, Thornhill-Joynes M, et al. Quantitative microbiology of pressure sores in different stages of healing. Diagn Microbiol Infect Dis. 1986;5:31–8.
40. Ehrenkranz N, Alfonso B, Nerneberg D. Irrigation-aspiration for culturing draining decubitus ulcers: correlation of bacteriologic findings with a clinical inflammatory scoring index. J Clin Microbiol. 1990;28:2389–93.
41. Georgios S, Nicos L. The evaluation of lower-extremity ulcers. Semin Intervent Radiol. 2009;26(4):286–95.
42. Galiano RD. ACS surgery: Principles and Practice. Chapter 27 Lower - extremity ulcers. 2008:7.

Role of Bacteria in Pathogenesis of Lower Leg Ulcers

9

Waldemar L. Olszewski

9.1 Introduction

Lower leg ulcer is a circumscribed necrosis of epidermis, skin, and occasionally also muscular fascia, tendon, or even underlying bone with sluggish granulation and delayed covering by keratinocytes migrating from the ulcer margins. Following skin microinjury the colonization of denuded surface by local skin and floating down perineal bacterial flora takes place. The predisposing factors are venous stasis with excess capillary filtrate, high tissue fluid pressure, erythrocyte extravasation, hemosiderosis and fibrosis, or ischemia in atherosclerosis and diabetes with decreased arterial supply of nutrients, or lymph stasis with excess tissue fluid, high tissue fluid pressure and fibrosis, or excessive fat deposition in the subcutis in pathological obesity with excess tissue fluid and high tissue fluid pressure. The common denominator, irrespective of predisposing factors, is colonization of the denuded surfaces by bacteria. Although bacteria may not necessarily be the primary etiological factor, they certainly are responsible for progression of ulcer or delayed healing.

9.2 Hypothesis

There are several questions to be answered before we can achieve a progress in healing of ulcers. They are as follows: (1) Why does ulcer occur more frequently in the calf and foot than in the upper limbs or elsewhere, (2) is it local microtrauma that initiates ulcer development, (3) why does a rapid colonization of ulcer by skin residential bacteria develop so fast, (4) do perineal bacteria contribute to the ulcer

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colonization, (5) do the normally saprophytic skin bacteria become virulent once they colonize the denuded surface, (6) why do the colonizing bacteria proliferate rapidly increasing the bacteria cell mass, (7) which bacterial strains dominate, (8) are there dormant bacteria in calf subcutaneous tissue (persisters), (9) does a local cellular memory to bacterial antigens exist stimulating immediate recruitment of granulocytes and macrophages, and (10) is there autoimmune reaction to own granulocyte and tissue debris and insufficient granulocyte autophagy of incorporated bacteria?

This chapter will be specifically devoted to the factors predisposing for bacterial colonization and subsequent proliferation of bacteria in lower leg venous, ischemic, diabetic, and lymphedema ulcers.

9.3 Lower Limb Skin Bacteria

Human skin has been considered to harbor a complex microbial ecosystem, with transient, short-term resident and long-term resident biota, based on the consistency with which they are isolated. S*taphylococcus*, *Micrococcus*, *Corynebacterium*, *Brevibacteria*, *Propionibacteria*, *and Acinetobacter* species are, among others, regularly cultivated from normal skin. *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* may be transient colonizers, especially in pathological conditions [1, 2] . These strains colonize any denuded skin surface of lower limbs, among them ulcers.

9.4 Venous Ulcers

Venous insufficiency of the lower limbs is characterized by venous blood hypertension in the upright position and subsequent development of chronic edema, with elevated tissue fluid pressure and its adverse effects on fibroblasts producing and depositing collagen. Skin becomes fibrotic. Even a minor injury may denude the surface and create port of entry for bacteria dwelling on the epidermis or in the sweat and sebaceous glands. The exact mechanism of formation of ulcer in limbs with venous insufficiency remains unclear. A large defect in skin and subcutis develops. This precludes healing by wound contraction and leaves space for the granulation tissue. However, it remains unclear why covering by the keratinocytes encroaching from the ulcer edge is so sluggish and often does not occur at all. Keratinocytes remain morphologically and functionally normal. They synthesize cytokines and chemokines necessary in the healing process [3] . Vascularization of granulation tissue is abundant. However, the granulation surface is covered by granulocytes and cellular debris. This may be the effect of bacterial colonization and chemoattraction of granulocytes lysing granulation cells. An autoimmune mechanism to own destructed cells maintaining the inflammatory process cannot be excluded.

9.4.1 Do Bacteria Colonizing Ulcers Originate From Foot, Calf, and Perineal Skin?

In order to answer the question whether foot and ulcer flora may be similar to that of perineum, we cultured skin smears (Tables 9.1 and 9.2) and compared bacterial phenotypes. Out of 17 toe web isolates, 13 were of the same phenotype as perineal isolates.

Could bacteria be present in and around the varicose veins?

The exact etiology of varicose vein formation and development of ulcer is still full of questions. Are these two entities linked with each other? Could dormant persister bacteria in leg subcutaneous tissue be responsible for vein wall destruction and subsequently ulcer formation?

We tried to detect bacteria in the varicose veins and subcutis using two techniques. Biopsy material was homogenized and cultured in routine media, and in another method, it was placed on bacteriological culture plates and observed for 3 weeks. In this last technique, tissue environment for bacteria was preserved and plate contained erythrocytes (iron). This mimicked a normal tissue situation. In addition, bacterial 16sRNA was identified in specimens [4] .

9.4.2 Bacterial Isolates in Varicose Veins

In our studies, varicose veins specimen stage 4 (CEAP classification) revealed presence of bacterial isolates in 40 %, whereas controls taken from healthy cadaveric organ donors contained live bacteria in only 4 % (Table 9.3). Disinfected skin specimens from the sites of varicectomy showed presence of microbes in 4 %. The dominant isolates from vein specimens were *Staphylococci*, preponderantly

Table 9.1 Numerical prevalence of bacterial isolates from perineal skin ($n = 15$ patients)

Bacilli	Cocci	
Gram positive	Gram negative	Gram positive
Corynebacterium 5	Pseudomonas 1	Staphylococcus aur 5
	Acinetobacter 1	Staphylococcus
		Coagulase –ve 10
	E. coli 1	Enterococcus 2
		Aerococcus 1
		Micrococcus 2

Table 9.2 Numerical frequency of bacterial isolates from toe web skin ($n = 12$ patients)

Bacilli Gram negative	Cocci Gram positive
Citrobacter 2	Micrococcus 2
Proteus 2	Staphylococcus
	Coagulase –ve 20

Table 9.3 Bacteriology of varices of great saphenous veins (GSV)

Varicose GSV		Control GSV and femoral vein
Staphylococci: Coagulase neg	22	
Epidermidis	13	
Hominis	4	
Hemolyticus	2	
Capitis	1	
Warneri	1	
Intermedius	1	
S. aureus	10	1
Micrococcus spp.	2	
Branhamella catarrhalis	1	
Aerococcus viridans	1	
Enterococcus faecium	3	1
Acinetobacter	1	
Gemella morbil	1	1
Strept. mitis	1	
Pseudomonas		1

coagulase negative; however, in a few cases *Enterococcus faecium* was also detected. *Staphylococci* were highly sensitive to antibiotics except of penicillin (Table 9.4). Thirty-three percent of isolates were methicillin resistant. The 16sRNA was detected in 69 % of specimens, evidently higher than the percentage of live bacterial cells.

Bacterial culture on the Hemoline plates revealed microbes migrating from the outer aspect of varices, adjacent fat but not muscles (Fig. 9.1).

9.4.3 Bacterial Isolates on Ulcers

Bacterial phenotypes on ulcer exudate remain similar to those identified on adjacent skin; however, the numerical distribution of strains becomes different (Table 9.5). Strains of Gram-negative Bacilli dominate over others, and the number of colonies is tripled (Tables 9.6 and 9.7). This may be the result of more favorable environmental conditions on the granulation tissue for some strains or less favorable for others. Interestingly, bacteria cultured from the ulcer surface revealed increasing resistance to antibiotics compared with the flora taken from normal leg skin (Tables 9.8 and 9.9).

Our studies clearly showed that bacterial colonization and superimposed infections are common in venous leg ulcers and contribute to poor wound healing. Necrotic tissue is laden with bacteria, while devitalized tissue impairs the body's ability to fight infection and serves as a pabulum for bacterial growth [5].

Table 9.4 Sensitivity to antibiotics of bacterial isolates from varicose fragments of the great saphenous vein

	Staph. coagulase negative	Staph. aureus
Penicillin	32	27
Cotrimoxazole	95	91
Gentamicin	95	82
Erythromycin	68	63
Clindamycin	74	73
Tetracyclines	68	73
Minocycline	100	100
Vancomycin	100	100
Teicoplanin	100	100
Rifampicin	100	100
Nor/quinolones	74	91
Fusidic acid	79	91
Nitrofurantoin	84	91
Quinupristin	100	100
Oxacillin	73	67
Penicillin	32	27
Cotrimoxazole	95	91
Gentamicin	95	82
Erythromycin	68	63
Clindamycin	74	73
Tetracyclines	68	73
Minocycline	100	100
Vancomycin	100	100
Teicoplanin	100	100
Rifampicin	100	100
Nor/quinolones	74	91
Fusidic acid	79	91
Nitrofurantoin	84	91
Quinupristin	100	100
Oxacillin	73	67

$n = 40$ specimens (in %)

9.5 Can Bacterial Flora Be Eradicated or at Least Attenuated?

9.5.1 Systemic Antibiotics

A recent Cochrane Review of 22 randomized control trials of systemic and topical antibiotics and antiseptics for venous ulcer treatment found no evidence that routine use of oral antibiotics improves healing rates. No between-group differences were detected in terms of complete healing for comparisons: antibiotics given according to antibiogram versus usual care, ciprofloxacin versus standard care/placebo,

Fig. 9.1 Fragments of tissue harvested from ischemic upper calf. (*1*) Bone marrow, (*2*) popliteal vein, (*3*) subcutaneous fat, (*4*) popliteal artery, (*5*) fat adjacent to artery, (*6*) skin bacteria migrate from subcutis. Confluent bacterial colonies of coagulase-negative *Staphylococci* formed around the specimens. Interestingly, bone marrow contained hemolytic bacteria

Table 9.5 Numerical frequency of bacterial isolates from varicose ulcer ($n = 56$ patients)

	Bacilli Gram negative	Cocci Gram positive	
Aeromonas	1	Staphylococcus aur	19
Citrobacter	2	Staphylococcus coagulase – ve	9
Acinetobacter	6	Streptococcus	4
Pseudomonas	18	Enterococcus	16
Klebsiella	3		
Providencia	6		
Enterobacter	1		
E. coli	2		
Serratia	2		
Proteus	9		
Pasteurella	1		
Morganella	2		
Alcaligenes fec	4		
Gram-positive Corynebacterium	8		

trimethoprim versus placebo, ciprofloxacin versus trimethoprim, and amoxicillin versus topical povidone-iodine [6].

Oral antibiotics may be indicated in patients with venous ulcer and inflammation of the surrounding tissues. It should be treated with systemic Gram-positive bactericidal antibiotics.

9.5.2 Topical Antibiotics and Antiseptics

Topically applied antimicrobials can be effective. Cadexomer iodine: more participants were healed when given cadexomer iodine compared with standard care [6, 7]. No between-group differences in complete healing were detected when cadexomer

Table 9.6 Prevalence of bacterial strains isolated from leg varicose ulcers and calf skin surface of normal subjects

	Cocci				
	Staphylococcus coag-ve	Staphylococcus aureus	Streptococcus	Enterobacter	Gram (−) cocci, bacilli, coryneforms
Varicose ulcer	1[a]	32	11	15	41
Normal calf skin	37[b]	37	0[b]	0[b]	24[b]

18 patients with varicose ulcer, 30 normal subjects
[a]Percent of isolates
[b]$p < 0.05$

Table 9.7 Frequency of bacteria isolates on perineal skin, calf skin, toe web, and varicose ulcer (in %)

Site of isolation	Strains/patient	Cocci		Bacilli		
		Gram positive	Gram negative	Spore forming	Spore nonforming	
				Gram positive	Gram positive	Gram negative
Perineum	2.40	66.7	0	0	13.9	19.4
Calf skin	1.47	68.2	4.5	9.1	4.5	13.7
Toe web	2.16	84.6	0	0	0	15.4
Venous ulcer	4.84[a]	38.9[a]	0	0	7.9	53.2[a]

[a]$p < 0.05$

Table 9.8 Sensitivity to antibiotics of bacterial isolates from 18 varicose ulcers and leg skin of 30 normals

	Gram (−) cocci, bacilli, coryneforms				
	Varicose ulcer			Normals	
Antibiotic	+++	+		+++	+
Penicillin	14[b]	0		25	4
Kanamycin	0	33	[a]	100	0
Tobramycin	66	33		100	0
Gentamicin	66	16	[a]	100	0
Tetracycline	16	0	[a]	100	0
Erythromycin	33	33		45	8
Cotrimoxazole	32	16	[a]	80	0

[a]$p < 0.05$
[b]Percent of sensitive isolates

iodine was compared with the following: hydrocolloid dressing, paraffin gauze dressing, dextranomer, and silver-impregnated dressings. Povidone iodine: no between-group differences in complete healing were detected when povidone-iodine was compared with the following: hydrocolloid, moist or foam dressings according to wound status, and growth factor. Silver-based preparations: no between-group differences in complete healing were detected when 1 % silver sulfadiazine ointment was compared with standard care/placebo and tripeptide copper complex, when

Table 9.9 Sensitivity to antibiotics of bacterial isolates from 18 leg varicose ulcers and calf skin of 30 normal controls

	Cocci				
	Varicose ulcer			Normals	
Antibiotic	+++	+		+++	+
Penicillin	31[b]	12		28	2
Oxacillin	55	0	[a]	73	0
Kanamycin	25	8	[a]	44	8
Tobramycin	29	35	[a]	75	15
Gentamicin	48	22	[a]	85	4
Tetracycline	28	42		61	2
Minocycline	16	16	[a]	100	0
Erythromycin	43	13		59	8
Lincomycin	37	12	[a]	69	6
Pristinamycin	70	20		100	0
Fosfomycin	45	8		77	0
Rifampicin	77	14		91	9
Fusidic acid	63	27		77	18
Vancomycin	58	8	[a]	88	2
Cotrimoxazole	46	15	[a]	63	16

[a] $p < 0.05$

[b] Percent of sensitive isolates

different brands of silver-impregnated dressings were compared, or when silver-impregnated dressings were compared with non-antimicrobial dressings [6].

Other topical antibiotics: more ulcers healed at four weeks when treated with an enzymatic cleanser (a nonantibiotic preparation) compared with a chloramphenicol-containing ointment. No between-group differences in complete healing were detected for framycetin sulfate ointment versus enzymatic cleanser, chloramphenicol ointment versus framycetin sulfate ointment, mupirocin ointment versus vehicle, and topical antibiotics given according to antibiogram versus an herbal ointment [6] .

9.6 Arterial Ischemic Ulcer

Arterial ischemic ulcers develop in the calf or dorsum of the foot in cases with obstruction of large arteries after an incidental trauma, insect bite, and skin scratching. They should be differentiated from the diabetic ulcers by other location and lack of diabetes symptoms. They are usually painful with intensive peri-ulcer skin inflammation [8] . Restoration of flow is crucial to infection control in arterial ulcers and must be addressed first. However, the colonizing bacterial flora hampers healing.

We were trying to identify the source of bacteria in this type of ulcers. They could originate from the surface of adjacent skin and/or from the preexisting dormant perister forms in the deep soft tissues. In our studies we harvested, in nondiabetic patients, fragments of arteries, muscles, and lymphatics from lower limbs,

Table 9.10 Prevalence of various bacterial strains in arteries of the lower limbs in patients with critical lower bacteria limb ischemia undergoing amputation (no toe and foot necrosis) ($n=60$)

	Arteries	
Bacteria	Calf	Thigh
S. aureus	28[a]	18 (0[b])
S. coagulase negative	22	25 (0[b])
Micrococcus	4	11 (0[b])
Enterococcus	12	18 (0[b])
Aerococcus	4	0 (11)
Clostridium	0	3 (0[b])
Bacilli	2	0 (0)
Pseudomonas	4	14 (0[b])
Proteus	4	7 (0[b])
Klebsiella	2	4 (0[b])
Enterobacter	4	0 (0)
Serratia	0	4 (0[b])
Acinetobacter	4[a]	0 (0)
Citrobacter	2[a]	0 (0)
E. coli	0	0 (0)

In parentheses values of healthy cadaver organ donors ($n=27$) (in%) [9]
[a]Calf vs. foot or thigh $p<0.05$
[b]Ischemic vs. normal tissues $p<0.05$

amputated because of uncontrollable rest pain in multilevel arterial obstructions without peripheral necrosis [9]. In over 50 % arterial specimens contained live bacteria (Table 9.10).

9.6.1 Bacterial Isolates in Arterial Walls

In group I of 60 ischemic limbs specimens of tibial and popliteal arteries contained bacterial cells in 60.6 % and femoral arteries in 30.8 % In the healthy femoral arteries, microbial cells were isolated in 11 % (ischemic vs. controls, p <0.05). The Gram-positive bacteria were sensitive to all antibiotics but penicillin. *Enterococcus* was sensitive to vancomycin (Table 9.11).

Optical evaluation of colonies formed from migrating bacteria on Hemoline plates revealed dominance of *Staphylococci* (Fig. 9.2). They were present in arteries, muscles, and subcutis. Single colonies of highly pathogenic bacteria, as quoted above, could also be seen in some specimens. Interestingly, microbes were also present in the bone marrow.

9.6.2 Microbial DNA in Arterial Wall

In group I, out of 60 samples of tibial, popliteal, and femoral arteries, the 16 s RNA gene was detected in 70 %. In 25 normal femoral arteries revealed presence of 16sRNA in 21 %.

Table 9.11 Sensitivity of Gram-negative bacterial isolates from femoral and popliteal artery wall to antibiotics in patients with acute leg ischemia undergoing reconstruction or amputation (in % of specimens) [9]

	Enterococcus			Staphylococcus		
	Faecium	Fecalis	Durans	Epidermidis	Aureus	Haemolyticus
Penicillin	75	0	100	0	0	0
Ampicillin	75	–	100	50	–	–
Cephalosporin. 1 g	0	0	0	100	100	–
Erythromycin	0	0	0	33	50	0
Clindamycin	0	0	0	0	33	0
Tetracyclines	50	0	0	100	33	0
Cotrimoxazole	0		0	33	100	0
Rifampicin	0	100	0	100	100	100
Ciprofloxacin	0	0	0	33	100	–
Vancomycin	100	100	0	100	100	100
Teicoplanin	100	100	100	75	100	100
Nitrofurantoin	75	100	100	33	100	100
Oxacillin	0	–	0	0	50	–
Gentamicin	0	0	50	0	75	0
Kanamycin hc	0					

11 patients, 26 specimens, 27 bacterial isolates

	Pseudomonas	Proteus mirabilis	Acinetobacter	Citrobacter
Amo/penicill. gr.a	0	50	0	0
Amox/clav. ac	0	75	0	0
Piper + tazobactam	75	100	50	–
Ticarcillin	75	50	0	0
Ctx/caphalo. 3 g	50	100	50	0
Ceftriaxone	0	100	50	–
Ceftazidime	0	100	50	–
Aztreonam	75	100	0	–
Imipenem	75	100	50	–
Ceftazidime 1	0	100	50	–
Cotrimoxazole	0	50	0	–
Tobramycin	75	50	50	–
Amikacin	100	100	50	–
Gentamicin	75	50	50	100
Netilmicin	75	50	50	100
Pef/quinolones 2 g	60	50	50	100
Ciprofloxacin	100	100		100

The bacterial strains detected in deep tissues of ischemic limbs could be the main source of microbes potentially colonizing totally ischemic regions and bring about formation of ulcer or even necrosis of limb fragments.

Fig. 9.2 Fragments of varicose great saphenous vein and adjacent tissues. (*1*) Fat adhering to the vein, (*2*) varix placed with external wall on the plate, (*3*) muscle, (*4*) varix placed with intima on the plate. Confluent colonies of coagulase-negative *Staphylococci* formed around the specimens

Systemic administration of antibiotics is indicated in cases with acute inflammatory changes. The duration of therapy with high doses should depend on the systemic symptoms. Subsequently, taking into account presence of bacteria in deep tissues, low doses should be given even for months. Topical administration of antibiotics has not been proved effective; however, antimicrobials can be applied as in the venous ulcers.

9.7 Diabetic Foot Ulcer

Ischemia in diabetics results from atherosclerosis of the leg vessels, often bilateral, multi-segmental, and distal, involving arteries below the knee. Considerable data support the observation that 10^5 organisms/g of tissue are necessary for infection and to allow invasive sepsis for most types of bacteria [10–12] .

The immune system is impaired in diabetic patients, and we should be aware of factors that increase the risk of infection for neuro-ischemic ulcers including the long-term ulceration (>30 days), presence of loss of sensation, and comorbidities associated with immunosuppression, renal insufficiency, long-term steroid use, etc. [13].

Bacteria colonize the diabetic ulcers. They evoke a local host inflammatory reaction preventing healing. However, they may also cause inflammation of tissues surrounding the ulcer with systemic symptoms.

We studied the bacterial flora from the edges of diabetic ulcers or fistulae in Wagner' stage IV (Table 9.12). In contrast to the venous ulcers, bacterial flora contained Gram-negative *Bacilli* and few *Cocci.* They revealed high resistance to most antibiotics (Tables 9.13 and 9.14).

Systemic treatment with antibiotics is mandatory in diabetic ulcer with acute inflammation of the ulcer surrounding tissues. The topical administration of antibiotics has not been proved effective. The other antimicrobial therapy remains the same as for the venous ulcer.

Table 9.12 Bacterial isolates from the bottom of diabetic foot ulcer ($n=25$pts)

Enterococcus faecalis	1
Enterococcus casseliflavus	1
Proteus mirabilis	3
vulgaris	1
Acinetobacter spp.	1
E. coli	1
Leuconostoc spp.	1
Acinetobacter anitratus	1
Morganella morganii	1
Staph. aureus	3
epidermidis	1
Streptococcus pyogenes	1
Pseudomonas spp.	1

Table 9.13 Sensitivity to antibiotics of Gram-negative bacteria from foot ulcer of diabetic patients (in%)

G (−)			
Amo/penicill. gr.a.	60	40	
Amox/clav. ac	30	50	20
Pic/ureidopen.	44	44	12
Piper + tazobactam	20	70	10
Ticarcillin	60	40	
Cft/cephalo. 1 g	70	30	
Cft/cephalo. 3 g	60	40	
Ceftriaxone	44	44	12
Ceftazidime	30	50	20
Aztreonam	44	56	
Imipenem	20	80	
Ceftazidime 1	60	40	
Cotrimoxazole	20	80	
Tobramycin	30	70	
Amikacin	50	50	
Gentamicin	40	60	
Netilmicin	20	80	
Pef/quinolones 2 g	30	70	
Ciprofloxacin	30	60	10
Piperacillin	100		
Cefoxtine	100		
Cyclines	100		
Guinolones 1 gen	100		

Table 9.14 Sensitivity to antibiotics of Gram-positive bacteria from foot ulcer of diabetic patients

G (+)			
Penicillin	62	38	
Oxacillin	67	33	
Cft/cephalo. 1 g	25	62	13
Ampicillin-sulbactam	22	78	
Gentamicin	33	12	55
Netilmicin	38	62	
Erythromycin	44	33	23
Clindamycin	62	38	
Pef/quinolones 2 g	54	23	23
Ciprofloxacin	26	37	37
Tetracyclines	55	33	12
Cotrimoxazole	11	89	
Nitrofurantoin	22	78	
Rifampicin	44	56	
Vancomycin		100	
Teicoplanin		100	
Methicillin	75	25	
Penicilline g	100		
Kanamycine	100		
Tobramycine	100		
Minocycline	100		
Linconycine	100		
Pristinamycine		100	
Fosfomycine		100	
Acide fusidique		100	

9.8 Lower Limb Lymphedema Ulcer

Ulcer development is one of the complications in chronic lymphedema. Although not frequent, it is a very serious condition [14] . Ulcers are usually formed in the lower parts of calf or dorsum of the foot. Denuded skin surface is colonized by skin flora. Oozing of lymph precludes covering of the surface by ulcer edge keratinocytes. In addition, microbes present in the lymphedematous tissues and lymph enhance the local host immune reaction [15]. Patients with obstructive lymphedema suffer from recurrent attacks of dermatolymphangioadenitis caused by bacteria present in a dormant state in the stagnant tissue fluid and lymph (Tables 9.15 and 9.16) (Fig. 9.3). This microflora is responsible for nonhealing of ulcers and poor healing after the debulking surgery. Interestingly, the detected bacteria are sensitive to most antibiotics (Tables 9.17 and 9.18).

Lymphatic ulcer should be treated by debulking of the fragment of ulcerated tissue. Systemic antibiotics should be given perioperatively and for as long as wound

Table 9.15 Prevalence of bacterial isolates from specimens obtained from lower limb tissues, lymph and lymphatics, and nodes of patients with secondary lymphedema. In parentheses are values from 30 healthy volunteers

Specimen	Number of specimens		% of positive cultured
	Total	Positive	
Calf surgical incision swab	41	4	10 (7)
Leg lymph	20	12	60[a] (7)
Lymphatics and nodes	20	6	33[a] (0)

[a] $p < 0.05$

Table 9.16 Numerical prevalence of bacteria isolated from specimens obtained from lymph-edematous legs

	Surgical wound swab	Lymph	Lymphatics and nodes
Number of specimens	41	20	20
Micrococcus Species Luteus		2	2
Staphylococcus Aureus Epidermidis Hemolyticus Hominis	2 1	12 2 2 6 2	4
Enterococcus faecium		2	
Corynebacterium		1	

Fig. 9.3 Lymph sample from lower limb during acute dermatolymphangioadenitis was spread on the plate. Multiple colonies of *Staph. aureus* and coagulase-negative *Staphylococci*, few *Enterococci*

Table 9.17 Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incision, lymph and lymph nodes in 54 European patients with lymphedema of lower limbs and 30 normal control

	Gram cocci, bacilli, coryneforms			
	Lymphedema		Normals	
	+++	+	+++	+
Penicillin	67[a]	0	27	5
Cefotaxime	100	0	80	25
Kanamycin	67	0	100	0
Tobramycin	83	0	100	0
Amikacin	67	0	100	0
Gentamicin	86	14	100	0
Tetracycline	71	0	80	0
Quinolones	83	17	100	0
Cotrimoxazole	67	0	80	0

[a]Percent of isolates

Table 9.18 Sensitivity to antibiotics of bacterial isolates from skin surface, surgical skin incisions, lymph and lymph nodes of 54 European patients with secondary lymphedema of the lower limbs and 30 normal controls

	Cocci			
	Lymphedema		Normals	
	+++	+	+++	+
Penicillin	24[a]	0	28	2
Oxacillin	72	0	73	0
Methicillin	80	0	80	0
Kanamycin	68	6	44	8
Tobramycin	74	5	75	15
Gentamicin	79	3	85	4
Tetracycline	49	0	61	2
Minocycline	96	4	100	0
Erythromycin	49	4	59	8
Lincomycin	60	14	69	6
Pristinamycin	92	1	100	0
Fosfomycin	57	6	45	8
Nitrofurantoin	85	6	54	25
Quinolones	72	18	62	12
Rifampicin	91	6	91	9
Fusidic acid	81	11	77	18
Vancomycin	92	0	88	2
Teicomycin	92	0	79	0
Cotrimoxazole	78	4	80	0

[a]Percent of isolates

healing is not completed. Thereafter, long-term penicillin (Penidure) should be given in a dose of 1,200,000 u., i.m., every 3 weeks for 1 year or longer, to prevent recurrence of ulceration and dermatolymphangioadenitis attacks.

References

1. Kloos WE, Musselwhite MS. Distribution and persistence of staphylococcus and micrococcus species and other aerobic bacteria on human skin. Appl Microbiol. 1975;30:381–5.
2. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science. 2009;326:1694–7.
3. Galkowska H, Olszewski WL, Wojewodzka U. Keratinocyte and dermal vascular endothelial cell capacities remain unimpaired in the margin of chronic venous ulcer. Arch Dermatol Res. 2005;296:286–95.
4. Olszewski WL, Zaleska M, Stelmach E, Swoboda-Kopec E, Jain P, Agrawal K, Gogia S, Gogia A, Andziak P, Durlik M. Cryptic bacteria of lower limb deep tissues as a possible cause of inflammatory and necrotic changes in ischemia, venous stasis and varices, and lymphedema. Surg Infect. 2015;16(3):313–22.
5. Halbert AR, Stacey MC, Rohr JB, Jopp-Mckay A. The effect of bacterial colonization on venous ulcer healing. Australas J Dermatol. 1992;33:75–80.
6. O'Meara S, Al-Kurdi D, Ovington LG. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev. 2008;(12):CD003557.
7. Holloway GA, Johansen KH, Barnes RW, et al. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. West J Med. 1989;151:35–8.
8. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45(Suppl S):S5–67.
9. Andziak P, Olszewski WL, Moscicka-Wesolowska M, Interewicz B, Swoboda E, Stelmach E. Skin own bacteria may aggravate inflammatory and occlusive changes in atherosclerotic arteries of lower limbs. Int Angiol. 2012;31:474–82.
10. O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess. 2000;4:1–247.
11. Lipsky BA, Peters EJ, Berendt AR, Senneville E, Bakker K, Embil JM, Urbančič-Rovan V, Jeffcoate WJ, International Working Group on Diabetic Foot. Specific guidelines for the treatment of diabetic foot infections 2011. Diabetes Metab Res Rev. 2012;28 Suppl 1:234–5.
12. Lipsky BA, et al. 2012 infectious diseases society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:1679–84.
13. Galkowska H, Wojewodzka U, Olszewski WL. Low recruitment of immune cells with increased expression of endothelial adhesion molecules in margins of the chronic diabetic foot ulcers. Wound Repair Regen. 2005;13:248–54.
14. Karnasula VM. Management of ulcers in lymphoedematous limbs. Indian J Plast Surg. 2012;45:261–5.
15. Olszewski WL, Jamal S, Manokaran G, Pani S, Kumaraswami V, Kubicka U, et al. Bacteriologic studies of skin, tissue fluid, lymph, and lymph nodes in patients with filarial lymphedema. Am J Trop Med Hyg. 1997;57:7–15.

Venous Ulcer

10

Himanshu Verma and Ramesh K. Tripathi

10.1 Introduction

Chronic wounds in legs associated with clinical and radiological findings of chronic venous insufficiency are termed as venous ulcers. Venous ulcers are one of the most common types of leg ulcers. Different studies have reported its prevalence ranging from 0.7 to 2.4 %, which further increases with ageing population [1, 2]. Typically venous ulcers are recurrent in nature and therefore have a huge impact in treatment cost. In the United States, annual cost of venous ulcer treatment is over 2.5 billion dollars a year, and the annual estimated cost in the United Kingdom is 300–600 million pounds [3, 4].

American Venous Forum suggests the definition for a typical venous ulcer as "A full-thickness defect of skin, most frequently in the ankle region, that fails to heal spontaneously and is sustained by chronic venous disease (duplex studies)" [5].

Treatment of venous ulcer needs careful clinical evaluation, correct identification of contributory etiological factors, and extensive imaging to look for level of obstruction and/or reflux. Based on the above factors, the most appropriate therapy is chosen among array of treatment modalities available (e.g.: compression, endovenous thermal ablation, sclerotherapy, venoplasty and stenting, and deep valve reconstruction).

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10.2 Pathophysiology of Venous Ulceration

Venous hypertension is key factor in all stages of venous insufficiency. Before looking into pathophysiology of chronic venous insufficiency and venous ulceration, it is important to understand basic venous physiology.

Venous system drains the blood volume back to the heart to maintain circulation circuit. When in supine position, pressure gradient between arteriovenous segments drives this flow and is aided by negative intrathoracic pressure due to upward movement of diaphragm in expiration [6].

While in upright position, hydrostatic force of blood column increases venous pressure in foot. However when measured with a direct cannula in foot vein, foot pressures dramatically decrease after a few tiptoe exercises as calf muscles empty venous channels on walking. This pressure is called ambulatory venous pressure. In normal circumstances, resting pressure in foot veins on standing ranges from 90 to 120 mmHg. Upon 7–9 tiptoe exercises, this pressure falls to a mean of 22 mmHg. In cases with venous incompetence or poor calf muscle pump, resting foot vein pressures are high, and these does not decrease after tiptoe exercise, which overall results in venous hypertension (Fig. 10.1a, b) [6, 7]. Venous hypertension is key to all pathological changes occurring in chronic venous insufficiency.

Multiple hypotheses have been proposed for venous ulceration. Fibrin cuff theory states that there is leakage of fibrinogen in extravascular space, and over time

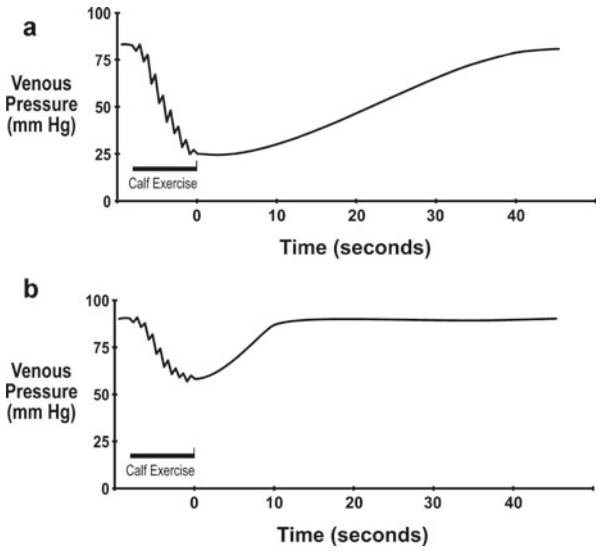

Fig. 10.1 (**a**) In a limb with normal venous pump, effects of exercise on calf volume and venous pressure measured on the dorsum of the foot. (**b**) Effects of exercise on calf volume and venous pressure measured on the dorsum of the foot in a patient with post-thrombotic syndrome and venous hypertension

pericapillary fibrin cuff is formed which causes ischemia of dermis making it prone for ulceration [8]. In another "leukocyte entrapment" theory, extravasation and activation of leucocytes has been given utmost importance, which further sets in a chronic inflammatory reaction [9].

Venous hypertension leads to extravasation of macromolecules and red blood cells, which further set in a secondary inflammatory reaction. Activated endothelial cells release vasoactive agents, inflammatory mediators, chemokines, express adhesion molecules, and prothrombotic precursors. Increased expression of ICAM-1, recruitment of leukocytes, and their endothelial transmigration leads to initiation of inflammatory cascades that have been regularly demonstrated in patients' venous ulcers. There is increased production of cytokines (TGF-β1, TNF-α, IL-1) and increased MMPs that have been shown to be a key component of development, chronicity, and the delay of healing of venous ulcers [8–10].

10.3 Clinical Assessment (Figs. 10.2 and 10.3)

Clinical assessment of patient with varicose veins should be carried out as outlined in Table 10.1. Additionally detailed examination of ulcer and surrounding is very important [11]. It is recommended to keep a photographic record of ulcers on every visit.

Assessment of calf muscle pump could be done clinically by looking at calf muscle volume and range of motion at ankle joint and comparing it with the contralateral side. Patients' psychological status should also be looked at, as long-lasting venous ulcers could precipitate severe depression [12]. Alternative diagnosis of ulcers in lower extremity should be ruled out specially if ulcer is present without background signs and symptoms of venous insufficiency or ulcer is present in atypical sites [13].

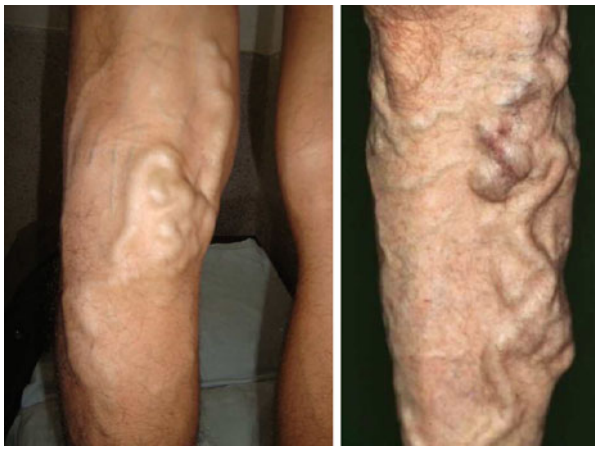

Fig.10.2 Varicose veins in popliteal region

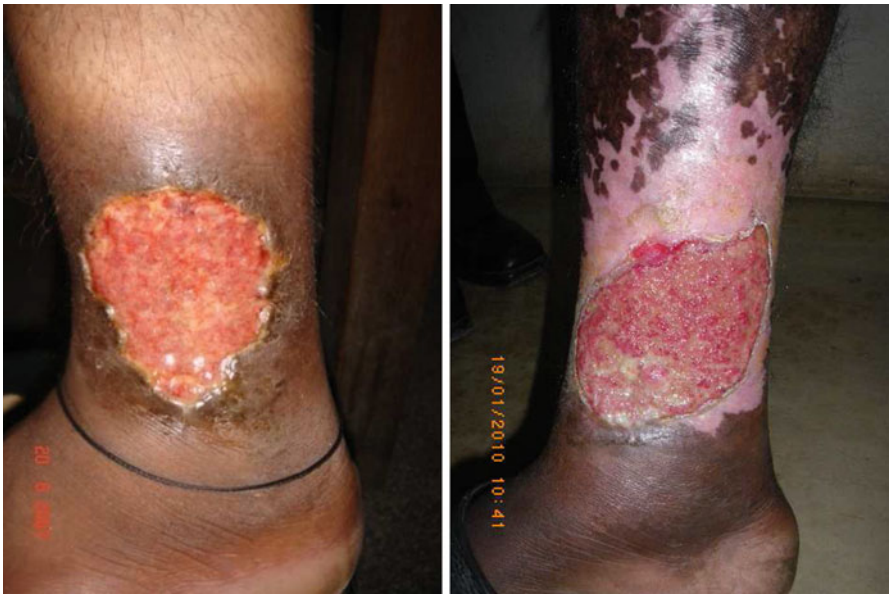

Fig. 10.3 Varicose ulcer

10.4 Investigations

There are multiple tests available to diagnose three key points in venous ulcer pathophysiology: (a) level and severity of obstruction, (b) level and severity of reflux, and (c) hemodynamic assessment of calf pump dysfunction. These tests could be categorized as noninvasive and invasive tests.

10.4.1 Noninvasive Investigations

- Venous duplex imaging
- Air plethysmography
- Photo plethysmography
- CT venogram
- MR venogram

10.4.2 Invasive Investigations

- Ascending and descending venography
- Ambulatory venous pressure
- Intravenous ultrasound

Table 10.1 Clinical evaluation

History
1. Basic details
(a) *Age*:
Younger, otherwise asymptomatic patients with family history: primary varicose veins
(b) *Female gender*: hormonal factors
(i) Primary: progesterone
(ii) Induced: oral contraceptive pills, postmenopausal hormone replacement therapy
(c) *Occupation*: disease of occupations involving prolonged standing
2. Chief complaints and history of present illness
Record symptoms and signs for each leg separately
(a) *Prominent veins*:
(i) Describe distribution of veins in patient's language, i.e., inner side of thigh, outer side thigh, inner /outer/aspect of leg/behind knee
(ii) Duration
(iii) Unilateral/bilateral
(iv) Associated symptoms: pure cosmetic or associated symptoms
(v) Any history of bleeding from veins
(b) *Leg swelling*:
(i) Unilateral/bilateral
(ii) In ankle region or in thighs as well
(iii) Relation to long-standing posture
(iv) Diurnal variation
(c) *Leg pain*:
(i) Anatomical distribution of pain
Most of patients with varicose veins have neurological claudication or knee joint disorder with associated asymptomatic varicose veins
(ii) Pain score (0–10): document to compare with posttreatment pain scores
(iii) Duration
(iv) Ask leading question:
Pain is in joints or in between joints (thigh/calf/leg)
Lower back pain
Multiple joint pains
Venous claudication
Venous claudication is defined as "bursting" thigh pain and "tightness" that develops during exercise in patients with iliofemoral venous thrombosis. Peripheral arterial disease is not a factor. The pathophysiology of venous claudication is related to the high outflow resistance associated with venous collaterals. Venous volume increases but proximal venous flow is unable to increase because of the fixed resistance of the collaterals, which results in the clinical syndrome
(d) *Itching*:
(i) Rule out localized itching due to skin disorder
(ii) Check for ongoing skin disorder treatment

(continued)

Table 10.1 (continued)

(e) *Night cramps*:		
(i) Frequency		
(ii) Variation		
(f) *Pigmentation*:		
(i) Pattern		
(ii) Progression		
(g) *Healed/active/recurrent ulcer*		
(i) Total number of ulcers		
(ii) Mode of onset of ulcer: spontaneous/traumatic		
(iii) Duration of ulcer; if healed, how long it took		
(iv) In recurrent ulcers: total number of events		
(v) If active soakage present: how many times dressing has to be changed		
3. Past history:		
(h) *Previous DVT*:		
(i) Direct evidence		
1. History of warf/acitrom intake		
2. Documented history of DVT		
3. History of regular INR monitoring		
(ii) Indirect evidence: especially if current symptoms started after the inciting event only		
1. History of acute onset painful swelling of lower limb in the past		
2. History of major orthopedic trauma/immobilization		
3. Major abdominal/neuro/ortho surgery		
4. Malignancy		
(i) *History of breathlessness*		
(i) Acute onset shortness of breath might be associated with episode of pulmonary embolism		
(ii) Chronic PE may result in pulmonary hypertension with secondary right heart failure		
4. Treatment history		
(i) Oral contraceptive use		
(ii) Hormone replacement therapy		
(iii) Oral anticoagulants		
5. Family history		
6. Personal history		
(a) Smoking		
7. Comorbidities		
Always to be recorded in all vascular cases		
	(✓?/×)	If yes: duration (years)
Diabetes		
Hypertension		
IHD		
Smoking		
Obesity		
Chronic renal failure		

Table 10.1 (continued)

Examination
Standing position in good light
(In presence of nurse when examining a female)
Inspection
1. Distribution of varicosities: GSV territory/SSV territory/other
(a) *Saphena varix*: blow out at saphenofemoral junction—look for visible cough impulse (Morrissey's sign)
(b) Lateral vein in thigh associated with limb hypertrophy and port-wine stain: *KT syndrome*
(c) Refluxing vein connecting GSV-SSV territory: *Giacomini vein*
(d) Abdominal veins: rule out IVC obstruction
2. Obvious limb swelling
(a) Differentiate from lymphedema (foot involvement)
(b) Differentiate from lipedema
3. Skin changes:
(a) *Redness*: local thrombophlebitis
(b) *Pigmentation*: distribution in leg
(c) *Lipodermatosclerosis* (LDS): localized chronic inflammation and fibrosis of skin and subcutaneous tissues of lower leg, sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which often is referred to as lipodermitis. LDS must be differentiated from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features
Try to pinch skin: in pigmentation it can be pinched easily whereas not in lipodermatosclerosis
(d) *Itching marks*
(e) *Atrophie blanche (white atrophy)*
Localized, often circular whitish, and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Sign of severe CVD, and not to be confused with healed ulcer scars. Scars of healed ulceration may also exhibit atrophic skin with pigmentary changes but are distinguishable by history of ulceration and appearance from atrophie blanche and are excluded from this definition
(f) *Corona phlebectasiae*
Fan-shaped pattern of numerous small intradermal veins on medial or lateral aspect of ankle and foot. Commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare
(g) *Eczema*: erythematous dermatitis, which may progress to blistering, weeping, or scaling eruption of skin of leg. Most often located near varicose veins but may be located anywhere in the leg. Usually seen in uncontrolled CVD but may reflect sensitization to local therapy
4. Characteristics of venous ulcer
(a) Site: premalleolar and malleolar region of ankle
(b) Superficial
(c) Sloping edges
(d) Healthy granulation tissue in base—if no infection
(e) Exudative, weepy
(f) Surrounding +/− skin maceration
(g) Pigmentation and lipedermatosclerosis in surrounding skin
Also inspect

(continued)

Table 10.1 (continued)

Scrotum for any obvious swelling
Groin for any lymph nodes
Abdomen for any previous abdominal surgery
Lateral aspect of thigh/knee for orthopedic procedures scar mark
Scar marks of any previous varicose vein surgery
Palpation
Feel the patient's legs from ankle to the groin in standing position
1. *SF junction reflux*:
Place middle and index finger tips over cribriform fossa. Ask patient to externally rotate the examined limb and flex at the knee 5–10°. Ask patient to cough with face turned to opposite side. Feel for an impulse on your fingertips
2. *Schwartz test*:
In the above test, place the other hand's index and middle finger at any point distal to SF junction in the anatomical course of GSV and feel the vibration transmitted by tapping at SF Junction. This indicates the level of serial valve incompetence in GSV starting from SF junction
3. *Trendelenburg test*:
Repeat the above in supine position and compress the SF junction and ask patient to rise into standing position and observe pattern of filling of distal veins
Note: Trendelenburg test can be performed by tourniquet application at different levels to check reflux from SF junction, mid-thigh perforator, above-knee perforators, and below-knee perforators following the same principle as the above
4. *SP junction reflux*:
Place middle and index finger tips over popliteal fossa just above the knee crease. Ask patient to extend the knee. Ask patient to cough. Feel for an impulse on your fingertips
5. *Perforator "blowouts"(Fegan's sign):*
Feel along the course of GSV and SSV and palpate any prominent defect in fascia with prominent varicose bulge, which may signify perforator incompetence at that level
6. *Modified Perthes test*:
With patient in supine position, limb is elevated and a tourniquet is tied below the saphenofemoral junction. Patient is then asked to walk for 50 m. Deep venous outflow obstruction is suspected if there is GSV or SSV
Varicosities or calf pain increase on walking
7. *Warning*: please remember all this may be possible in thin patients, and may not be visible or palpable in obese patients
8. Feel for thrill to rule out AV fistula
9. Check for *pedal edema*
(a) Pitting
(b) Nonpitting
(c) Brawny
10. Palpate all *peripheral arterial pulses* and record ankle-brachial index
11. *Measurements*
(a) Height
(b) Weight
(c) Limb length

Table 10.1 (continued)

(d) Limb circumference	
(i) Calf level: 10 cm below tibial tuberosity	
(ii) Thigh level: 15 cm above medial condyle of femur	
12. *Pes equinus*:	
Palpate and assess ankle movements: fixed flexion deformity is generally a contraindication for venous intervention	
Also palpate	
1. Groin for lymph nodes	
2. Abdominal/pelvic/testicular mass	
3. Direction of flow in abdominal veins, if present	
Auscultation:	
SF junction SP junction Bruit	
C E A P classification (Fig. 10.4)	
Clinical classification C0: no visible or palpable signs of venous disease C1: telangiectasies or reticular v C2: varicose veins C3: edema C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche C5: healed venous ulcer C6: active venous ulcer *S*: symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction *A*: asymptomatic	**Etiologic classification** Ec: congenital Ep: primary Es: secondary (post-thrombotic) En: no venous cause identified
Anatomic classification As: superficial veins Ap: perforator veins Ad: deep veins An: no venous location identified	**Pathophysiologic classification** Pr: reflux Po: obstruction Pr, o: reflux and obstruction Pn: no venous pathophysiology identifiable
Impression at end of history and examination	
1. Diagnosis? (CEAP)	
2. Does this patient have symptomatic venous disorder?	
3. Do his symptoms are purely due to varicose veins?	
4. Does this patient have primary of secondary varicose veins?	
5. Are symptoms severe enough to proceed for treatment?	
6. Does patient need other contributory symptoms to be treated first, e.g., back pain and knee joint pain?	

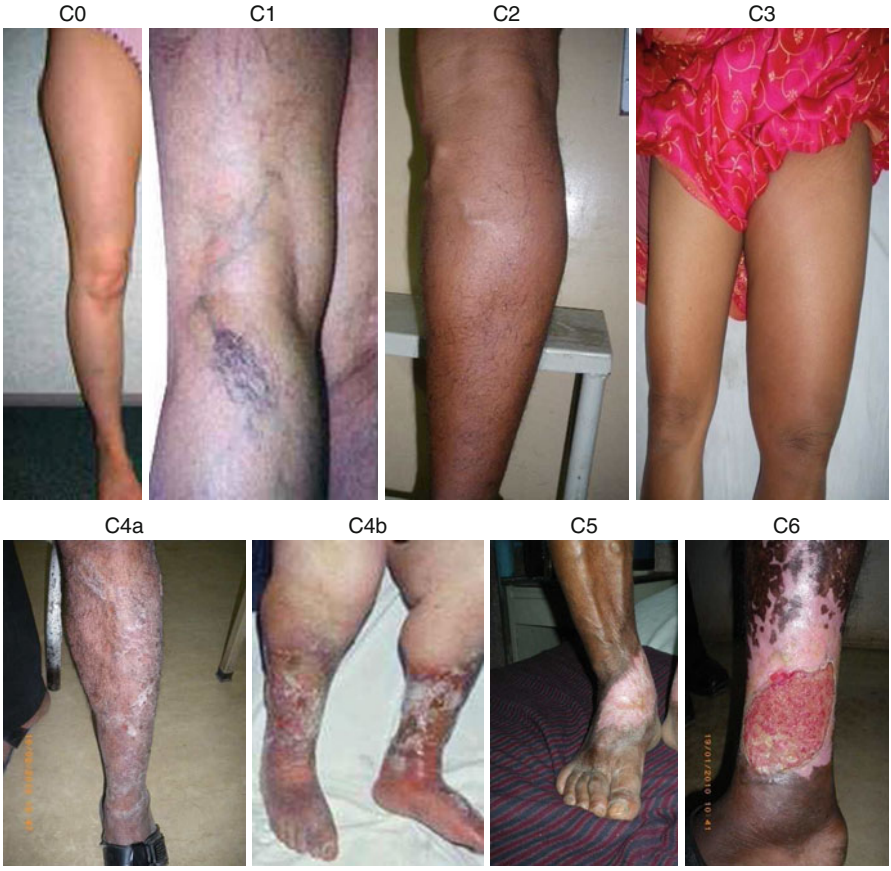

Fig. 10.4 CEAP

10.4.2.1 Noninvasive Tests

Venous Duplex Imaging

Venous duplex imaging has become the favored technique for evaluation of CVI to confirm the diagnosis and assess its etiology and anatomy. A venous duplex reflux examination combines B-mode and color-flow imaging of the deep and superficial veins and pulsed Doppler assessment of the direction of flow. The standard venous duplex examination assesses for venous thrombosis or obstruction as well as changes associated with chronic thrombotic disease which are the presence of an organized, hyperechoic, heterogeneous, noncompressible thrombus firmly adherent to the vein wall on DUS. Duplex ultrasound criteria used to differentiate acute, subacute, and chronic obstruction have been listed in Table 10.2 [14–18].

Reflux is assessed with provocative maneuvers, which may involve Valsalva maneuver or augmenting flow with distal limb compression in the reverse Trendelenburg position. The preferred method, however, involves the use of

Table 10.2 Duplex ultrasound criteria used to differentiate acute, subacute, and chronic obstruction

	Acute (days to weeks)	Subacute (weeks to months)	Chronic (months to years)
Size	Distended	No longer distended because of lysis	Reduced; sometimes unable to be traced by duplex ultrasound
Echogenicity	*Echolucent*: acute thrombi do not contain dense material	*Moderate echogenicity*: increased cellular components	*Echogenic*: as the clot ages, fibroblasts and collagen deposits form
Lumen characteristics	The lumen is noncompressible or partially compressible and often has spongy texture on compression	Recanalization with adherence of residual thrombus to the vein wall	Partial recanalization with filling defects and reflux may be present
Wall characteristics	Thin and smooth	Thickened	Thickening with luminal reduction as a result of an inflammatory response from the thrombus
Flow characteristics	Absence of flow/fillings defects	Partial recanalization	Partial recanalization with reflux
			Enhanced flow in dilated collateral veins
Thrombus characteristics	Presence of a tail	Decreased linear extension of the thrombus	
Collateral veins	Absent	May be present	Often found around the obstructed segments

rapid cuff inflation-deflation in the upright position [18]. Reversal of flow in the superficial venous system lasting longer than 0.5 s indicates valvular incompetence. Deep system reflux is considered abnormal when reversal of flow exceeds 1 s. Longer duration of reflux (or greater reflux times) and higher reflux velocities and volumes have been used to assess the severity of reflux [15, 16]. However, the severity of disease as determined by duplex imaging correlates weakly with clinical manifestations. Despite such limitations, the venous duplex reflux examination is considered the mainstay of noninvasive evaluation of CVI. It provides information about the anatomic distribution involving the deep, superficial, and perforator venous systems—useful information to help guide therapy.

Photoplethysmography (PPG)

PPG uses light absorbance by hemoglobin as a reflection of blood volume in the venous and capillary networks in the skin to estimate the degree of venous stasis. Relative changes in blood volume in the dermis of the limb are determined by measuring the backscatter of light with a probe containing a photosensor [19]. The PPG

probe is placed on the foot, followed by repetitive contraction of the calf muscles to empty blood from the veins of the foot. The time required for blood to refill the vessels of the skin, detected by increased backscatter of light, is determined after stopping muscle contraction. This venous refill time is the time required for the PPG tracing to return to 90 % of its baseline. The measure has been shown to correlate with invasive techniques for diagnosing CVI. A venous refill time of less than 18–20 s is indicative of CVI, whereas a venous refill time greater than 20 s suggests normal venous filling. The test does not provide specific information about anatomic distribution. There is poor correlation of the severity of disease as gauged by refill times with other methods because this parameter depends on factors such as reflux volume and capacitance of the reservoir. The technique has also been used to assess muscle pump function and venous outflow by measuring venous emptying during calf muscle contraction and limb elevation, respectively. Though capable of providing an assessment of overall venous physiologic function, PPG is most useful for determining the absence or presence of disease or CVI. It has best supplemental value with duplex to give overall anatomical as well as physiological diagnosis [19, 20].

Air Plethysmography

Air plethysmography (APG) is based on measurement of changes in limb volume by displacement of air in a cuff surrounding the calf during maneuvers to empty and fill the venous system. Air plethysmography is used to assess the contribution of each—reflux, obstruction, and muscle pump dysfunction, respectively.

Venous outflow is assessed during rapid deflation of a venous occlusive cuff placed on the proximal portion of an elevated limb. The primary parameter in assessing outflow is the outflow fraction at 1 s, with greater than 38 % being considered normal and less than 28 % indicating severe obstruction. Venous filling is evaluated by placing the limb in a dependent position, and the rate of refill is used to determine the presence and severity of reflux. The key parameter is the venous filling index, which is calculated by measuring 90 % of the venous volume and dividing this by the time required to fill 90 % of the venous volume after resumption of an upright position. The venous filling index is less than 2 mL/s in normal limbs, and values above 4 mL/s have been found to correlate with the severity of CVI. The venous filling index may be the best parameter for detection of abnormal reflux; it has a sensitivity of 70–80 % and a positive predictive value of 99 %. The function of the calf muscle pump is determined after a single and ten repetitive contractions during toe raises. The volume of blood ejected with one tiptoe maneuver divided by the venous volume is the ejection fraction. The severity of CVI has been shown to correlate with the venous filling index and ejection capacity. Air plethysmography provides quantitative information about global venous function and may be used to select and monitor response to intervention [21, 22].

CT Venogram

Visualization of Iliac veins and IVC is often limited in duplex examination. The development of high-resolution computed tomography (CT) with contrast enhancement has allowed extension of its use for the evaluation of venous disease. The

technique is most useful in the evaluation of centrally located veins and their surrounding structures to assess for intrinsic obstruction or extrinsic compression. Optimal imaging of the venous system requires the use of intravenous contrast material, with appropriate timing of image acquisition based on venous filling. Features suggestive of obstructive venous pathology in CT venogram could be narrowing of iliac veins, transpelvic or transpubic collaterals, eccentric filling defects, compression of IVC or iliac vein with iliac artery, etc. [23].

MR Venogram

Magnetic resonance imaging has been refined to allow detailed imaging of the venous system. This technique uses differences in the signal detected from protons within biologic tissue subjected to radiofrequency energy to assess flow within vessels and adjacent structures. The technique is useful to assess disease within veins of various sizes and provides utility in assessing obstructive disease and venous malformations. As with CT, magnetic resonance venography may provide useful anatomic detail before venous interventions. In comparison to CT, MR venogram delineates intraluminal webs, spurs, trabeculations, as well as wall thickening better [23].

10.4.2.2 Invasive Tests

Ascending Venography

Ascending venography is mainstay diagnostic tool for iliac vein obstruction available worldwide. Transfemoral ascending venography demonstrates obvious stenotic area, transpubic and trans-pelvic collaterals, filling defects, and trabeculations. Inflation of a semi-compliant balloon across suspected area of stenosis could demonstrate stenosis in the form of an hourglass waist. In cases where disease is extending in thigh, trans-popliteal or trans-short saphenous ascending venogram could be done for accurate delineation for suitable treatment of ilio-caval disease (Fig. 10.5) [24–26].

Descending Venography

Once obstruction is ruled out by ascending venography, descending venography is performed. Patient is strapped on table in 50–60 % of upright position. Contralateral common femoral vein or jugular approach is used to access. Contrast is injected into the IVC first for iliocavogram then into the segments of interest which are imaged sequentially. It is the definitive test to identify the level of reflux and the segment involved so is used for planning for valve repair or valve transplantation [27].

Kistner et al. developed a classification system used commonly to categorize the severity of deep venous reflux and the functional integrity of the venous valves (Table 10.3). With the use of descending venography, candidates are selected for deep venous valve repair or transplantation, which is offered to patients with grade 3 or 4 reflux who have recurrent symptoms of venous insufficiency after treatment of superficial varicosities and perforator venous incompetence [27].

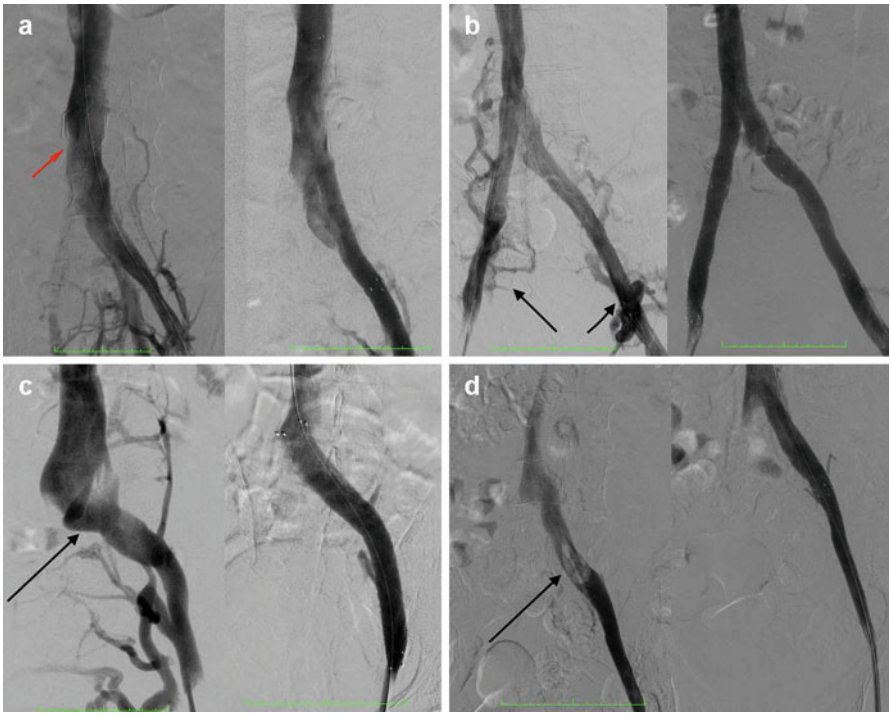

Fig. 10.5 Ilio-caval obstructive pathology on ascending venography and results following venous stenting. (**a**) Multiple recanalized veins along with previous IVC filter suggestive of post-thrombotic syndrome. (**b**) Multiple tens pelvic and trans-lumbar collaterals. Note disappearance of collaterals post stenting. (**c**) Classical "May-Thurner" syndrome: compression of the left iliac vein by the right iliac artery. (**d**) Filing defect in common iliac vein in a patient with chronic ilio-caval DVT and active venous ulcer

Table 10.3 Grades of venous reflux

Grade	Description
0	Normal valvular function with no reflux
1	Minimal reflux confined to the upper part of the thigh
2	More extensive reflux, which may reach the lower part of the thigh; a competent valve is present in the popliteal vein, and there is no reflux to the calf level
3	Reflux as above but associated with popliteal valvular incompetence and leakage of contrast material into the calf veins
4	Virtually no valvular competence with immediate and dramatic reflux distally into the calf; this type of reflux often opacifies incompetent calf perforators

From Kistner et al. [27] and Herman et al. [49]

Intravascular Ultrasonography (IVUS)
It is the gold standard investigation for assessment of ilio-caval obstruction. It is mainly used for intraluminal anatomic evaluation of the veins. So it is very useful for assessing valves, venous wall, side branches, webs and trabeculations, thrombus, external compression, or stenosis as well as in diagnosis and endovascular management of May-Thurner syndrome and accurate placement of stents. However, the unavailability at majority of centers in the world and higher cost are limitations in routine use of IVUS [28, 29].

10.5 Treatment

10.5.1 Lifestyle Modification

It has been shown that poor mobility and exercise status are major factors in recurrence of venous ulcers. Supervised exercise therapy is focused on weight loss, increasing angle plantar flexion and dorsiflexion range of motion, and increasing calf muscle strength to improve healing of ulcer and decrease ulcer recurrence [30].

10.5.2 Compression Therapy

Single-layer compression therapy with graduated pressure stockings is standard first-line treatment for all stages of chronic venous insufficiency. It applies graded external compression to the legs and opposes the hydrostatic forces of the venous hypertension. An external compression of maximum 60 mmHg has been shown to be safe even in patients with an ankle-brachial index of 0.5 and above. Treatment with 30–40 mmHg compression stockings results in significant improvement in pain, swelling, skin pigmentation, activity, and well-being if compliance of 70–80 % is achieved [31].

The commonly used compression therapy includes elastic stockings, multilayered bandaging, and nonelastic paste gauze boots.

Multilayered bandage provides rapid decrease in venous hypertension in active venous ulcers. So in authors' practice, multilayered bandage is added specially if there is calf muscle dysfunction to heal ulcers faster. Once healing is achieved, compression is switched over to compression stockings. SVS guidelines do not suggest compression bandages or stockings if the ankle-brachial index is 0.5 or less or if absolute ankle pressure is less than 60 mmHg [32].

However, poor compliance to all type of compression therapy has been a historical problem. Also requirement of lifelong compression and recurrence after discontinuing compression makes compression only as supporting treatment and not definitive therapy for venous ulcers.

10.5.3 Pharmacological Therapy

Many drug formulations have been tried for venous insufficiency, but most of them failed to prove to be advantageous over placebo.

Flavonoids
Flavonoids affect leukocytes and the endothelium by modifying the degree of inflammation and reducing edema. A micronized purified flavonoid fraction, Daflon, has been shown to reduce edema-related symptoms as either primary treatment or in conjunction with other therapy [33].

Pentoxifylline
It has been found to be useful in ulcer healing when used along with compression therapy. Mechanism is still not explained [33].

Aspirin and other antiplatelets have been used for healing of ulcer but their role is still not defined [33].

10.5.4 Wound and Skin Care

Noninfected ulcers should be dressed with normal saline; although a variety of the dressings are available, none of them are found to be advantageous over saline if the underlying venous pathology is corrected. For infected ulcers, silver-impregnated dressings are found to be effective in controlling infection and restoring tissue integrity. If exudates are excessive, hydrocolloid dressings should be used for soaking it and to prevent excoriation of the surrounding skin. Skin care includes proper hygiene and moisturization of the skin to prevent tissue breakdown due to dryness which may act as portal for infection and cellulitis [33, 34].

10.6 Treatment of Superficial Venous Reflux

10.6.1 Open Surgery

10.6.1.1 High Ligation of the Saphenous Vein
The great saphenous vein is ligated at its junction with femoral vein along with ligation of all six tributaries around saphenofemoral junction (SFJ). However, ligation alone without GSV stripping has shown very high rate of recurrence [33, 35].

10.6.1.2 Great Saphenous Vein Stripping
It is one of the classic operations for the varicose veins. Objective here is to remove the entire GSV and avulse the tributaries and perforators, so as to reduce the chances of recurrence.

Under general, regional, or tumescent anesthesia, a groin crease incision is made and SF junction is dissected out. All tributaries of GSV at SFJ are identified and

ligated with care. After high ligation of the SFJ and transection from the great saphenous vein (GSV), the vein stripper is introduced from the end of GSV at the knee level and advanced up SFJ where the head of the stripper is delivered from the great saphenous vein at the transected end. The head of stripper is ligated to the end of GSV which is now invaginated, and the whole vein is stripped inside out. Incision sites are closed and compression stockings are applied.

When stripping is done for below-knee GSV, the chances of saphenous nerve injury are high; hence, foam sclerotherapy or avulsion stab phlebectomy should be done. Risk of hematoma formation is also high [33, 35].

10.6.1.3 Ambulatory Phlebectomy

This is the procedure to remove the bulging varicosities on an outpatient basis, under local anesthesia. Muller developed the stab avulsion method that is now in widespread use. The characteristics of Muller's AP technique are absence of venous ligatures, exclusive use of local infiltration anesthesia, immediate ambulation after surgery, 2-mm incisions, absence of skin sutures, and a postoperative compression bandage kept in place for 2 days then replaced with daytime compression stockings [36].

10.6.1.4 Endovenous Thermal Ablation

Endovenous thermal ablation with LASER or radiofrequency is based on the principle of heat-induced thermocoagulation of vein wall proteins. This is followed by brief period of compression resulting in permanent closure of superficial refluxing veins.

Procedure is performed under local tumescent anesthesia with ultrasound guidance followed by thermal ablation. Saphenous vein is percutaneously accessed and the catheter advanced cephalad toward the saphenofemoral junction. Tumescent anesthesia is given around the vein. Purpose of tumescent anesthesia is to absorb heat generated by catheter therefore decreasing chances of skin burn, shrink the vein to increase catheter vein wall contact area to achieve improved thermocoagulation, and avoid injury to saphenous nerve and prevent postoperative paresthesia. Mobility is resumed almost immediately, and the patient is encouraged to walk as much as possible specifically in initial weeks following procedure.

Endovenous thermal ablation has become gold standard treatment for superficial axial reflux. It is less morbid than open surgery and essentially a day-care procedure. It has significant reduction in perioperative pain and wound-related complications when compared to open surgery and has similar long-term occlusion rates [33, 37].

There has been many studies comparing LASER vs RFA; however, there has been no significant difference in outcomes, although a few studies have shown lesser perioperative pain with RFA closure [37, 38].

10.6.1.5 Foam Sclerotherapy

Foam sclerotherapy works on the principal of chemical-induced endothelial damage, which sets in thrombosis and eventually fibrosis. Sclerosants in their "foam" constituency have been used to decrease the total dosage required as well as increase total contact time, as stable foam stays in vein and replaces blood column. Mostly it has been used to treat smaller size of veins, i.e., reticular and thread veins and small

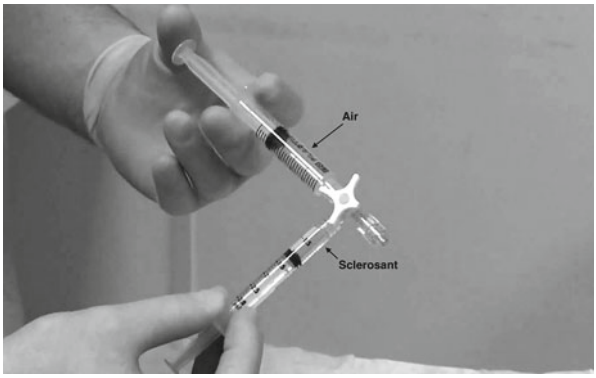

Fig. 10.6 Foam sclerotherapy with Tessari technique

varicose veins. However, the use of sclerotherapy in combination with LASER or RFA has shown better results.

A form of stable foam is prepared by Tessari technique (Fig. 10.6). The sclerosant is diluted with CO_2 or O_2 or air in a ratio of 1:4 sclerosant—air dilution and a foam created by mixing them by 25 passage to and fro in two syringes. It is injected in the veins under ultrasound guidance.

Common sclerosing solutions used are 1 and 3 % sodium tetradecyl sulfate, 1 and 3 % polidocanol sodium morrhuate, and 20 % hypertonic saline [38].

Painful thrombosis of varicosities is the most common complication seen, which if occurs is managed by a small nick on the hardened vein to release the inflamed thrombus. Usually it results when there is lack of adequate compression or foam has been given in very large varicosity.

In practice larger varicosities may be removed surgically by stab phlebectomy along with GSV ablation, whereas smaller varicosities are treated with foam sclerotherapy [38, 39]. In patients with active venous ulcer, foam sclerotherapy of perforators underneath the ulcer bed is an important adjuvant therapy.

10.7 Treatment of SSV Reflux

Treatment of isolated SSV reflux is matter of debate. However, if iliac vein obstruction has been either ruled out or corrected, isolated SSV reflux is treated in similar way as GSV reflux, either by open surgery or by endovenous ablation with or without foam sclerotherapy [33, 40] (Table 10.3).

10.7.1 Treatment of Deep Venous Obstruction

Ilio-caval venous obstruction has been recognized as one of the major contributor to chronic venous insufficiency. It is classified as primary or non-thrombotic iliac vein lesions (NIVLs) and post-thrombotic iliac vein obstruction. Plain angioplasty in venous stenosis has shown to have severe recoil, and stenting is always

recommended after a significant stenosis is identified. Raju et al. have shown an excellent 5-year patency of iliac vein stenting. However, primary and secondary 5-year patency markedly dropped from limbs with NIVLs to limbs with post-thrombotic limbs (79 and 100 %, 57 and 86 %, and 54 and 74 %, respectively) [41]. The use of IVUS during iliac vein stenting has helped to diagnose missed lesions and accurate assessment of venous stenosis [28].

In situations where stenotic/occlusive disease is extending below the inguinal ligament, either stents could be extended below the inguinal ligament. Alternatively endovenectomy of common femoral vein ensuring good inflow from profunda vein could be combined with iliac vein angioplasty and stenting [26, 46].

10.7.2 Treatment of Deep Venous Reflux

Majority of venous ulcers heal with the combination of compression therapy, ablation of superficial reflux, and correction of deep venous reflux. Raju et al. showed that after correction of iliac vein obstruction, many patients still might be having residual reflux, but ulcer heals despite its presence [34].

However, a small subgroup of patients with venous ulcer, who either have primary valvular insufficiency or Kistner grade 2–4 reflux with active venous ulcer after iliac vein stenting, may benefit from deep vein valve reconstruction [33]. There are many strategies of deep vein valve repair that are out of scope for discussion in this text but can be referenced from their source [41–46].

10.8 Recurrent Venous Ulcer

The biggest disappointing event for patient as well for treating doctor is recurrence after initial healing. However, this needs careful evaluation. Adequacy of previous procedure is first assessed. If previously patient underwent superficial venous ablation, repeat duplex should be done to look for any evidence of missed anterior accessory vein, incomplete ablation, or recanalization of great saphenous vein.

In case of previous iliac vein stenting, a repeat venogram should be done to check for missed cranial or caudal stenotic area, in stent stenosis or occlusion [47, 48].

Conclusion

Venous ulcers are multifactorial. Accurate assessment of all contributory factors is required. Compression therapy is recommended in most of patients. Endogenous treatment of superficial reflux should be done if significant reflux is found. Correction of iliac vein obstruction with angioplasty and stenting is needed in the presence of obstructive disease. Selected subgroup of patients may benefit from deep vein valve repair. Upon recurrence of ulcer, a thorough evaluation should be done to look for any missed or new area of reflux or obstruction.

References

1. Rabe E, Pannier-Fischer F, Bromen K, et al. Bonner Venenstudie der DeutschenGesellschaftfürPhlebologieepidemiologischeUntersuchungzurFrage der Häufigkeit und Ausprägung von chronischenVenenkrankheiten in der städtischen und ländlichenWohnbevölkerung. Phlebologie. 2003;32:1–14.
2. Fischer H. Venenleiden-EinerepräsentativeUntersuchung in der Bundesrepublik Deutschland (TübingerStudie). München: Urban und Schwarzenberg; 1981.
3. Simka M, Majewski E. The social and economic burden of venous leg ulcers: focus on the role of micronized purified flavonoid fraction adjuvant therapy. Am J Clin Dermatol. 2003;4(8):573–81.
4. Nelzen O. Leq ulcers: economic aspects. Cost effectiveness analysis of leg ulcers. Phlebology. 2000;15:110–4.
5. O'Donnell TF Jr, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, Lurie F, Henke PK, Gloviczki ML, et al. Society for Vascular Surgery; American Venous Forum. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2014;60(2 Suppl):3S–59.
6. Meissner MH, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg. 2007;46:4S–24.
7. Pollack AA, et al. Venous pressure in the saphenous vein at the ankle in man during exercise and changes in posture. J Appl Physiol. 1949;1:649–62.
8. Burnand KG, et al. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. BMJ. 1982;285:1071–2.
9. Falanga V, et al. The "trap" hypothesis of venous ulceration. Lancet. 1993;341:1006–8.
10. Coleridge Smith PD, et al. Causes of venous ulceration: a new hypothesis. BMJ. 1988;296:1726–7.
11. Abbade LP, Lastória S, Rollo Hde A. Venous ulcer: clinical characteristics and risk factors. Int J Dermatol. 2011;50(4):405–11.
12. Jones J, Barr W, Robinson J, Carlisle C. Depression in patients with chronic venous ulceration. Br J Nurs. 2006;15(11):S17–23.
13. Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. Semin Interv Radiol. 2009;26(4):286–95.
14. Ruckley CV, Evans CJ, Allan PL, Lee AJ, Fowkes FG. Chronic venous insufficiency: clinical and duplex correlations. The Edinburgh Vein Study of venous disorders in the general population. J Vasc Surg. 2002;36(3):520–5.
15. Labropoulos N, et al. Definition of venous reflux in the lower-extremity veins. J Vasc Surg. 2003;38:793–8.
16. Neglen P, et al. Hemodynamic and clinical impact of ultrasound-derived venous reflux parameters. J Vasc Surg. 2004;40:303–10.
17. Lurie F, et al. Multicenter assessment of venous reflux by duplex ultrasound. J Vasc Surg. 2012;55:437–45.
18. Markel A, et al. A comparison of the cuff deflation method with valsava's maneuver and limb compression in detecting venous valvular reflux. Arch Surg. 1994;129:701–5.
19. Nicolaides AN, et al. Photoplethysmography in the assessment of venous insufficiency. J Vasc Surg. 1987;5:405–12.
20. Abramowitz HB, et al. The use of photoplethsmography in the assessment of venous insufficiency: a comparison to venous pressure measurements. Surgery. 1979;86:434–41.
21. Criado E, et al. The role of air plethysmography in the diagnosis of chronic venous insufficiency. J Vasc Surg. 1998;27:660–70.
22. Shiraishi Y. Relationship between arterial inflow rate and venous filling index of the lower extremities assessed by air plethysmography in subjects with or without axial reflux in the great saphenous vein. Ann Vasc Dis. 2014;7(3):306–11.

23. Arnoldussen CW, de Graaf R, Wittens CH, de Haan MW. Value of magnetic resonance venography and computed tomographic venography in lower extremity chronic venous disease. Phlebology. 2013;28((Suppl 1)):169–75.
24. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology. 1957;8:419–27.
25. Negus D, Fletcher EW, Cockett FB, Thomas ML. Compression and band formation at the mouth of the left common iliac vein. Br J Surg. 1968;55:369–74.
26. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg. 2006;44(1):136–43.
27. Kistner RL, Ferris EB, Randhawa G, Kamida C. A method of performing descending venography. J Vasc Surg. 1986;4(5):464–8.
28. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg. 2002;35(4):694–700.
29. Raju S, Kirk OK, Jones TL. Endovenous management of venous leg ulcers. J Vas Surg: Venous Lymp Disordrs. 2013;1(2):165–72.
30. Heinen MM, van der Vleuten C, Uden CJ, de Rooij MJ, Evers AW, van Achterberg T. Physical activity and adherence to compression therapy in patients with venous leg ulcers. Arch Dermatol. 2007;143:1283–8.
31. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2012;(11): CD000265.
32. Partsch H, Clark M, Mosti G, Steinlechner E, Schuren J, Abel M, et al. Classification of compression bandages: practical aspects. Dermatol Surg. 2008;34:600–9.
33. O'Donnell Jr TF, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, Lurie F, Society for Vascular Surgery; American Venous Forum, et al. Management of venous leg ulcers: clinical practice guidelines of The Society for Vascular Surgery ® and the American Venous Forum. J Vasc Surg. 2014;60(2 Suppl):3S–59.
34. Rodeheaver GT. Wound cleansing, wound irrigation, wound disinfection. In: Krasner D, Kane D, editors. Chronic wound care: a clinical source book for healthcare professionals. Wayne: Health Management Publications; 1997. p. 97–108.
35. Sarin S, Scurr JH, Coleridge Smith PDC. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. Br J Surg. 1992;79:889–93.
36. De Roos KP, Neumann HA. Muller's ambulatory phlebectomy for varicose veins of the foot. Dermatol Surg. 1998;24(4):465–70.
37. Johnson CM, McLafferty RB. Endovenous laser ablation of varicose veins: review of current technologies and clinical outcome. Vascular. 2007;15(5):250–4.
38. Biemans AA, Kockaert M, Akkersdijk GP, van den Bos RR, de Maeseneer MG, Cuypers P, et al. Comparing endovenous laser ablation, foam sclerotherapy, and conventional surgery for great saphenous varicose veins. J Vasc Surg. 2013;58(3):727–34.
39. Nesbitt C, Eifell RK, Coyne P, Badri H, Bhattacharya V, Stansby G. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for great saphenous vein varices. Cochrane Database Syst Rev. 2011;(10):CD005624.
40. Gibson KD, Ferris BL, Polissar N, et al. Endovenous laser treatment of the short saphenous vein: efficacy and complications. J Vasc Surg. 2007;45:795–801.
41. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. J Vasc Surg. 1994;19:391–403.
42. Neglén P, et al. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg. 2007;46:979–90.
43. Raju S, Fredericks R. Valve reconstruction procedures for nonobstructive venous insufficiency: rationale, techniques, and results in 107 procedures with two- to eight-year follow-up. J Vasc Surg. 1988;7:301–10.
44. Perrin M. Reconstructive surgery for deep venous reflux: a report on 144 cases. Cardiovasc Surg. 2000;8:246–55.

45. Tripathi R, Sieunarine K, Abbas M, Durrani N. Deep venous valve reconstruction for non-healing leg ulcers: techniques and results. ANZ J Surg. 2004;74:34–9.
46. Verma H, Rajesh S, Tripathi R. Reduction internal valvuloplasty (RIVAL) is a new technical improvement on plication internal valvuloplasty for primary deep vein valvular incompetence. J Vasc Surg: Venous Lymp Dis. 2014;2:383–9.
47. Reeder SWI, Céline E, BirgitteMaessen-Visch M, Kees-Peter de Roos HA, Martino N. Recurrence of venous leg ulceration. Rev Vasc Med. 2013;1(4):63–5.
48. McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, Daniel PF, Keagy BA. Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. J Vasc Surg. 2002;35(4):723–8.
49. Herman RJ, Neiman HL, Yao JS, et al. Descending venography: a method of evaluating lower extremity venous valvular function. Radiology. 1980;137:63–9.

Arterial Ulcer

11

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11.1 Introduction

Arterial ulcers, commonly referred to as ischemic ulcers, are wounds that won't heal due to inadequate arterial blood flow or low perfusion pressure to the tissues of lower extremities. Precipitating events to the arterial ulcers vary. Such impairment can occur acutely (e.g., trauma, thrombosis) or chronically (e.g., atherosclerosis). Both acute and chronic arterial insufficiency can lead to the formation of lower extremity ulcers. Arterial insufficiency can occur at any level, from large arteries to arterioles and capillaries. Tissue ischemia that leads to leg ulcers tends to occur more in the setting of large vessel or mixed disease [1, 2]. For proper treatment of leg ulcers, it is important to be aware of the different types of leg ulceration, their clinical features, and the various diagnostic and treatment modalities.

11.2 Epidemiology

It is thought that the incidence of ulceration is rising as a result of aging population and increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes. A number of epidemiological studies have been conducted and have found a similar prevalence of leg ulceration ranging from 0.11 to 0.18 % of the general population [3–5]. In diabetic population, about 15 % will be affected with

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foot ulcers during their lifetime and about 85 % of all amputations are preceded by an ulcer [6]. Worldwide most common chronic wounds are because of chronic venous disease and represent 65 % of ulcers on the leg followed by arterial and neuropathic ulcers, which together make 95 % of leg ulcers.

11.3 Etiology

Arterial ulceration can be caused due to involvement of large to medium-sized and small-sized vessels. The most common cause is atherosclerotic disease of the large- and medium-sized arteries. Small vessel involvement is seen in vasculitis which leads to blood vessel stenosis/occlusion with resultant tissue ischemia, especially in the presence of palpable pulses. Other causes include diabetes, thromboangiitis, pyoderma gangrenosum, thalassemia, and sickle cell disease, some of which may predispose to the formation of atheroma. The etiology of arterial ulcer is mentioned in Table 11.1 [7].

Table 11.1 Etiology of arterial ulcer

Arterial occlusion
Peripheral arterial disease (arteriosclerosis)
Diabetes
Arterial thrombosis/macrothromboembolism and microthromboembolism (fibrin, platelets)
Fat embolism (hypercholesterolemia, hyperlipidemia)
Detachment of cholesterol-containing plaques from aorta, aneurysm, or atrium (atrial fibrillation)
Thromboangiitis obliterans (Buerger disease)
Arteriovenous anastomosis (congenital/traumatic)
Trauma, rupture, infection, vascular procedures
Fibromuscular dysplasia
Microcirculatory disorders
Raynaud phenomenon, scleroderma
Hypertension: ulcus hypertensivum (Martorell ulcer)
Increased blood viscosity (increased fibrinogen level, paraneoplastic, paraproteinemia, leukemia)
Blood transfusion reactions
Vasculitis
Small vessel: small vessel-leukocytoclastic vasculitis, microscopic polyangiitis, Wegener granulomatosis, allergic granulomatosis (Churg–Strauss), Henoch–Schonlein purpura, essential cryoglobulinemic vasculitis, erythema induratum Bazin, livedo reticularis, livedo vasculitis, and Sneddon syndrome
Medium-sized: polyarteritis nodosa, Kawasaki disease
Large vessel: giant cell arteritis (polymyalgia rheumatica, Takayasu arteritis)
Hematological disorders
Sickle cell anemia, other forms of anemia, thalassemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, essential thrombocythemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythemia, leukemia, monoclonal dysproteinemia (Waldenstrom disease, myeloma), polyclonal dysproteinemia (cryofibrinogenemia, purpura, hyperglobulinemia, cold agglutinins)

Arterial ulceration almost always involves bony high point and is due to pressure necrosis where the relatively mild pressures involved are sufficient to cause ischemia where the arterial perfusion pressure is low.

Arterial ulcers are associated with pain making them very distinct from venous ulcers. Vascular pain is a complex issue leading to sympathetic changes causing skin hyperalgesia, dystrophic skin with shinny appearance.

According to a recent report, chronic kidney disease (CKD), hypertension, and myocardial ischemia may also be associated with increased risk of developing foot ulcers including severe ulcers that necessitate amputation [8].

11.4 Clinical Features

11.4.1 History and Assessment

The first step toward diagnosis of any leg ulcer is to compile a comprehensive history and assessment of the patient (Table 11.2) [9]. This should include general health status, social and occupational situation, past and current medical history of relevant diseases (such as deep vein thrombosis, diabetes, autoimmune disorders, inflammatory bowel disease, and connective tissue disease), condition of the skin, current vascular status, limb size and shape, and history and status of the ulcer.

The patient should be asked about lower extremity pain, paresthesia, anesthesia, and claudication. It is important to determine the duration of ulceration and whether it is a first episode or recurrent. Pain is a major problem for patients with leg ulcers unless there is a neuropathic component. Lack of pain, therefore, suggests a neuropathic etiology. Patients should also be asked about their mobility.

A typical arterial ulcer is located distally in extremities (toes, heels, and bony prominences of the foot) and usually present with nocturnal rest pain. The ulcer appears "punched out," with well-demarcated edges and a pale, nongranulating, often necrotic base (Fig. 11.1a), which differentiates it from other types of ulcers (Table 11.3). The surrounding skin may exhibit dusky erythema and may be cool to touch, hairless, thin, and brittle, with a shiny texture. The toe nails thicken and become opaque and may be lost [10]. Gangrene of the extremities may also occur.

Vasculitic ulcers tend to have some characteristics similar to ischemic ulcers, including their location, size, and shallow depth. There are several typical differences, however. Vasculitic ulcers frequently have irregular shapes and borders (Fig. 11.1b). Additionally, the floor of the wound tends to be necrotic with significant vascularity. The surrounding skin is usually hyperemic rather than pale. Vasculitis may also feature other cutaneous manifestations, including palpable purpura, petechiae, and persistent urticaria [1].

A rare condition exists called Martorell ulcer (Fig. 11.1c), seen in patients with prolonged, severe, or suboptimally controlled hypertension [11]. The ulceration is secondary to tissue ischemia caused by increased vascular resistance. The ulcers are usually located at the lower limb, above the ankle region, contain black necrosis and are extremely painful. By definition, the distal arterial pulsations are normal, and the diagnosis is made by histological examination, which shows concentric intima thickening and marked hypertrophy of the media of small-sized and medium-sized

Table 11.2 Characteristics of different types of ulcers

Cause	Site/no	Size/shape	Floor/base	Edge	Surrounding skin	Pain	Associated Vasc Sx
Arterial	Malleoli Foot (dorsum) Ant. shin	Small, punched out	Deep Poorly developed Necrotic Minimal granulation Little bleed	Flat ± gangrenous	Lack inflammation Pale mottled ±gangrene	Yes Significant	Rest pain Claudication P.Hx ulcers or surgery or angioplasty or tissue loss
Venous	Gaiter	Often large and messy	Shallow Granulating	Sloping	Lipodermatosclerosis ±2° lymphedema ± atrophie blanche	Yes	No arterial Sx unless combined. Previous Ulcers/DVT/ compression Rx etc.
Neuropathic	Pressure areas – foot (great and little toe), May be Charcot's foot	Deep	Often based on joint/tendon/bone Indolent	Indolent	Look for deformity of the foot ±Callus Acute on chronic inflammation	No	No vascular Sx unless superimposed PVD
Infective	Atypical position	Variable	±Granulation, slough	Variable	Variable Cellulitis May be normal	Variable	Well-perfused skin, no chronic changed unless chronic infection
Trauma	Atypical	Ragged in some cases	Bleeding, Should granulate	Trauma dependent	Often normal	Yes	Hx trauma
Vasculitis	Often multiple	Small	Inflamed, indurated base	Variable	± rash/inflammation. Background of palpable purpuric change	Yes	Look for skin/joint/CREST/ genital/serosal/constitutional manifestations/deep organ manifestations

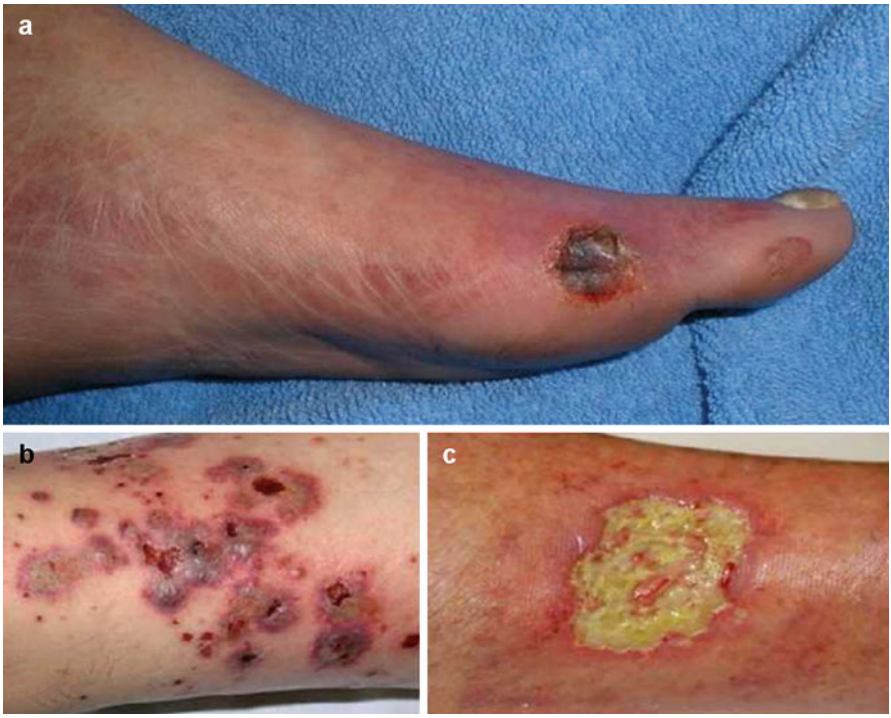


Fig. 11.1 (**a**) Arterial ulcer, (**b**) vasculitic ulcers, (**c**) Martorell ulcer

arteries, and by exclusion of other conditions that may cause ulceration in this area. The differential diagnosis consists of arteriosclerotic occlusion of small-sized arteries, diabetic angiopathy, vasculitis, thromboembolic occlusion (e.g., in atrial fibrillation), and pyoderma gangrenosum. Treatment consists of reducing hypertension, adequate control of pain, and local wound care [12].

Examination of the arterial system may show a decreased or absent pulse in the dorsalis pedis and posterior tibial arteries. There may be bruits in the proximal leg arteries, indicating the presence of atherosclerosis.

Clinical course of the ulcer can suggest its etiology. Possible considerations to rule out include diabetes; hypertension; hyperlipidemia; coronary artery disease; alcohol and tobacco use; thyroid, pulmonary, renal, neurologic, and rheumatic diseases; and specifically cutaneous factors including cellulitis, trauma, and recent surgery.

11.5 Diagnosis

Diagnosis includes blood investigations for risk factor screening and noninvasive and invasive vascular investigations.

Table 11.3 History and assessment of the patient with limb ulcer

Patient
History of ulcer development
Past and current medical problems
General health status
Nutrition
Social, occupation
Mobility problem
Limitations to self-care
Obesity
Skin changes
Arterial
Malignant
Autoimmune
Vascular assessment
Pedal pulses
Ankle–brachial pressure index
Limb factors
Edema
Circumferences
Lymphedema
Orthopedic problems
Sensation and pain
Ulcer
Site-venous, arterial, pressure
Appearance
Size measure
Wound base
Exudate level
Surrounding skin

11.6 Blood Investigations

Blood investigations such as complete blood count, erythrocyte sedimentation rate, blood sugar, lipid profile, renal function tests, and liver function tests are essential in patients with chronic leg ulcers.

Laboratory screening tests for vasculitis: urine analysis for proteinuria, hematuria, cylindruria, routine and immunohistopathology of skin biopsies, antinuclear antibodies, rheumatoid factor, complement C4, circulating immune complexes, paraproteins, immunoglobulin fractions, antineutrophil cytoplasmic antibodies (ANCA), serological tests, and cultures for underlying infections [13].

11.7 Vascular Investigations [7]

Vascular investigations aid in the management of the arterial ulcer and also aid in differentiating the type of ulcer.

11.7.1 Ankle–Brachial Index (ABI)

Ankle–brachial index of less than 0.90 is considered abnormal. ABI for PAOD vary from <0.80 to <0.97,9 [14, 15], and a cutoff value of <0.9 is 97 % sensitive for isolated aortoiliac disease and 89 % sensitive for femoropopliteal disease. More than 50 % of patients with PAOD due to an abnormal ABI may not have limb ischemia but a decrease in their functional activity limiting their quality of life. Furthermore, for most of the described studies in the last two decades, the screening value for PAOD is defined by a resting ABI ≤0.9. Less than 0.45: severe, limb threatening.

11.7.2 Toe Systolic Pressure Index (TSPI)

In diabetics arterial disease tends to be more severe and widespread. In addition, calcification of the media is common in these patients, making it difficult to measure ankle pressures. However, because medial calcification does not extend into the digital arteries, it is possible to assess perfusion pressure by measuring toe systolic pressure using either a strain-gauge sensor or a photoplethysmograph. In measuring toe pressure, it is important to record both the absolute pressure and the index. Normally, the TSPI should be >0.60. Variability of the measurement is ±17 %. The absolute levels of systolic pressure may be of value in estimating the healing potential when an ulcer is present. If the absolute pressure is ≤30 mmHg, healing is unlikely to occur without some form of intervention [14].

11.7.3 Transcutaneous Oxygen Tension (TcPO2)

Transcutaneous oxygen tension ($TcPo_2$) measurement is a noninvasive diagnostic study that provides information about the supply and delivery of oxygen to the underlying microvascular circulation by recording the partial pressure of oxygen at the skin surface. The amount of oxygen detected by the sensor is a balance of oxygen delivery and local physiologic demands and reflects the metabolic status of the skin. The $TcPo_2$ measurement is used in determining amputation level, wound healing evaluation, hyperbaric therapy, and peripheral arterial disease assessment, including the status of spinal cord stimulation and revascularization procedures. For wound healing to occur, studies found that the $TcPo_2$ should be >40 mmHg, and impaired wound healing is noted with values between 20 and 40 mmHg.

11.7.4 Duplex Ultrasound Scan

Duplex scan uses the combination of gray scale (B-mode) for vessel morphology and color pulsed wave Doppler techniques. It is safe and inexpensive and can provide functional information about vessel stenosis. The primary criteria of intra-arterial peak systolic velocity (PSV) and ratio of PSV between the site of stenosis and adjacent normal vessel are used to gauge the degree of stenosis. Duplex ultrasound scan has a sensitivity of 99 % and 80 % and a specificity of 94 % and 91 % for the femoropopliteal and tibial segments, respectively, as compared with arteriography. Duplex scanning also is useful in follow-up studies of patients who have undergone some form of intervention. In particular, patients who have undergone femoropopliteal or distal saphenous vein grafts [16] benefit from close follow-up because 20 to 30 % develop myointimal hyperplastic lesions that can be detected by duplex scanning before graft failure occurs.

11.7.5 Contrast Tomography (CTA) and Magnetic Resonance (MRA) Angiography

Advances in both CTA and MRA provide clinicians with the opportunity to obtain a high-resolution, 3-dimensional (3-D) road map of the peripheral arterial tree in patients, particularly when planning revascularization strategies.

MRA can be performed using contrast-enhanced (CE-MRA) approach or noncontrast-enhanced, flow-sensitive techniques that take advantage of the difference in signal properties between static tissue and flowing blood. These noncontrast MRA techniques include time-of-flight (TOF) MRA, ECG-gated partial-Fourier fast spin echo (FSE), and steady-state free precession (SSFP).

CTA requires the use of iodinated contrast media for visualization of the vasculature. Injection rates vary depending on protocol but typically are in the range of 4–6 mL/s delivered intravenously by a dual channel power injector. Main disadvantage other than limitations in patients with renal impairment is noted in vessels with dense calcifications which have high attenuation and may lead to blooming artifact and resultant overestimation of stenosis [17].

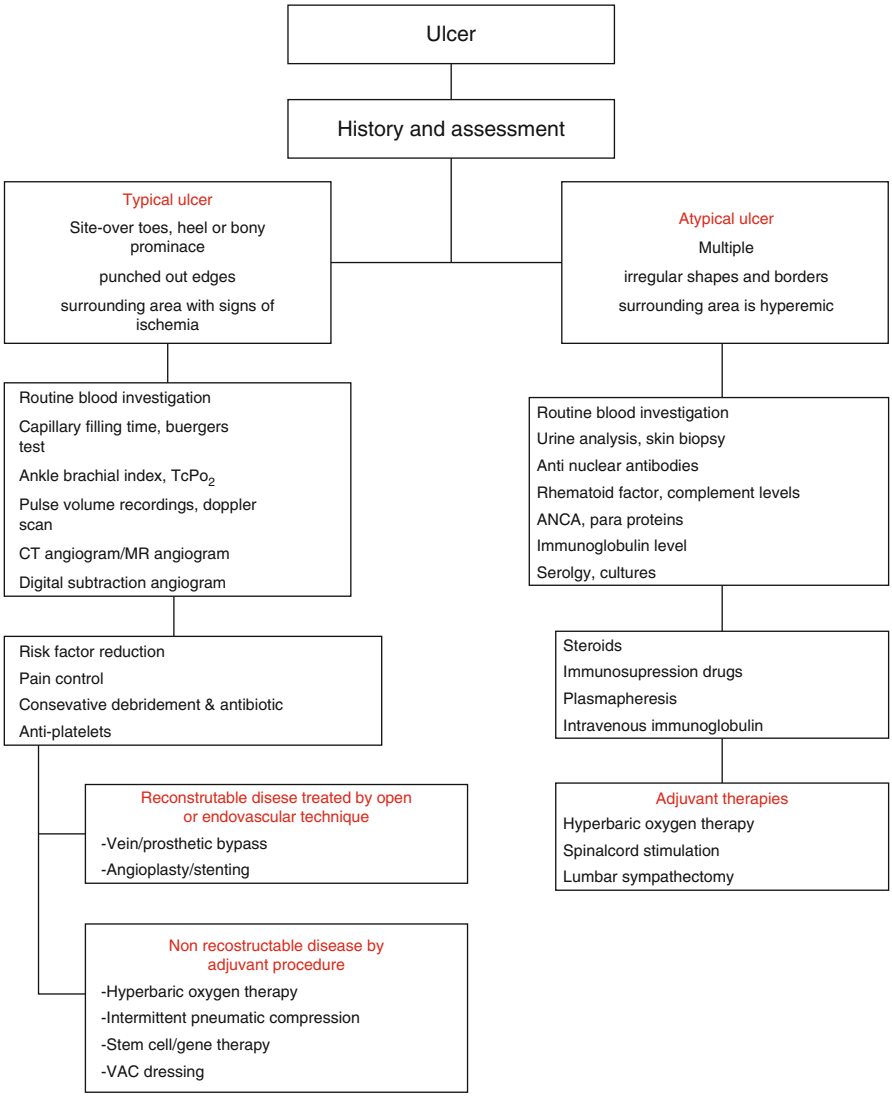
11.7.6 Digital Subtraction Angiography

Invasive digital subtraction angiography (DSA) has been the accepted standard for evaluation of lower extremity atherosclerosis. Although DSA is a robust technique for diagnosing significant arterial stenosis or obstruction, it provides a 2-D view of the vessels, which may underestimate the degree of stenosis for tortuous vessels.

Invasive digital subtraction angiography has the advantage of dual role in the management of arterial ulcer where the diagnosis and treatment of the lesion can be achieved at the same time avoiding multiple procedures and investigations.

The main disadvantages are the arterial puncture with the risk of local complications (i.e., hematoma), allergic reactions, and the development of contrast-induced nephropathy particularly in patients with preexisting renal disease or cardiac failure [6]. The risk of contrast nephropathy can be reduced by pre-procedure intravenous hydration. Given these risks, DSA should preferably be performed once the decision to perform a revascularization has been made.

11.8 Algorithm of Arterial Ulcer Management



11.9 Treatment

Wound healing in patient with underlying peripheral vascular disease may be further disturbed by a complex interplay of several other factors such as the presence of necrotic tissue, infection, poor glycemic control, abnormal mechanical loading of the ulcer, and comorbidities. Treatment should therefore also be focused on intensive wound care, treatment of infection, blood glucose control, biomechanical offloading, and treatment of comorbidities.

The impact of peripheral arterial circulation on wound healing depends on its hemodynamic significance. Well-collateralized, localized peripheral arterial disease (PAD) may have minimal effect on healing, whereas poorly collateralized, multisegmental PAD can prevent wound healing or lead to progressive tissue loss.

The primary goal of the treatment of arterial ulcers is to increase circulation to the area, either surgically or medically.

Management of arterial ischemic ulcers classically includes:

- Risk factor reduction
- Antiplatelet medication
- Lipid-lowering agents
- Pain control
- Conservative debridement
- Improvement of circulation
- Treatment is also directed at the pathogenic causes of arterial disease
- Adjuvant therapies

11.9.1 Risk Factor Reduction

Risk factor reduction is the most significant issue to be addressed in peripheral vascular disease. Risk factor reduction also involves lifestyle modification which includes regular exercise, cigarette smoking cessation, and diet management. Other risk factor reductions include control of diabetes mellitus, elevated homocysteine levels, hyperlipidemia, and hypertension [7].

Regular exercise therapy coupled with risk factor modification, especially smoking cessation, is the mainstay of conservative therapy for intermittent claudication. In fact, critical review of the available literature suggests that exercise therapy is the most consistently effective medical treatment for this condition [18].

Cigarette smoking is the most significant independent risk factor for the development of chronic peripheral arterial occlusive disease and is associated with the progression of established disease and a higher likelihood of disabling claudication, limb-threatening ischemia, amputation, and the need for intervention [19]. In addition, many observational studies report poorer patency of lower extremity vascular reconstructions among smokers [20]. Because of the adverse general health effects of cigarette smoking and the marked increase in morbidity and mortality from cardiopulmonary causes among smokers, patients with intermittent claudication should be vigorously counselled to stop smoking.

11.9.2 Antiplatelet and Vasodilator Medication

Antiplatelet therapy may modify the natural history of chronic lower extremity arterial insufficiency. The beneficial effect of aspirin and clopidogrel is most likely due to prevention or retardation of platelet thrombogenesis on the surface of atherosclerotic plaque; experimental and clinical trial evidence suggests that aspirin has no effect on the progression of atherosclerosis [21].

Vasodilation and antiplatelet effects of certain drugs could theoretically improve fibrinolytic activity, improving arterial insufficiency and minimizing ulceration. Vasodilators, although commonly used in the past, failed to increase blood flow and did not relieve symptoms. Vasodilators are ineffective because large vessel dimensions are fixed by the atherosclerotic process and collaterals are maximally dilated in patients with intermittent claudication. Rheologic agents like pentoxifylline, a methylxanthine derivative are used in treatment of intermittent claudication with limited benefits. In patients with peripheral arterial disease, pentoxifylline has been reported to improve abnormal erythrocyte deformability, reduce blood viscosity, and decrease platelet reactivity and plasma hypercoagulability.

11.9.3 Lipid-Lowering Agents

Lipid-lowering agents mainly statins or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors significantly reduce coronary events in patients with hypercholesterolemia. HMG-CoA reductase inhibitors block the endogenous synthesis of cholesterol and lower LDL levels. Additionally statins have an anti-inflammatory effect on the plaque and help cease the atherosclerotic process.

11.9.4 Pain Control

Patients with rest pain or worsening claudication, or both, and a nonhealing ulcer should be referred to a vascular surgeon. Significant pain is common in patients with arterial ulceration and may be exacerbated by dressing changes; opioid analgesia may be necessary during the wait for surgery.

11.9.5 Pressure Area Management

Poorly fitting footwear may create pressure areas that lead to further ulceration. Patients need to be advised to wear well-fitting, closed footwear. Refer to a podiatrist or orthotist should be made if specialized footwear is required.

11.9.6 Conservative Debridement and Antibiotics

Infection can cause rapid deterioration in an arterial ulcer, and treatment with systemic antibiotics should be started.

Initially, these should be treated empirically (with broad-spectrum penicillin or macrolide or quinolone antibiotics) until definitive culture and sensitivities are available. It is not appropriate to debride arterial ulcers as this may promote further ischemia and lead to the formation of a larger ulcer [10].

11.9.7 Improvement of Circulation

Revascularization options include endovascular and open surgical interventions. Endovascular techniques include angioplasty with or without stenting in order to restore normal blood flow to the ischemic site (Figs. 11.2, 11.3, and 11.4). Open surgeries include endarterectomy for isolated lesions especially in common femoral artery [22], anatomical bypass (aorto-bifemoral/aortoiliac/femoropopliteal/femorodistal bypass) or extra-anatomical bypass (axillo-bifemoral/fem–fem crossover) (Fig. 11.5).

11.9.8 Endovascular Intervention

In recent years, there has been a dramatic increase in the use of interventional radiological procedures for the treatment of acute and chronic lower extremity arterial disease. This reflects advances in vascular imaging that have made percutaneous transluminal angioplasty (PTA) more feasible, the development of newer intravascular stents, and the more widespread use of intra-arterial thrombolysis for the treatment of peripheral arterial thrombosis.

Although the majority of patients with symptomatic aortoiliac disease do not require an invasive intervention, for those with incapacitating claudication or

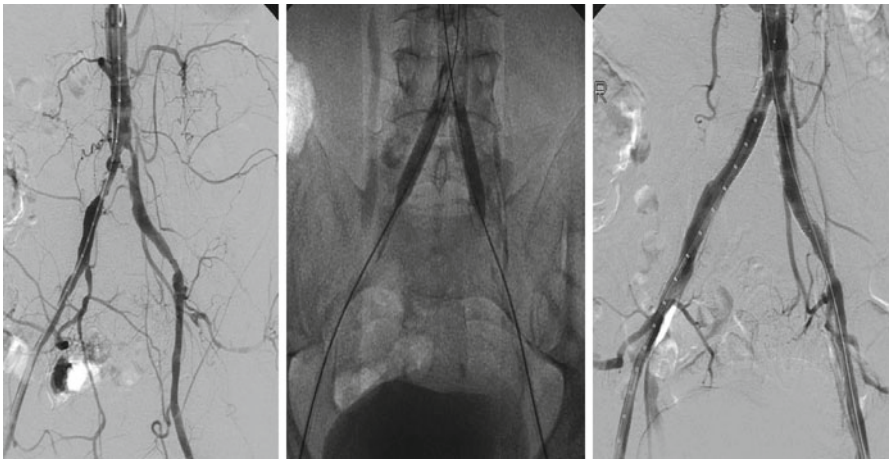


Fig. 11.2 Aortoiliac stenting

limb-threatening ischemia, angioplasty and lower extremity bypass surgery are the two major therapeutic options. Currently, the primary indications for an interventional procedure in patients with lower extremity arterial disease include: (i) incapacitating claudication interfering with work or lifestyle and (ii) limb salvage in patients with limb-threatening ischemia as manifested by pain at rest, nonhealing ulcers, and/or infection or gangrene.

Factors predictive of a favorable outcome included claudication as the indication for the procedure, a stenotic rather than occlusive lesion, good distal runoff, and a more proximally situated lesion.

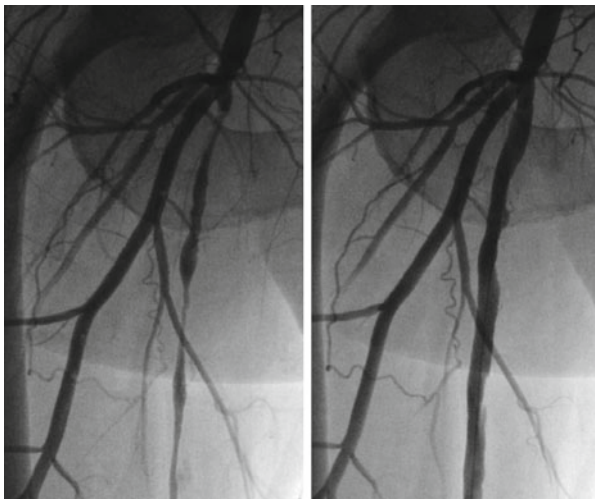


Fig. 11.3 Superficial femoral artery angioplasty

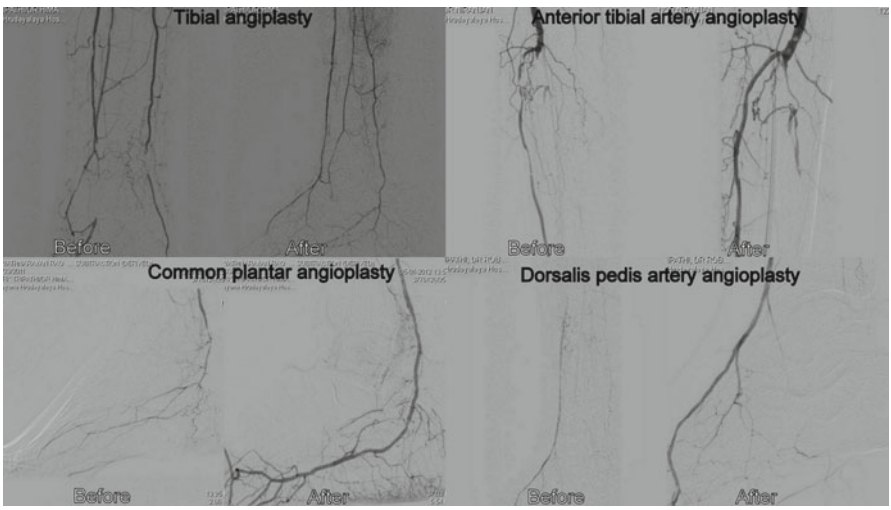


Fig. 11.4 Infrapopliteal angioplasty

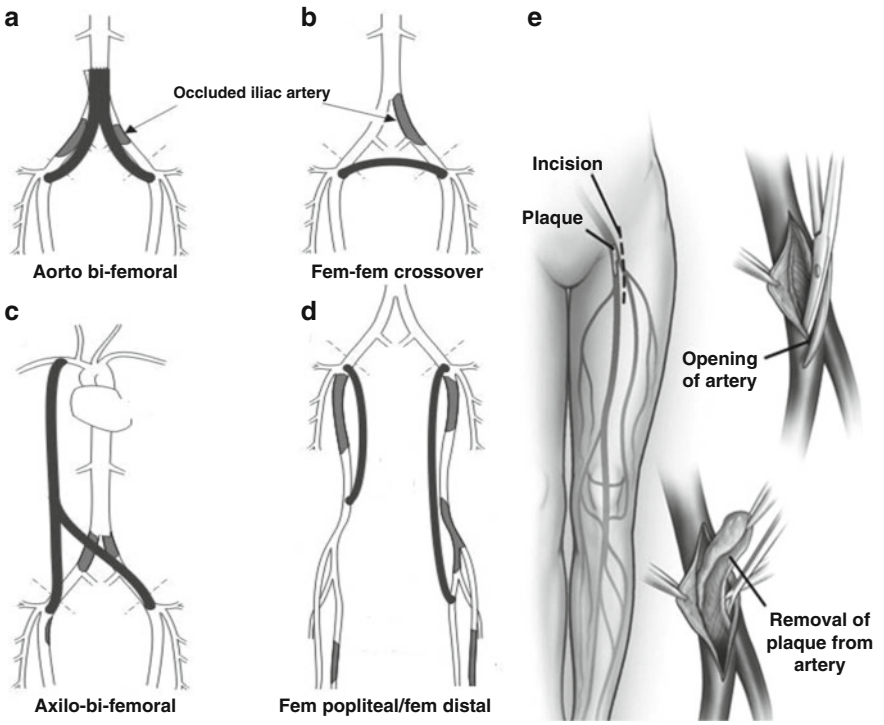


Fig. 11.5 Open surgical procedures: (**a**, **d**) Anatomical bypass procedures, (**b**, **c**) extra-anatomical bypass procedure, and (**e**) endarterectomy procedure

11.9.9 Open Surgical Intervention

There is general agreement that surgical treatment is indicated to relieve symptoms of limb-threatening ischemia, including ischemic pain at rest, ischemic ulcers, and gangrene. Intermittent claudication is considered only a relative indication for surgical treatment and then only after an adequate trial of nonsurgical therapy. Presently there is no consensus regarding disease severity, whether assessed by symptoms or hemodynamic parameters, for which operative treatment of claudication is appropriate.

11.9.10 Vasculitis Ulcer Treatment [23]

Glucocorticoids (prednisone, prednisolone, or others), often referred to as "steroids," are an important part of treating most forms of vasculitis. The dose and length of treatment depend on how bad the disease is and how long the patient has had it. These drugs help reduce inflammation but can have long-term side effects.

Other drugs like immune-suppressing drugs because of their side effects may be less serious than those of glucocorticoids. This is called "steroid-sparing" treatment.

Cyclophosphamide is the strongest of these drugs, and doctors may prescribe it when severe disease endangers vital organs. For less serious vasculitis, patients may receive methotrexate, azathioprine, or other immune-suppressing drugs. Doctors often prescribe these drugs to treat other rheumatic diseases, but they are useful for vasculitis, too. Newer drugs designed to treat other autoimmune and inflammatory diseases may also help vasculitis. Researchers found that one of these drugs, rituximab, effectively treats severe cases of certain forms of vasculitis. These include granulomatosis with polyangiitis, microscopic polyangiitis, and cryoglobulinemic vasculitis. Some patients with the most severe cases of these diseases may receive plasma exchange ("plasmapheresis") or intravenous immunoglobulin (often called "IVIg").

11.9.11 Adjuvant Therapies [13]

- Hyperbaric oxygen therapy
- Intermittent pneumatic compression (IPC)
- Ultrasound, electrostimulation, and spinal cord stimulation
- Lumbar sympathectomy
- Vacuum-assisted wound closure (VAC)
- Stem cell therapy and gene therapy with vascular endothelial growth factor (VEGF) may be of benefit for healing arterial ulcers, especially in patients with critical limb ischemia who are not candidates for revascularization.

11.9.12 Amputation

Limb-threatening ischemia typically occurs in elderly patients with multiple severe coexisting medical conditions making revascularization surgery responsible for many systemic complications. Unfortunately, a decision not to perform revascularization in the setting of limb-threatening ischemia makes amputation virtually inevitable. This is a problem because amputation is in itself a surgical procedure involving risks and length of hospitalization at least equivalent to those of revascularization and with a far less desirable outcome from the patient's point of view. Although a more minimalistic procedure, the postoperative support of the patient by physiotherapy and rehabilitation facilities is the most important consideration prior to decision making.

Cardiovascular morbidity and mortality are markedly increased in patients with PAD; these patients have an overall mortality at 5 years of 50 %. In patients who had a major amputation, these figures are even more dismal, with a 50 % mortality at 2 years [24].

Conclusion

Treatment of arterial/ischemic ulcers should therefore not be solely focused at the foot but should also aim to improve this poor survival. This cardiovascular risk management should include support for cessation of smoking, treatment of hypertension, and prescription of a statin as well as low-dose aspirin or clopidogrel.

References

1. Hess CT. Arterial ulcer checklist. Adv Skin Wound Care. 2010;23(9):432.
2. Graham ID, Harrisson MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. Adv Skin Wound Care. 2003;16:305–16.
3. Cornwall JV, Dore CJ, Lewis JD. Leg ulcers:epidemiology and aetiology. Br J Surg. 1986;73:693–6.
4. Bakker K, et al. The year of the diabetic foot. Diabetes Voice. 2005;50(1):11–4.
5. O'Brien JF, Grace PA, Perry IJ, et al. Prevalence and aetiology of leg ulcers in Ireland. Ir J Med Sci. 2000;169(2):110–2.
6. Norgen L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45(Suppl S):S5–67.
7. Mekkes JR, Loots MAM, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148(3):388–401.
8. Amir O, Liu A, Chang ALS. Stratification of highest risk patients with chronic skin ulcers in a Stanford retrospective cohort includes diabetes, need for systemic antibiotics, and albumin levels. Ulcers. 2012;2012:Article ID 767861, 7 p.
9. Ghauri ASK, Nyamekye IK. Leg ulceration: the importance of treating the underlying pathophysiology. Phlebology. 2010;25(Supplement 1):42–51.
10. Grey JE, Enoch S, Harding KG, ABC of Wound Healing. Venous and arterial leg ulcers. BMJ. 2006;332(7537):347–50.
11. Graves JW, Morris JC. Martorell's hypertensive leg ulcer: case report and concise review of the literature. J Hum Hypertens. 2001;15:279–83.
12. Harriet W, Hopf MD, et al. Guidelines for the treatment of arterial insufficiency ulcers. Wound Repair Regen. 2006;14:693–710.
13. Armitage M, Roberts J. Caring for patients with leg ulcers and an underlying vasculitic condition. Br J Community Nurs. 2004;Suppl:S16–22.
14. Orchard TJ, Strandness Jr DE. Assessment of peripheral vascular disease in diabetes: report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association, September 18–20, 1992, New Orleans, Louisiana. Circulation. 1993;88:819–28.
15. Dowd GS, Linge K, Bentley G. Measurement of transcutaneous oxygen pressure in normal and ischaemic skin. J Bone Joint Surg. 1983;65:79–83.
16. Mattos MA, van Bemmelen PS, Hodgson KJ, Ramsey DE, Barkmeier LD, Sumner DS. Does correction of stenoses identified with color duplex scanning improve infrainguinal graft patency? J Vasc Surg. 1993;17:54–66.
17. Kock MC, Dijkshoorn ML, Pattynama PM, Myriam Hunink MG. Multi-detector row computed tomography angiography of peripheral arterial disease. Eur Radiol. 2007;17:3208–22.
18. Ernst E, Fialka V. A review of the clinical effectiveness of exercise therapy for intermittent claudication. Arch Intern Med. 1993;153:2357–60.
19. Cronenwett JL, Warner KG, Zelenock GB, Whitehouse Jr WM, Graham LM, Lindenauer M, Stanley JC. Intermittent claudication: current results of nonoperative management. Arch Surg. 1984;119:430–6.

20. Herring M, Gardner A, Glover J. Seeding human arterial prostheses with mechanically derived endothelium: the detrimental effect of smoking. J Vasc Surg. 1984;1:279–89.
21. Hirsh J, Dalen JE, Fuster V, Harker LB, Salzman EW. Aspirin and other platelet-active drugs: the relationship between dose, effectiveness, and side effects. Chest. 1992;102(suppl4): 327S–36.
22. Abbas M, et al. Open endarterectomy of the SPT segment: an experience. Ann Vasc Surg. 2007;21:39–44.
23. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. Br Med J. 1987;294(6584):1389–91.
24. Hinchliffe RJ, Andros G, Apelqvist J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev. 2012;28 Suppl 1:179–217.

Diabetic Foot Ulcers

12

Giacomo Clerici and Ezio Faglia

12.1 Introduction and Magnitude of the Problem

"Diabetic foot" is one of the most common and feared complications associated with diabetes. It is estimated that almost 15 % of people with diabetes will develop foot ulcers requiring medical care during their lifetime. Diabetic foot ulcers are a major cause of hospital admission and thus impose a large financial burden on healthcare systems. Diabetic patients who develop foot ulcers are at greater risk of dying prematurely than those without this complication [1] (Fig. 12.1); in particular, not only ischemic diabetic foot ulcers but also neuropathic ulcerations are related to increased mortality in individuals with diabetes [2] (Fig. 12.2).

Alarmingly, foot ulceration often results in lower extremity amputation, i.e., the loss of the entire foot, and such amputations account for more than half of nontraumatic major (above-the-ankle) amputations in the diabetic population. Prevention of lower extremity amputation is thus the primary goal of diabetes management. There remains the question of whether this goal can be achieved, as data that are relevant to this issue remain elusive. The number of amputations in diabetics appears unchanged during the last decade; however, the rates of amputation vary in different institutions and in different countries [3, 4]. Figure 12.3 summarizes data on the incidence of major amputations in the past and in recent years.

The amputation rate data might lead one to speculate that the efforts devoted to improving diabetes care have proven ineffective and, therefore, have been useless. This remains a matter of debate for two reasons. First, the average life expectancy of those with diabetes has increased by almost a decade in a single generation in many developed countries. It is well established that neuropathy and arteriopathy,

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Fig. 12.1 Mortality in diabetes patients with and without diabetic foot ulcers (DFU)

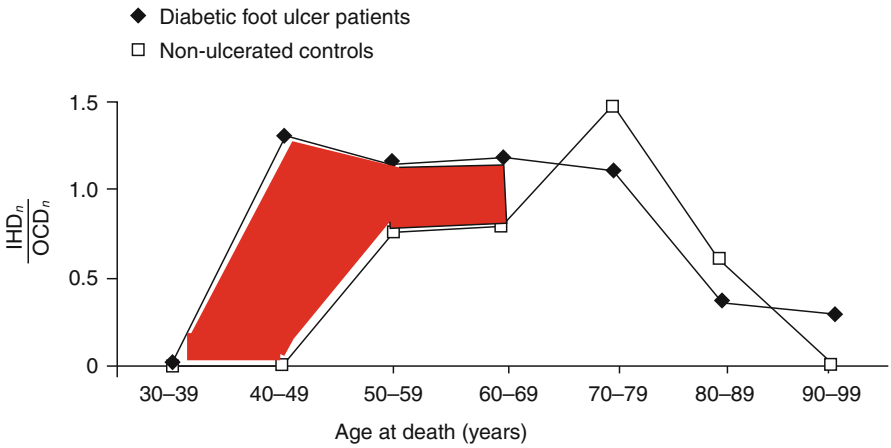

Fig. 12.2 Mortality in diabetes patients with and without neuropathic diabetic foot ulcers (nDFU)

which are the pathogenetic factors that contribute most to the formation of diabetic foot ulcers, become more common with increasing age. Therefore, the number of patients with diabetic foot and, consequently, the number of candidates for amputation are predicted to increase gradually over time. With this in mind, it becomes clearer that preserving the rate of amputation is itself the achievement of an important goal. Second, in order to decrease amputation rates, we need patients to have better access to highly skilled care at medical centers. According to a recent report, the rates of hospitalizations for nontraumatic lower extremity amputations in the USA declined significantly in the diabetic population between 1996 and 2008, while rates among those without diagnosed diabetes changed little [5] (Fig. 12.4). These findings are particularly notable considering the higher prevalence rates and greater severity of foot disease in diabetic subjects compared with the general population. Moreover, these findings completely differ from results obtained in a previous study [6].

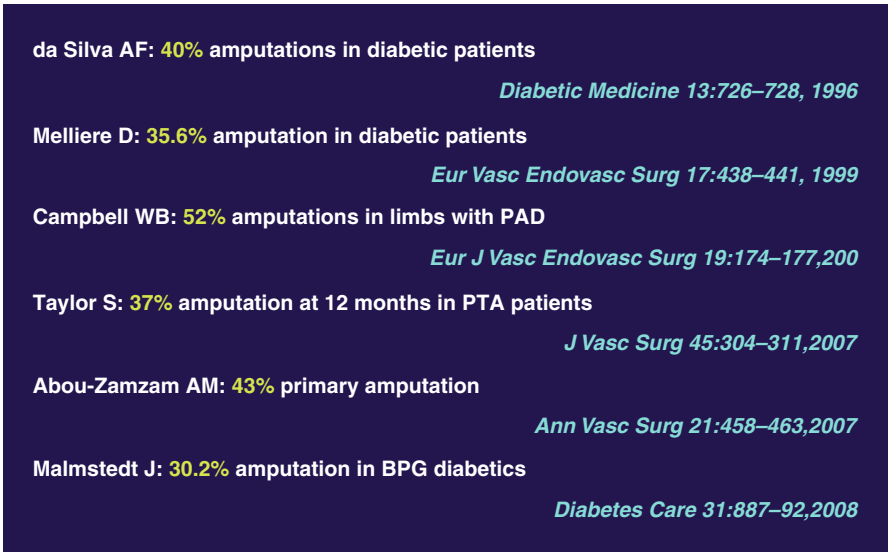

Fig. 12.3 Amputation rates in diabetes patients in the past and in recent years

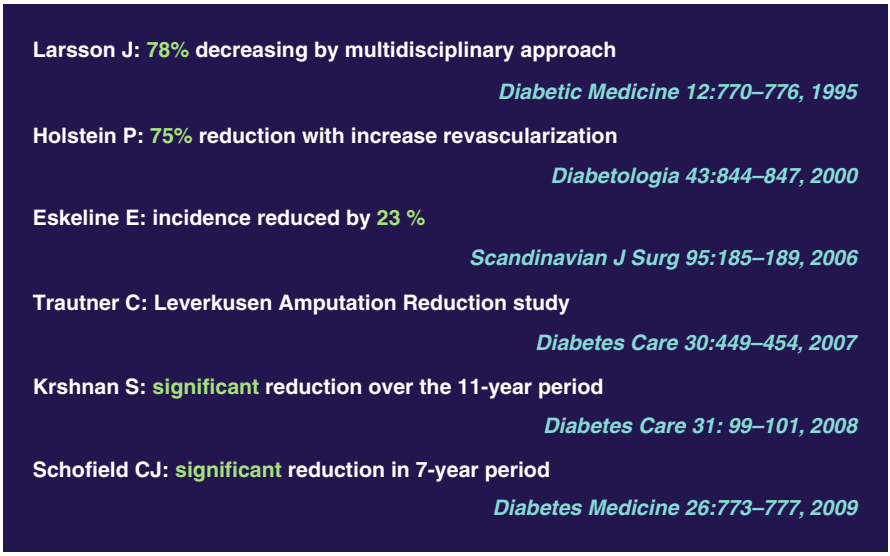

Fig. 12.4 Reduction in the amputation rate in diabetes patients in the past and in recent years

These data can only be explained by increased awareness of foot problems and increased availability of highly skilled foot care in centers in the USA. Questions remain about care in many other countries. Do these countries have an adequate number of skilled diabetic foot centers? Are all diabetic patients with foot ulcers referred to specialized hospitals? These questions should concern all diabetes associations as well as the national healthcare organization. Undoubtedly, in Italy the approach to amputation prevention in patients with diabetic foot, and particularly the establishment of specialized diabetic foot clinics for comprehensive multidisciplinary foot care programs, is very appreciated by many clinicians, including those who performed the US study cited above [7]. In Italy, the rates of major amputations at multidisciplinary centers dedicated to diabetic foot care have progressively decreased from the beginning of the 1990s into the 2000s. Faglia et al. and Lombardo et al. [8, 9] note that the amputation rate in patients with diabetes in Italy decreased by more than 30 % from 2001 to 2010 as a result of a team approach and improved awareness of diabetes-associated foot problems.

How can this goal be achieved elsewhere? Amputation is the consequence of a nonhealing foot ulcer that causes severe damage to tissues and bone. Thus, the development of effective approaches to preventing and treating diabetic foot ulcers should be the primary goal. The development of standard protocols for comprehensive, multidisciplinary diagnoses and effective treatment is mandatory for improving care (Fig. 12.5). The first step in the management of diabetic foot is to understand the problems associated with diabetic foot.

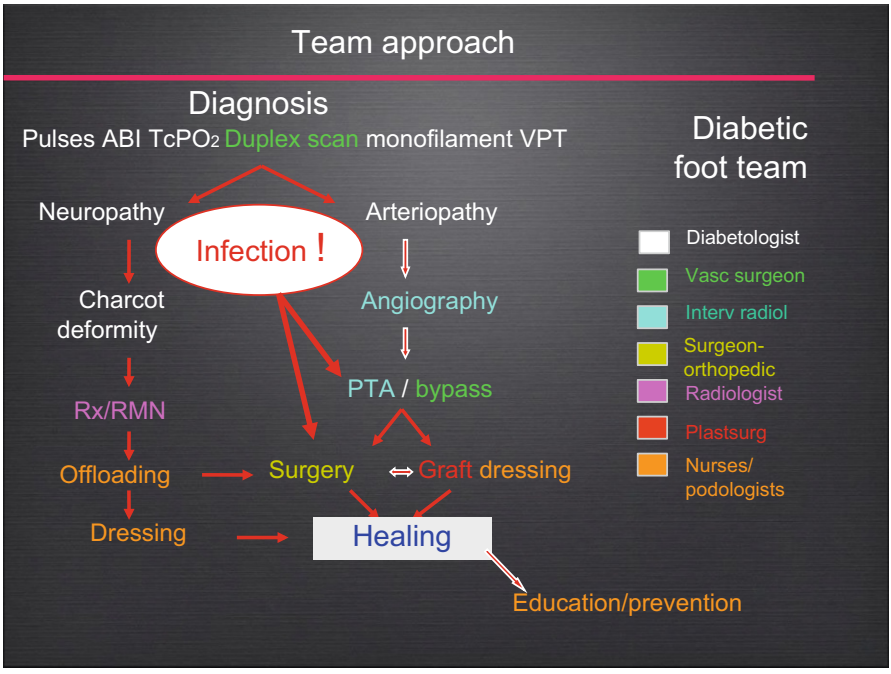

Fig. 12.5 A diabetic foot care flow chart

12.2 Definition

The WHO criteria define diabetic foot as "the foot of diabetic patients with ulceration, infection and/or destruction of deep tissue, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb." After the establishment of this definition, the subsequent two meetings of the Interassociative Working Group of the Italian Association of Diabetologists defined diabetic foot as "the foot with anatomical and functional alterations caused by occlusive peripheral arteriopathy and/or by diabetic neuropathy" (Fig. 12.6). In terms of prevention, this definition includes patients without evident foot lesions who are nonetheless at risk of developing foot ulcers according to established and validated classifications systems.

Diabetic foot develops from complications of diabetic neuropathy of the lower extremities or from complications of occlusive peripheral arteriopathy; in both scenarios, the complications undermine the structural integrity and/or function of the foot. These two conditions, namely, neuropathy and ischemia, differ considerably in terms of their pathophysiology, diagnosis, therapeutic approach, and prognosis. However, the coexistence of both conditions, termed neuroischemic foot, has been reported in many diabetic patients, especially in the elderly population. Infection of foot ulcerations is one of the most common and serious complications leading to amputation in patients with diabetes.

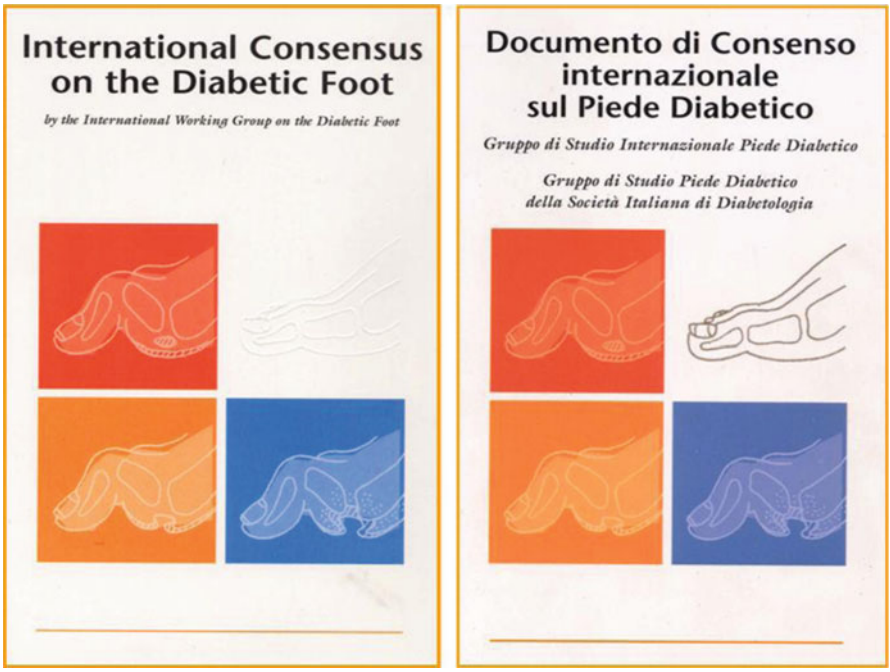

Fig. 12.6 International consensus on the diabetic foot provided by the IWGDF and the Italian version of the consensus

12.3 Clinical Features of Diabetic Foot

Neuropathy usually results in a insensitive deformed foot. A neuropathic foot is warm and well perfused with palpable pedal pulses; the skin is usually dyschromic. Figure 12.7 shows images of some neuropathic feet. Bilaterality of the neuropathy is a classic characteristic independent of the presence or absence of an ulcer (Fig. 12.8).

In contrast to the neuropathic foot, the ischemic foot is generally a cool, subcyanotic foot. The subcutaneous venous network is visible through the skin and is tiny; pedal pulses are hardly palpable or absent (Fig. 12.9). Although patients with occlusive peripheral arteriopathy usually present with bilateral steno-occlusive lesions, clinical complications usually affect only one lower extremity. However, complications may also occur over time in the contralateral limb [10] (Fig. 12.10). Note that while clinical signs of neuropathic foot are clearly visible, the clinical signs of ischemic foot are hard to see, and instrumental examinations are required to make the diagnosis.

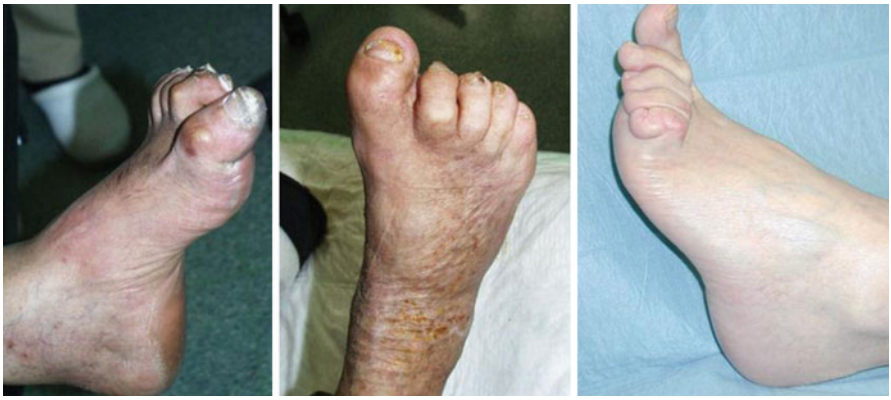

Fig. 12.7 The typical appearance of neuropathic foot in patients with diabetes

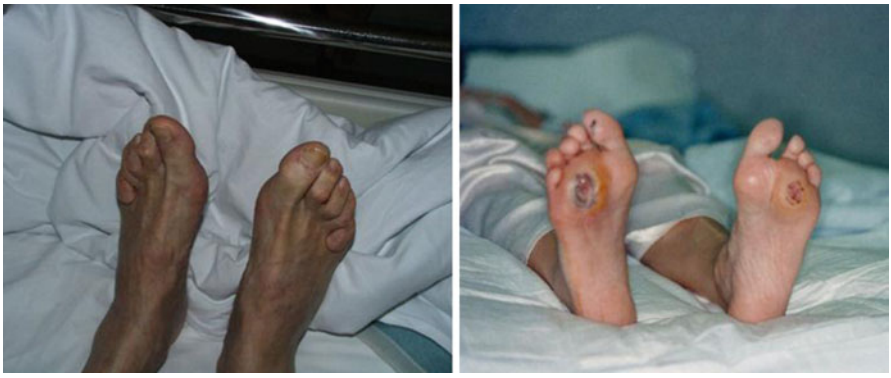

Fig. 12.8 Bilateral deformities and diabetic foot ulcers in patients with diabetes

Ischemic and neuropathic ulcers differ in their clinical presentation. The etiopathogenesis of the ischemic foot ulcer is usually related to friction. Accordingly, the site of ulceration can be located anywhere on the foot (e.g., on the dorsum of the foot or on the margins of the foot) (Fig. 12.11). In contrast, the etiopathogenesis of the neuropathic foot is related to mechanical forces of gait. Because of this, neuropathic ulcers mainly occur on the plantar aspect of the foot and on areas that, due to foot distortion, are exposed to weight-bearing forces (Fig. 12.12).

Diabetic foot frequently presents with unusual clinical manifestations. There may be lesions in different areas of the foot according to the type of trauma; however, the signs differ between the two ulcer types (Table 12.1). The features reported

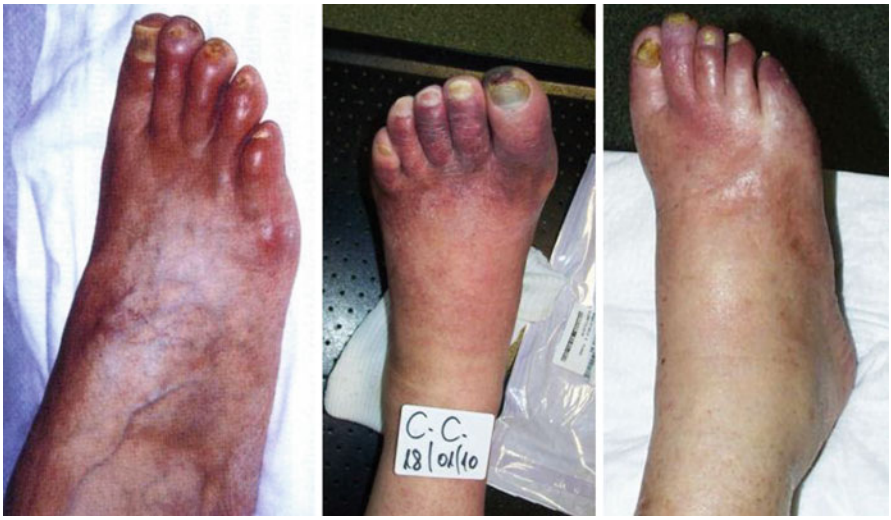

Fig. 12.9 The typical appearance of ischemic foot in patients with diabetes

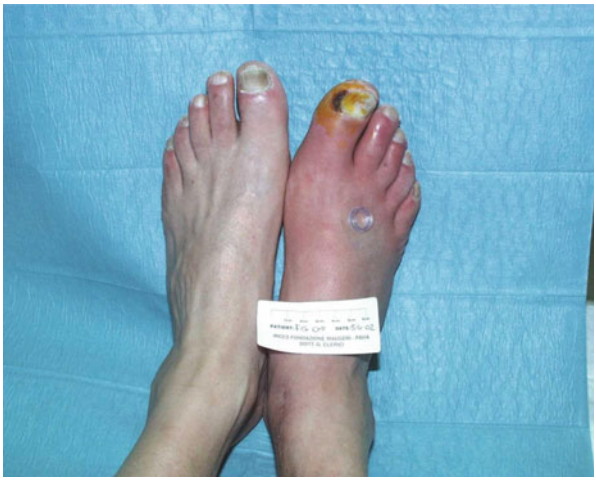

Fig. 12.10 Critical right limb ischemia in a patient with diabetes and less obvious ischemic signs on the left foot

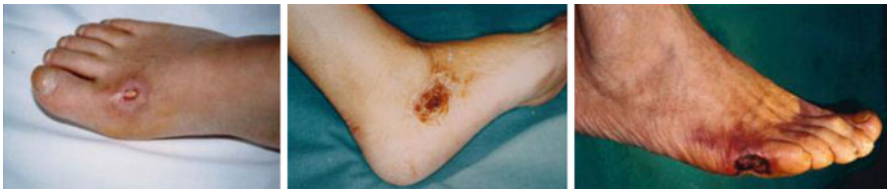

Fig. 12.11 The ulceration site can be located anywhere on the feet of patients with diabetes

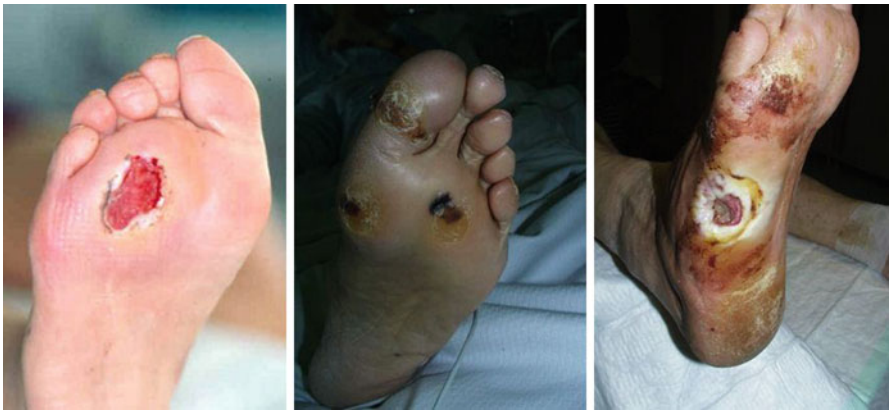

Fig. 12.12 Neuropathic ulcers in characteristic hyperpressure areas of the feet of patients with diabetes

Table 12.1 Characteristics of neuropathic versus ischemic foot ulcers

Neuropathic ulcer	Ischemic ulcer
Painless	Painful
Normal pulses	Absent pulses
Regular margins, typically punched-out appearance	Irregular margin
Often located on plantar surface of foot	Commonly located on toes, glabrous margins
Presence of calluses	Calluses absent or infrequent
Loss of sensation, reflexes, and vibration	Variable sensory findings
Increased in blood flow (atrioventricular shunting)	Decreased in blood flow
	Collapsed veins
Dilated veins	Cold foot
Dry, warm foot	No bony deformities
Bony deformities	Pale and cyanotic in appearance
Red or hyperemic in appearance	

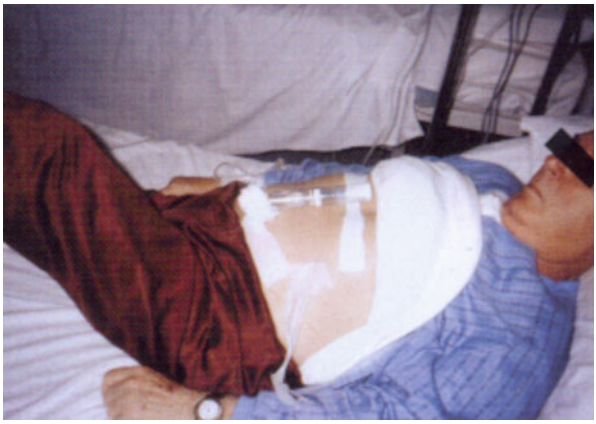

Fig. 12.13 Patient with rest pain because of critical limb ischemia that was treated with analgesic drugs. The medication was administered with a pump

here are related to noninfected ulcers, since infected ulcers, both neuropathic and ischemic, present with different clinical signs.

In general, neuropathic foot is associated with little or no pain, while ischemic foot is always associated with rest pain (Fig. 12.13); however, rest pain may be absent in some patients with arteriopathy. Elderly diabetic patients with arteriopathy often develop neuropathy that can attenuate or cancel ischemic pain, thus preventing prompt and accurate diagnosis of arteriopathy, which has serious consequences.

Differential diagnosis is the first step in the management of an ulcer. Diabetes specialist Michael Edmonds notes, "An important prelude to successful treatment is the differentiation between two main syndromes: the neuropathic foot and the neuroischemic foot" [11]. Differential diagnosis is an important prerequisite not only to prevent amputation but also to reduce mortality [12].

The signs of neuropathic ulcers differ in some ways from those of ischemic ulcers (Table 12.1). Most of these differences may be irrelevant, with the exception of the absence of palpable pedal pulses in elderly neuroischemic patients. There are also some differences regarding the type of ulcer that is found in neuropathic versus neuroischemic foot. Figure 12.14 shows an example of a neuropathic foot with a typical plantar lesion and an example of a critically ischemic foot with multiple typical gangrenous ulcers. Neuropathic foot presents with ulcerations that are usually located on the plantar aspect of the metatarsal heads. However, ulcerations can also occur in areas of the foot that are exposed to biomechanical stress, such as the top or dorsum of the toes (in "pied en griffe"), the midfoot (in flat feet), lateral areas of the foot, or other areas (Fig. 12.15). Ischemic foot also presents with ulcerations of areas that are subjected to pressure, which can even include the plantar aspect of the foot (Fig. 12.16).

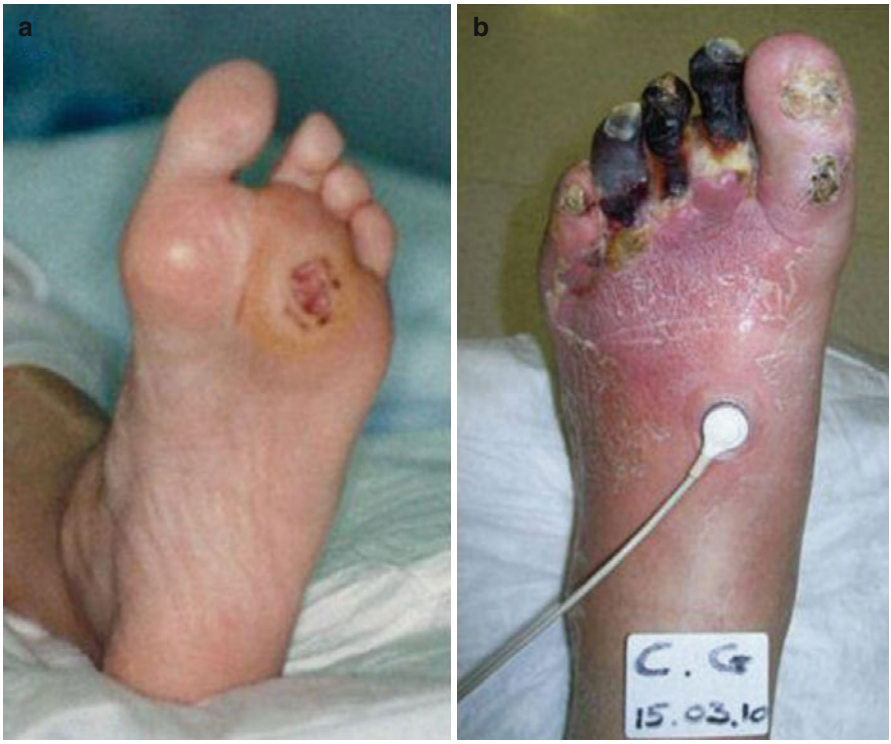

Fig. 12.14 (**a**) Typical neuropathic plantar ulcer under the third metatarsal head and (**b**) typical ischemic gangrene of the forefoot

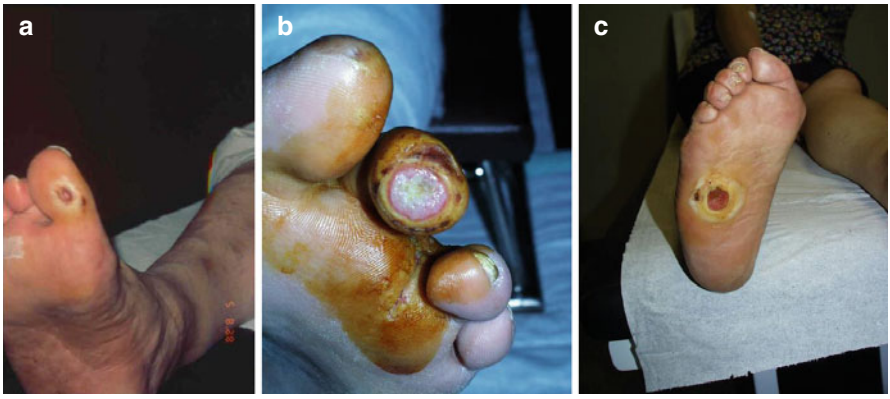

Fig. 12.15 Neuropathic ulcers can occur on areas of the foot that are exposed to biomechanical stress, such as the top (**b**) or dorsum or plantar (**a**) aspect of the toes or the plantar aspect of the foot (**c**)

Although diabetic foot ulcers can have many signs and symptoms, selecting the most appropriate diagnostic and therapeutic approaches requires accurate identification of the type of ulcer after considering the clinical findings and etiopathogenetic factors. In addition, the appropriateness of the treatment and management must be constantly assessed to ensure that the patient receives the best possible care.

12.4 Neuropathic Diabetic Foot Ulcers

Together with arteriopathy, neuropathy contributes to the etiopathogenesis of diabetic foot ulceration [13, 14]. According to the Eurodiale study, neuropathy accounts for almost half of all foot ulcers, and arteriopathy accounts for the remaining half (Table 12.2). Although the Eurodiale study may have had some bias, the findings highlight the potential role of these two pathogenetic factors in the formation of foot

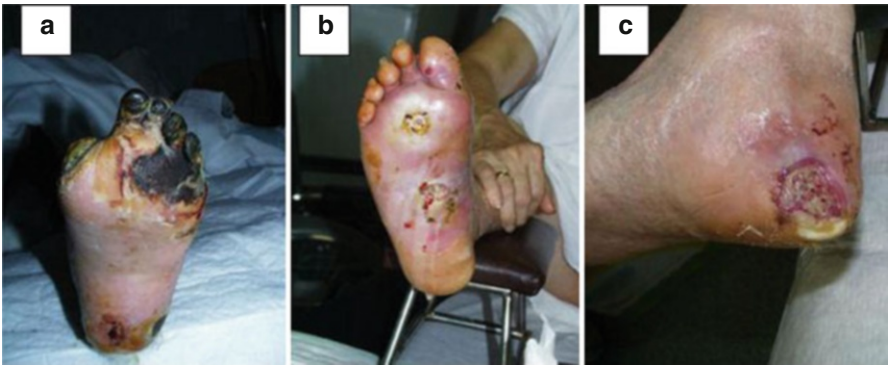

Fig. 12.16 Ischemic feet can present with ulcerations on areas of the foot that are exposed to pressure, even on the plantar aspect

Table 12.2 The incidence of neuropathy, arteriopathy, and infection in patients with diabetic foot ulcers

Stage	Definition	Number of patients	Percentage of study population	
A	PAD –, infection –	270	24	51
B	PAD –, infection +	305	27	
C	PAD +, infection –	205	18	49
D	PAD +, infection +	347	31	

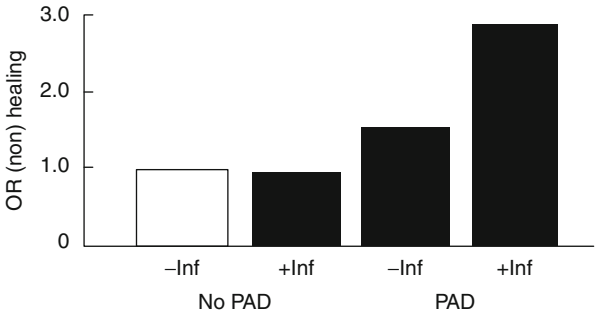

Fig. 12.17 The risk of nonhealing of diabetic foot ulcers in the Eurodiale study population

ulcers in diabetic patients [15]. Further analysis of the study showed that arteriopathy and infection, rather than neuropathy per se, were associated with poor healing [16] (Fig. 12.17).

The 1988 San Antonio Conference on Diabetic Neuropathy defined diabetic neuropathy as the presence of symptoms and/or signs of peripheral (somatic and/or autonomic) nerve dysfunction in people with diabetes mellitus that lack other causes for peripheral neuropathy. This definition is still widely accepted by the scientific and medical communities [17]. There are many types of diabetic neuropathies that have a variety of clinical manifestations, some of which are similar to those observed in nondiabetic neuropathies [18]. Diabetic neuropathy can be difficult to treat [19]. Neuropathy is most commonly classified as symmetrical sensorimotor neuropathy and autonomic neuropathy, focal/multifocal varieties (e.g., cervical radiculo-plexus neuropathies, multiple mononeuropathy) [20]. Distal symmetrical mixed sensorimotor polyneuropathy, which typically shows a "stocking distribution," is the most common type of neuropathy that contributes to the pathogenesis of diabetic foot ulcers (Fig. 12.18).

Autonomic neuropathy also contributes to the pathogenesis of diabetic foot ulcers, although to a lesser extent [21]. Figure 12.19 shows a foot with typical signs of autonomic neuropathy, namely, dehydrated skin, ungual mycosis, and swelling. This chapter does not discuss the pathogenesis of diabetic neuropathy or other diabetes-related neuropathies. The interested reader can find further details on this topic in reference Spallone and Morganti [22].

Sensorimotor diabetic neuropathy cannot be diagnosed based on a single symptom or test. Rather, the diagnosis must be based on at least two neuropathic abnormalities in signs, symptoms, nerve conduction, or quantitative sensory test results [23].

Diagnostic tests include:

- Symptoms/signs (clinical scores in diabetic neuropathy)
- Quantitative sensory testing:
  - Semmes-Weinstein monofilament examination
  - Tuning fork/biothesiometer testing
  - Thermal threshold testing
- Instrument-based tests (cardiovascular tests and electromyography)

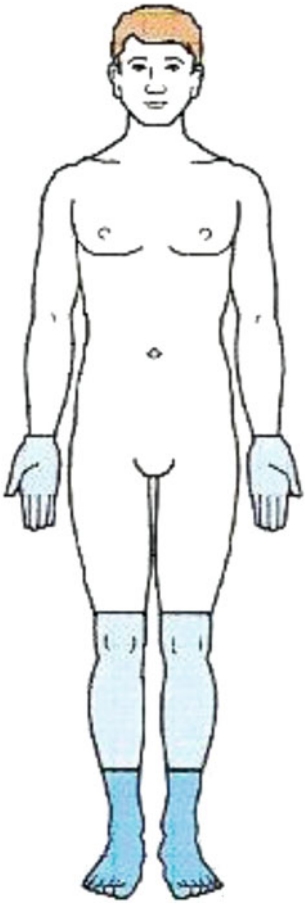

Fig. 12.18 The typical "stocking distribution" of sensorimotor changes in diabetes

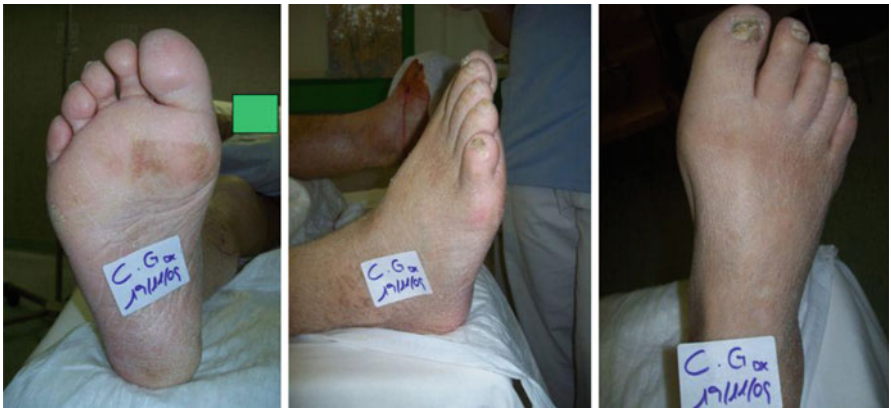

Fig. 12.19 A neuropathic foot showing typical signs of autonomic neuropathy: dehydrated skin, ungual mycosis, and swelling

A neuropathy severity grading system has been reported by the American Diabetes Association [11].

Clinical signs of neuropathic foot usually include:

- Claw/hammer toe deformity
- Valgus deformity of the great toe
- Overlapping toes
- *Pes cavus* deformity
- Prominent metatarsal heads
- Plantar hyperkeratosis
- Venous turgidity
- Dry skin

Plantar hyperkeratosis and prominent metatarsal heads are the most common signs of motor neuropathy. Venous stiffness and dry skin are typical signs of dysautonomia. Diabetic neuropathy may affect sensory nerves (sensory neuropathy), motor nerves (motor neuropathy), and the autonomic nervous system (autonomic neuropathy). Diabetic patients with neuropathic foot exhibit muscle imbalance, alterations in sensory perception, and disordered autonomic function.

12.4.1 Sensory Neuropathy

In the foot, sensory neuropathy affects both proprioceptive sensory organs and afferent sensory nerve fibers. The most serious consequence is the loss of pain sensation. In the absence of pain, external nociceptive stimuli that are the result of excessive mechanical forces (e.g., tight-fitting shoes) are ignored; therefore, patients are not alerted to address the cause of the excessive pressure. Consequently, ulcers may develop. Thus, any physical trauma as a consequence of sensory neuropathy may result in a lesion. Sensory neuropathy can be promptly diagnosed using simple, noninvasive tools. Guidelines for sensory examination that are still valid were published in the 1990s [24] and include the following tests:

Pain sensation (pinprick test using a sterile pin: patients may feel pain or a needle sensation) (Fig. 12.20)
Light touch sensation (using cotton balls) (Fig. 12.21)
Temperature sensation (using steel or tubes filled with warm or cold water)

These tests are rather subjective assessment methods. Other inexpensive, simple, and more objective methods are available. Semiquantitative sensory testing can be performed using the Semmes-Weinstein monofilament [25, 26]. In this test, patients close their eyes while a nylon monofilament is applied to specific sites on the foot; obviously, hyperkeratotic areas should be avoided. The reliability of a patient's response should be verified with a "false touch" [27]. The monofilament is constructed so that it buckles when a force exceeding the level indicated on the filament is applied. The absence of a "pin and needle" sensation at one or more

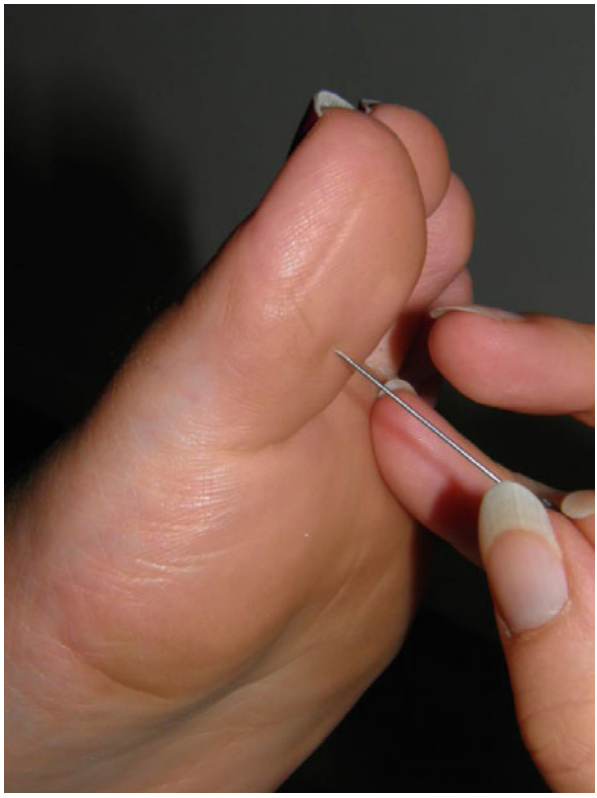

Fig. 12.20 The pinprick test for pain sensation

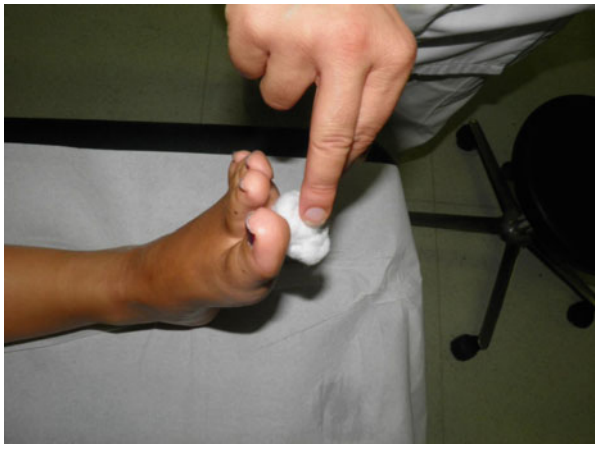

Fig. 12.21 The sensation test using a cotton ball

anatomical sites on the plantar surface of the foot is a sign of impaired sensory nerve function, and the absence of sensation on 6 or more areas of the foot is a sign of sensory loss. Figure 12.22 illustrates the technique used for monofilament testing.

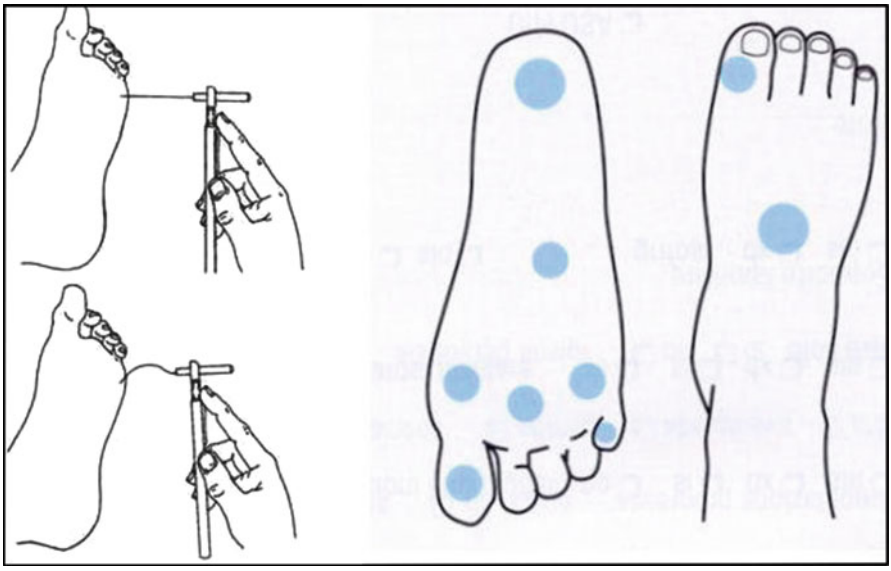

Fig. 12.22 The technique used for monofilament testing

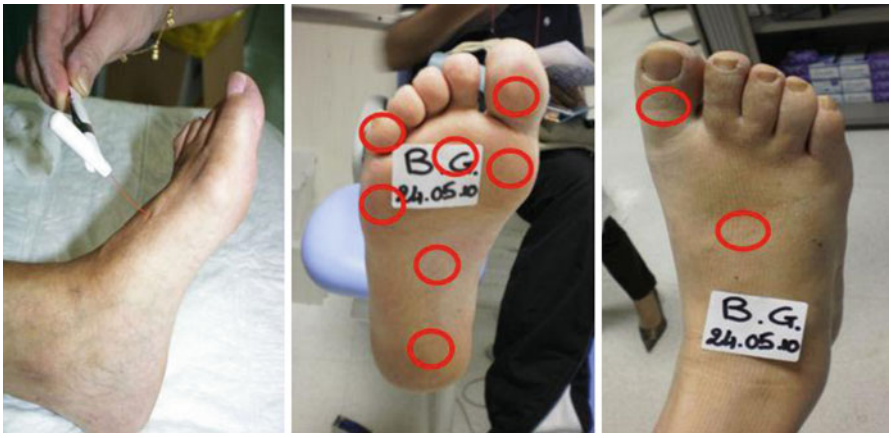

Fig. 12.23 The monofilament test as performed on a patient. *Red circles* indicate the different areas to which the monofilament is applied

Figure 12.23 shows some pictures of the monofilament test being performed on a patient. For quantitative sensory testing, a tuning fork or biothesiometer that transmits vibrations with variable frequencies is applied to the malleolus and on the dorsum of the first metatarsal heads (Fig. 12.24) of the patient's foot. Sensory loss occurs when no vibration is sensed or when only vibrations with frequencies greater than 25 V are perceived [28, 29]. Loss of the ability to sense touch and vibration is usually associated with loss of pain sensation, which puts a patient at high risk of

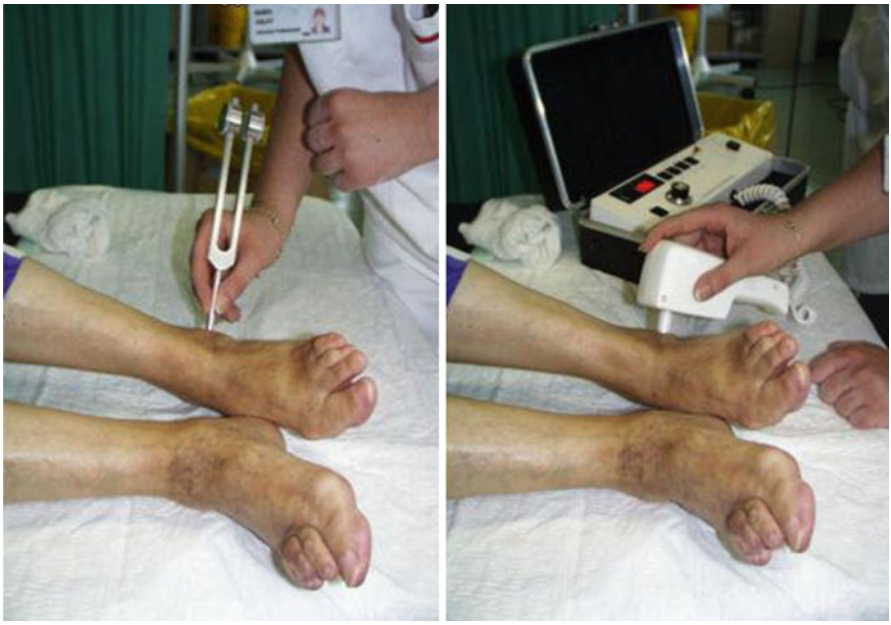

Fig. 12.24 A tuning fork and biothesiometer are applied to the malleolus of a patient for quantitative sensory testing

foot ulceration. Patients that only perceive tuning fork vibrations with frequencies greater than 25 V may be at risk for foot ulcer development. A biothesiometer may also be used as a screening tool to evaluate the efficacy of a treatment.

Since small fiber nerve function cannot be assessed with electromyography, either biopsy or thermal threshold testing may be performed [30–33]. Notably, standardized techniques for thermal threshold testing are still lacking. A cutaneous thermometer (Molliter, Civitanova Marche Italy) or more complex instruments (case IV device, Medoc, NeuroQuick) can be used [34–36] (Figs. 12.25, 12.26, and 12.27).

An inability to feel pain is the major cause of foot ulcers in diabetic patients. Physical trauma due to tight shoes, a hot electric blanket, walking with bare feet, or foreign bodies in the shoes or socks, for example, may be ignored due to the loss of pain sensation. Such trauma can lead to the formation of nonhealing ulcers. Figure 12.28 shows an example of a foot lesion caused by the use of an electric heating blanket.

12.4.2 Motor Neuropathy

Motor neuropathy affects the large myelin fibers that innervate the foot muscles and leads to progressive hardening of the fascial tissues and to weakening and atrophy of the lumbrical and interosseous muscles. Motor neuropathy leads to an imbalance in toe flexor/extensor muscle strength, which leads to the typical claw-toe

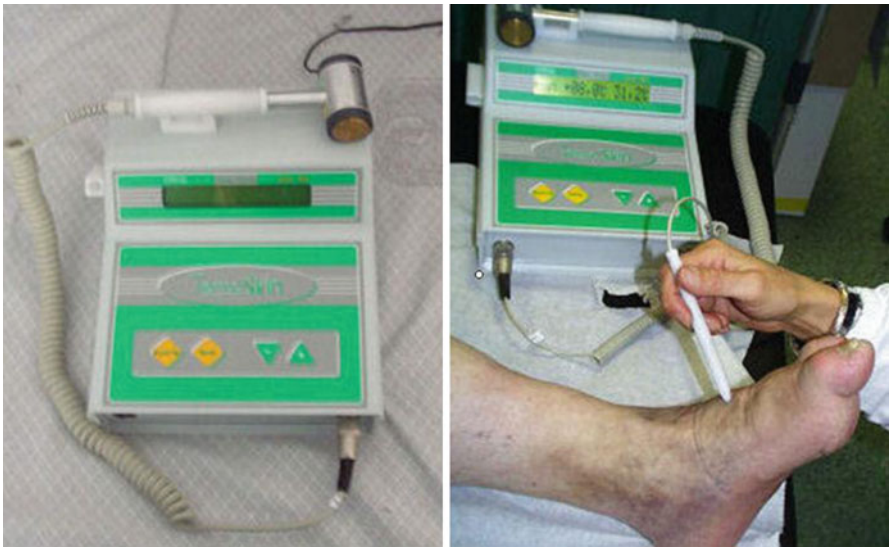

Fig. 12.25 Thermoskin (see the text)

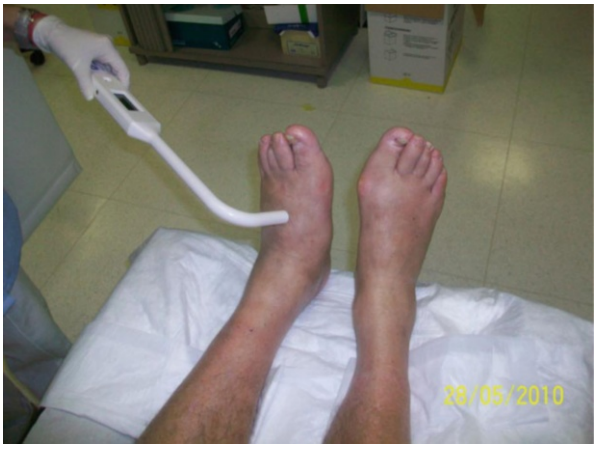

Fig. 12.26 An infrared thermometer is applied to the skin of a patient with diabetes

deformity. Claw toe involves protrusion of the metatarsal heads and high plantar arches (*pes cavus* deformity) (Fig. 12.29). Many studies note that diabetic neuropathy is associated with muscle atrophy [37]. In terms of the signs of diabetic neuropathy, the tendons of the dorsum of the foot become more prominent as a consequence of extensor muscle atrophy (Fig. 12.30).

The muscle imbalance resulting from motor neuropathy also leads to alterations in the distribution of the protective fatty cushions that are underneath the heads of the metatarsal bones [38]. As a consequence of this dysmorphism, the weight-bearing area of the foot is reduced. This is a pathogenetic factor, since pressure on

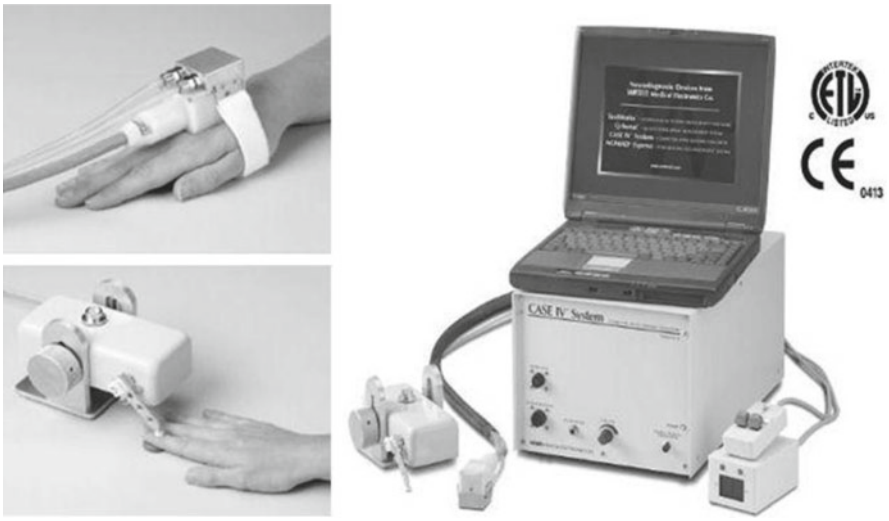

Fig. 12.27 Case device (see the text)

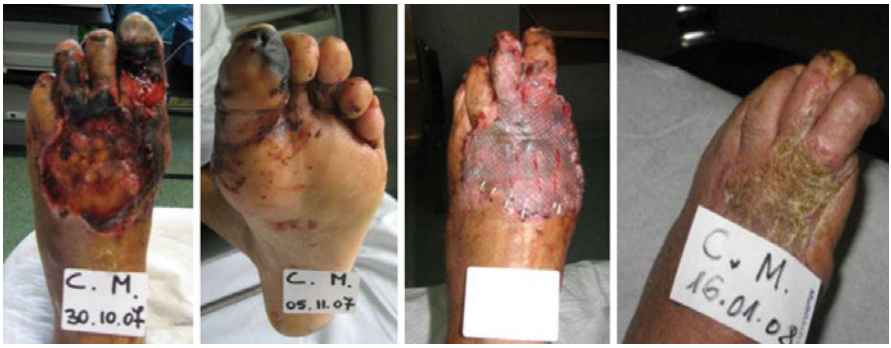

Fig. 12.28 Foot lesion caused by an electric heating blanket: the burn led to amputation of the first ray and closure by autologous skin grafting

the weight-bearing surface increases as the surface area decreases. Time also plays an important role in the pathogenesis of the lesion [39]. Figure 12.31 illustrates the importance of the size of the weight-bearing surface. As a result of a decreased weight-bearing surface, some areas of the foot, such as metatarsal heads, the tips of the toes, and the calcaneus, are exposed to excessive load (Fig. 12.32).

In the neuropathic foot, the *pes cavus* deformity results in increased weight-bearing pressure on the metatarsal heads, while the flatfoot deformity results in increased weight-bearing pressure on the midfoot (Fig. 12.33). As a protective response to the excessive mechanical forces, hyperkeratosis develops on areas of the skin that are exposed to overload (Fig. 12.34). In general, neuropathy leads to bilateral hyperkeratosis; however, the severity and progression of hyperkeratotic lesions

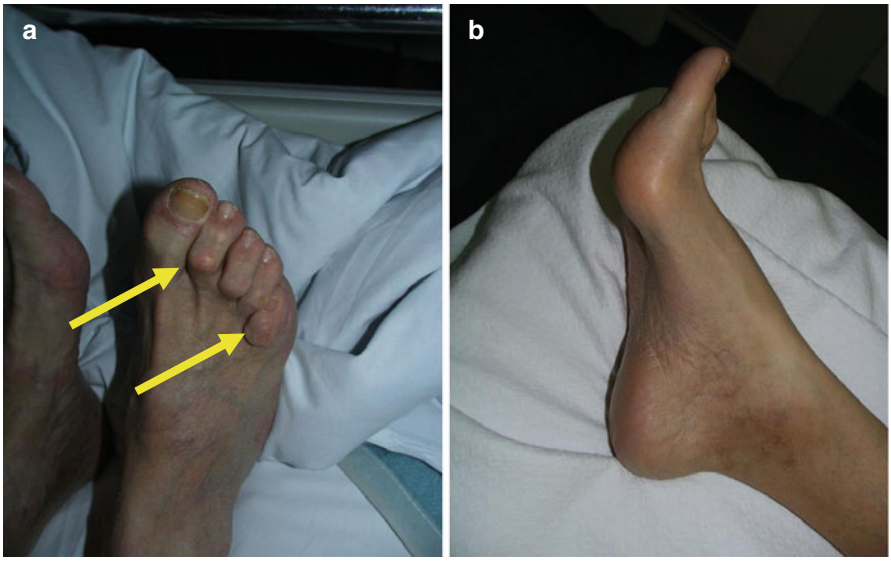

Fig. 12.29 (**a**) A foot showing a typical claw-toe deformity with dorsal hyperkeratosis (*arrows*) due to excessive pressure. (**b**) A foot with a pes cavus deformity

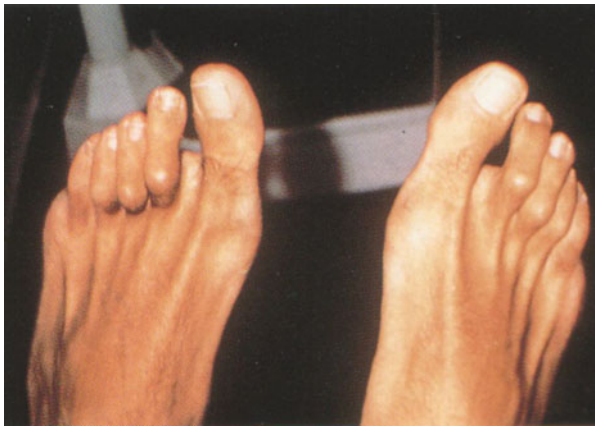

Fig. 12.30 A claw-toe deformity with prominent tendons of the extensor muscles in a patient with motor neuropathy

in neuropathic feet can vary depending on the location of the lesion (Fig. 12.35). Hyperkeratosis functions as a protective response only for a limited period of time. Indeed, persistence of overload can cause a hematoma that eventually evolves into nonhealing ulcers that are at high risk of becoming infected (Fig. 12.36).

Along with bilateral hyperkeratosis, neuropathic patients often present with bilateral plantar foot ulcers (Fig. 12.37). However, any area of the foot can be exposed to excessive weight-bearing forces, depending on the type and the extent of the foot deformity. For example, in patients with claw toes, distal phalanges or the

Fig. 12.31 Different weight-bearing surfaces of the foot (see the text for the description)

dorsum of the toe may be exposed to overload, and the plantar aspect of the midfoot may be affected in patients with flatfoot (Fig. 12.38). In fact, toes are frequently affected by motor neuropathy, and a great variety of foot deformities can arise. Thus, foot deformity itself may be a sign of motor neuropathy (Fig. 12.39). Motor neuropathy can be diagnosed using the Achilles tendon and patellar (knee-jerk) reflex tests; however, these methods can be difficult to perform on patients with mobility problems (Fig. 12.40).

Progressive thickening of the plantar fascia and the Achilles tendon, which seems to be related to deposits of the glycosylation products of collagen fibers, leads to retraction of the plantar fascia, Achilles tendon, and several foot joints [40, 41]. Plantar fascia retraction leaves the metatarsal heads unprotected and, together with Achilles tendon retraction, can lead to foot deformity. Then, in turn, foot deformity overloads the metatarsal heads. The hardening of joint capsules contributes to the development of a "rigid foot" that poorly absorbs shear and friction forces during gait.

The use of electroneurography for assessing motor nerve conduction velocity is still a matter of debate [42, 43]. This is a useful diagnostic test for differentiating between radiculopathies and other painful neuropathies and for assessing the effectiveness of different treatment approaches. However, it does not provide useful information about the risk of developing foot ulcers and does not help diagnose sensorimotor neuropathy in patients with foot ulceration.

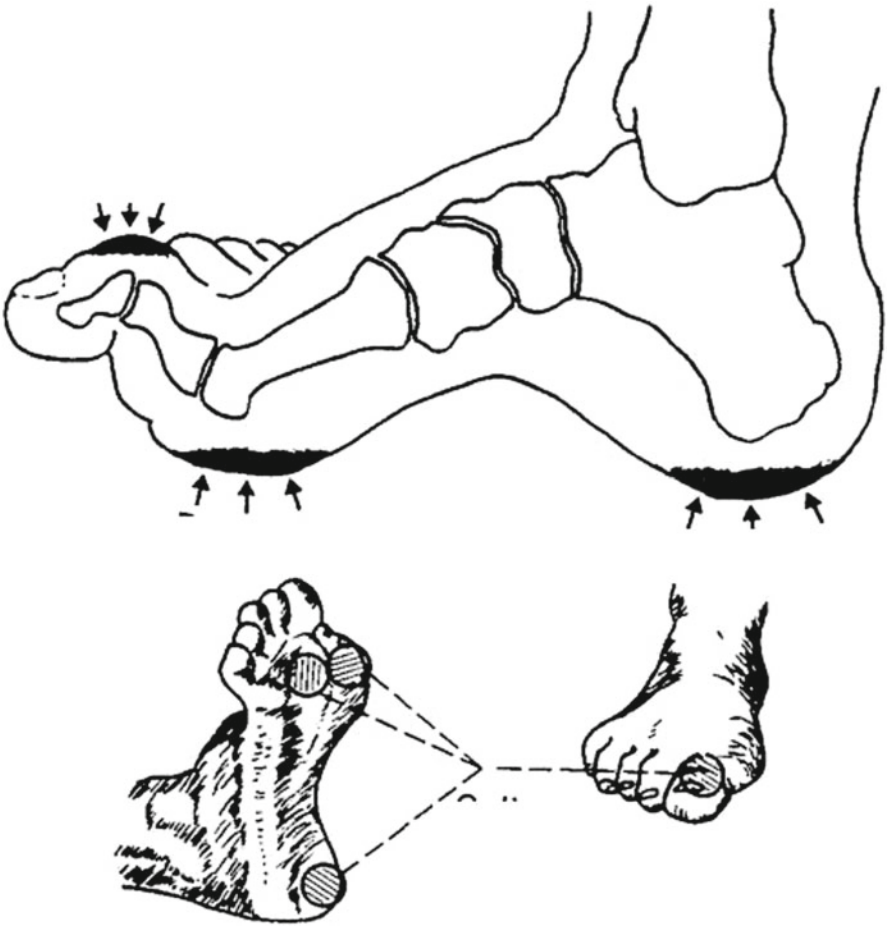

Fig. 12.32 Schematic representation of areas of the foot that can be exposed to hyperpressure

12.4.3 Autonomic Neuropathy

The role of diabetic autonomic neuropathy in the pathogenesis of diabetic foot appears to be less important than the role of diabetic sensorimotor neuropathy; however, very little is actually known about its role. Autonomic neuropathy occurs in 10–15 % of patients with diabetes and in 30–40 % of patients with sensory neuropathy [21, 44]. Diagnosing autonomic neuropathy can be difficult, since many time-consuming tests (at least 3 of the 5 typical cardiovascular reflex tests) and at least one electrocardiographic evaluation should be. One commercially available diagnostic tool is the Neuropad test. This test is based on a simple visual indicator that uses color changes that reflect the integrity of skin sympathetic cholinergic innervation [45–47] (Fig. 12.41).

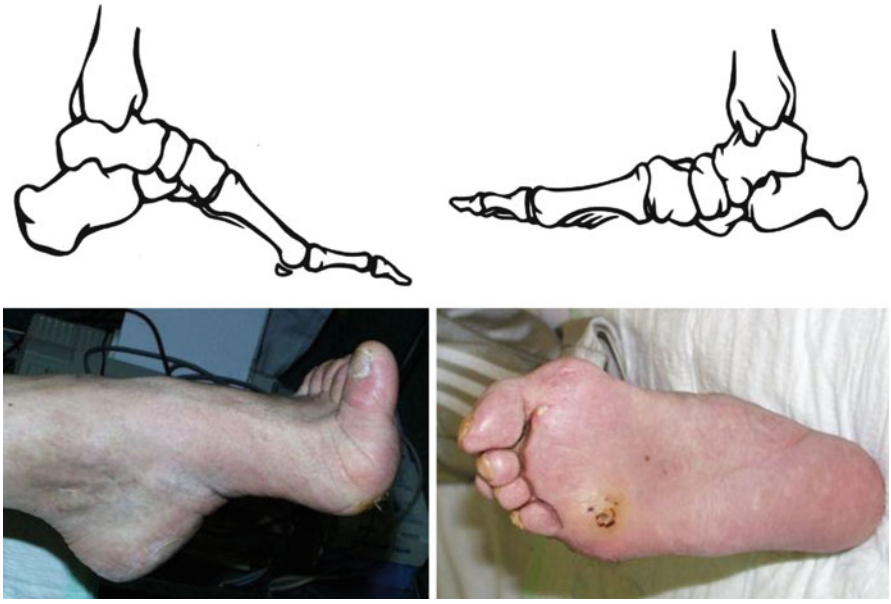

Fig. 12.33 Feet showing typical cavus foot deformities (*left*) and flatfoot deformities (*right*)

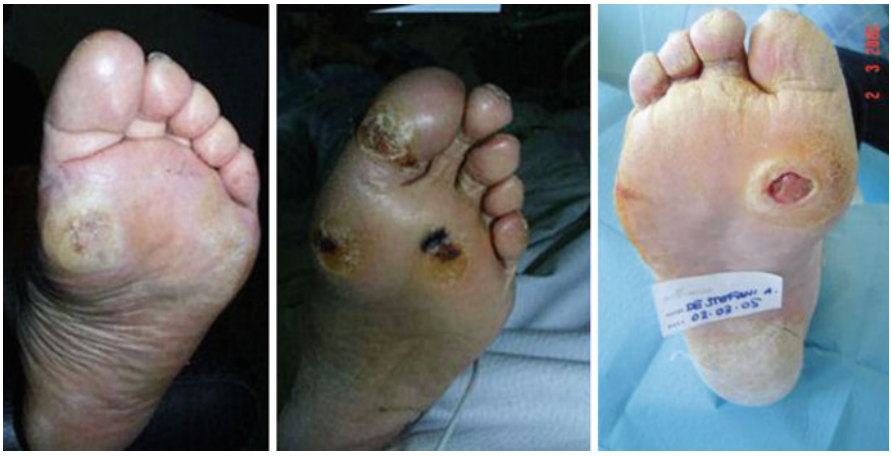

Fig. 12.34 (*Left* to *right*): Examples of increasingly severe hyperkeratosis in neuropathic feet

One visible clinical sign of autonomic neuropathy is extremely dry skin on the foot due to alterations in the sudomotor fibers that innervate the sweat glands (Fig. 12.42). Sudomotor dysfunction leading to dry skin on the foot is associated with foot ulceration [48] because dry skin breaks easily and can easily become infected (Fig. 12.43). Since sudomotor dysfunction and pH alterations predispose diabetes

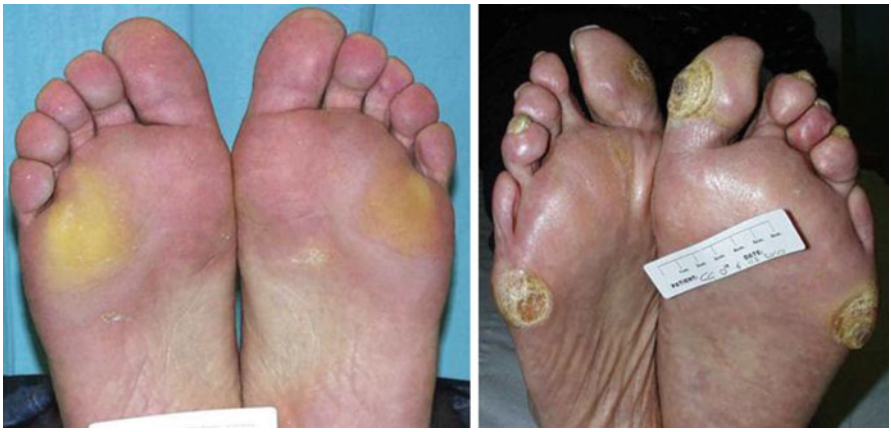

Fig. 12.35 Symmetrical bilateral hyperkeratosis in neuropathic feet

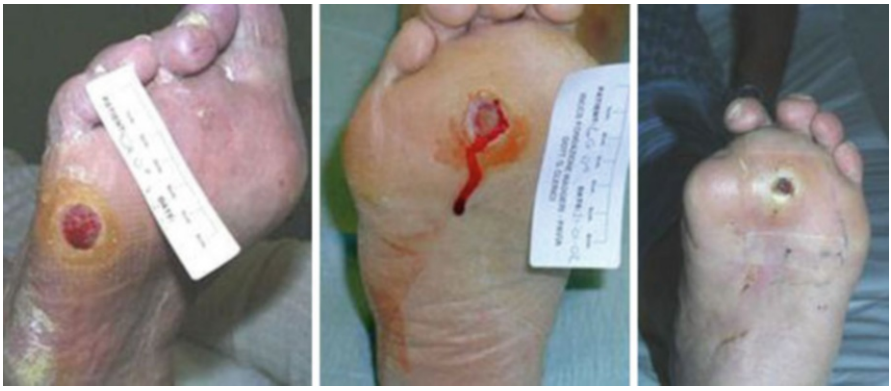

Fig. 12.36 Examples of neuropathic ulcers that developed in hyperpressure areas

patients to dermatophyte colonization and growth, autonomic neuropathy is often associated with ungual mycosis. Autonomic neuropathy may also result in alteration of microvascular regulation [21, 45–49]. Arteriovenous anastomoses of microvascular flow in the skin are associated with skin function and trophism [50]. The arteriovenous anastomotic shunt flow is regulated by sympathetic axons that mediate vasoconstrictor tone. By reducing this tone, autonomic neuropathy impairs the neurogenic vascular response to external stimuli such as heating and strain. Figure 12.44 shows a patient with autonomic neuropathy and typical turgidity of the veins.

High oxygen levels have been observed in the venous blood of patients with diabetic foot. Others have reported the formation of arteriovenous communication

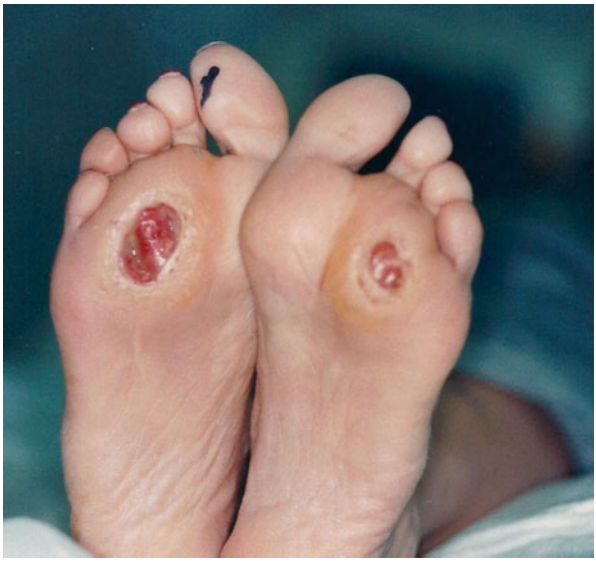

Fig. 12.37 Bilateral plantar foot ulcers

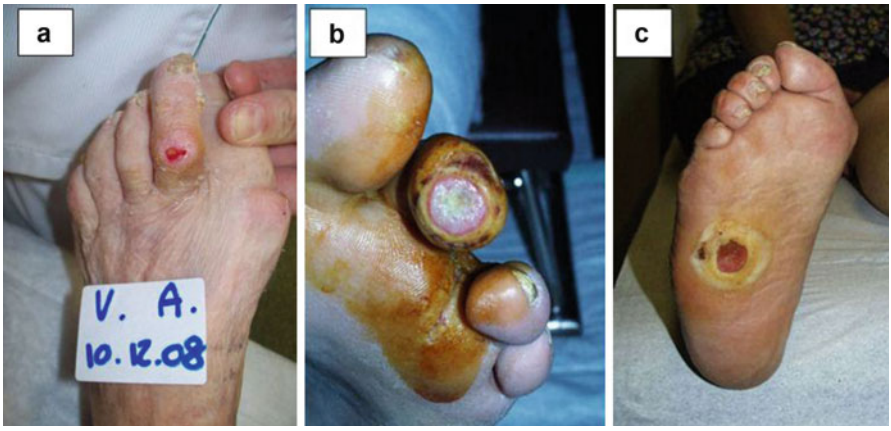

Fig. 12.38 Ulcer on the (**a**) dorsum and (**b**) tip of the second toe as a result of a claw-toe deformity. (**c**) An ulcer on the plantar surface of the midfoot as a consequence of a flatfoot deformity

that is probably related to arteriovenous shunting of vital blood in small vessels [51], but the implications of these findings remain unclear. However, autonomic dysfunctions, including alterations in heart-rate variability, are associated with increased mortality in patients with diabetes [52, 53].

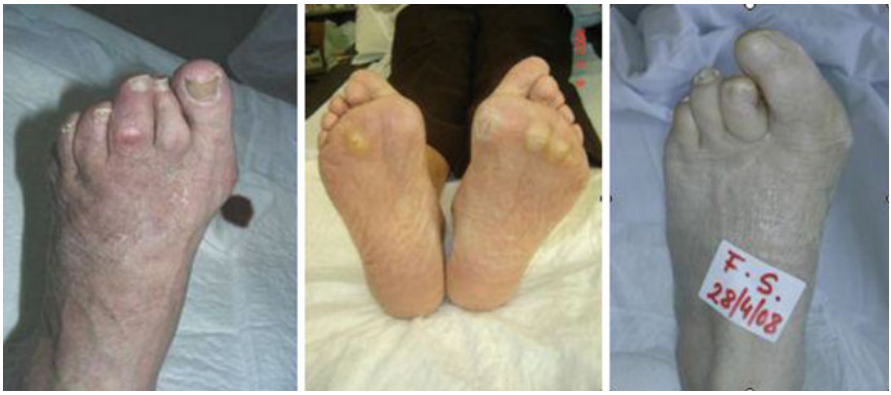

Fig. 12.39 Feet showing foot deformities related to motor neuropathy

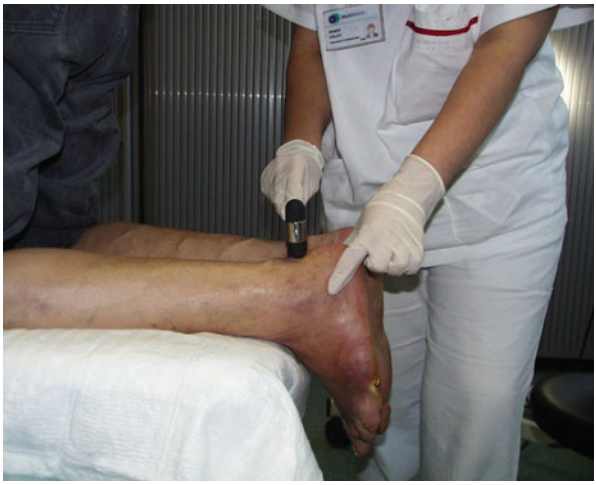

Fig. 12.40 The Achilles tendon reflex test

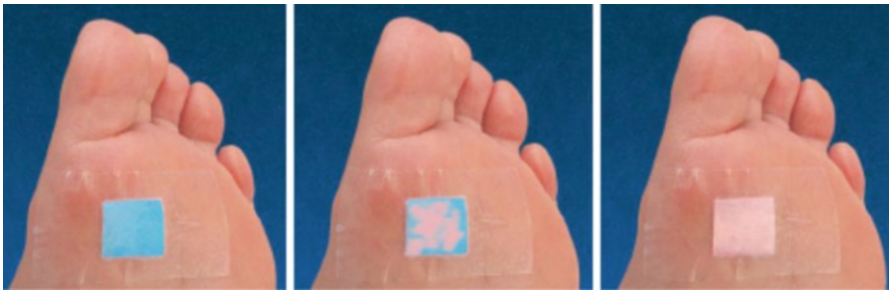

Fig. 12.41 Application of Neuropad plaster to the plantar surface of the foot of a patient with dysautonomia. The color changes reflect sweat gland function

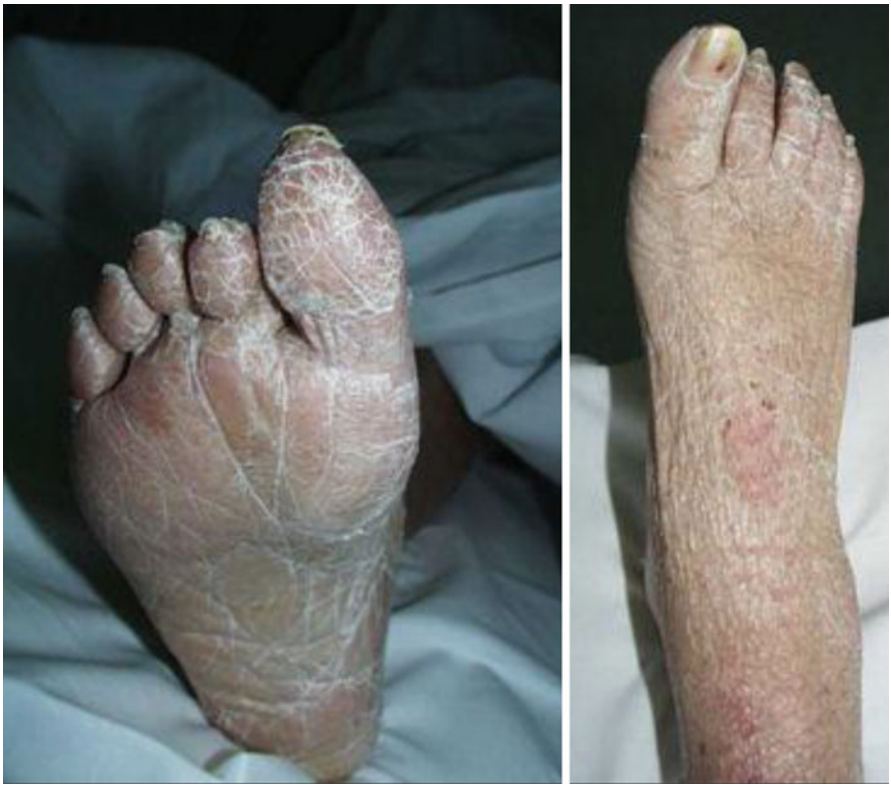

Fig. 12.42 The foot of a patient with autonomic neuropathy shows severe dryness

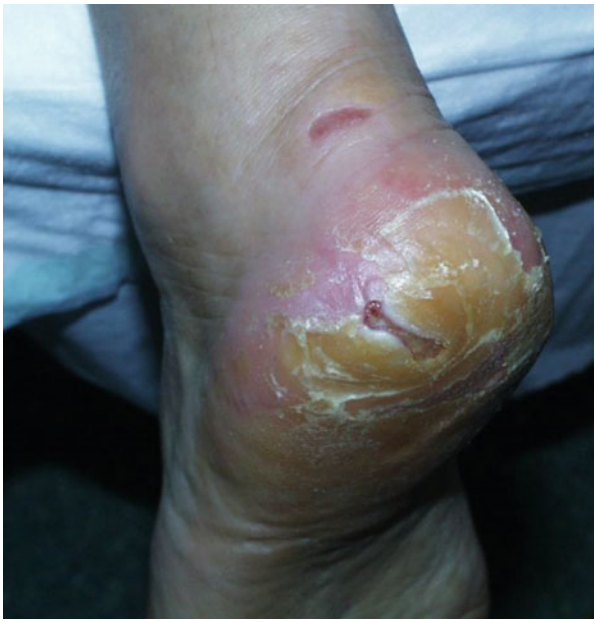

Fig. 12.43 An example of a hyperkeratotic heel fissure

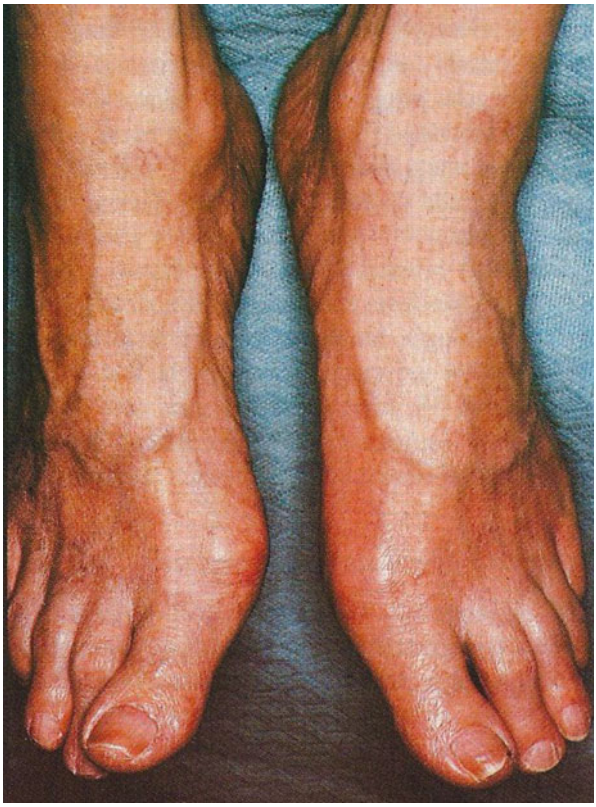

Fig. 12.44 Venous turgidity is clearly evident in the feet of this patient with autonomic neuropathy

12.5 Management of Neuropathic Foot Ulcers

As noted above, neuropathic ulcers typically occur on the plantar surface of the foot, and for this reason, diabetic foot has also been termed "mal perforant plantar" [54]. The forefoot is the most common site of ulceration [55]. Treatment of plantar ulcers requires that the cause, namely, the overload, be removed. First, debridement is performed to completely remove necrotic tissue, exudate, and metabolic waste. Hyperkeratosis may affect the viability and growth of the underlying cells and, consequently, may prevent healing. Accordingly, hyperkeratotic tissue should also be removed. However, debridement is only the first step in ulcer management and must be followed by offloading techniques (Fig. 12.45).

As the healing times for ulcers can be rather long, restriction of patient mobility (e.g., bed rest, use of a wheelchair, etc.) is contraindicated as it can result in muscle hypertrophy, joint rigidity, or thromboembolic events. Thus, offloading is key for ulcer treatment. The gold standard is based on the use of total contact cast (TCC) systems, which completely releases the foot from overload while allowing patient mobility [39, 56, 57]. The first TCCs were rarely

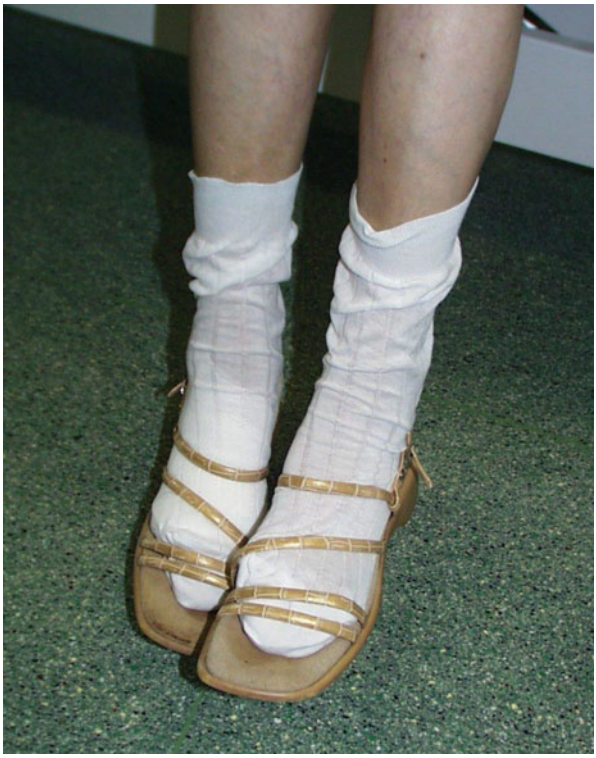

Fig. 12.45 A patient with a neuropathic foot: after ulcer debridement and dressing, the patient can wear regular footwear rather than an offloading device

Fig. 12.46 A total contact cast (TCC) customized using fiberglass bandages

used in clinical practice because they were made of plaster, which often led to ulcer formation due to excessive friction [58, 59]. Subsequently, Italian clinicians developed offloading systems using materials that were more adaptable to variations in foot and leg circumferences during walking [60] (Fig. 12.46).

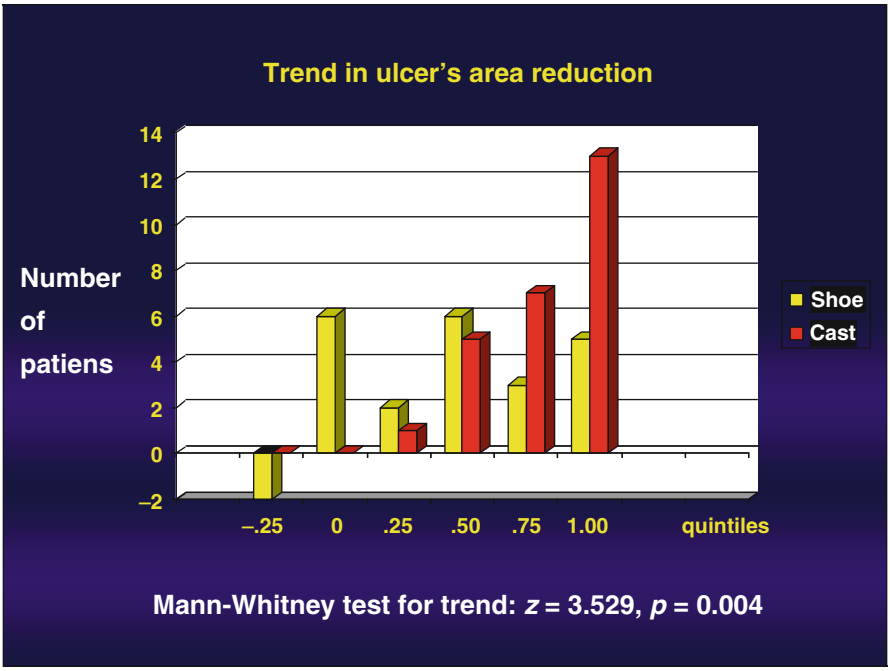

Fig. 12.47 Ulcer size is reduced after the use of therapeutic shoes or offloading systems: see the text for the description

Compared to therapeutic shoes, TCCs accelerate the healing of plantar ulcers; moreover, complete healing occurs more frequently (Fig. 12.47). The effectiveness of these systems has been proven in many studies [61–63]. TCCs are usually changed every week and should be worn until the ulcer is completely healed. However, the use of TCCs can pose some problems and is contraindicated in patients with arteriopathy or infected ulcers. Recent studies, performed in collaboration with Italian investigators, demonstrated that the efficacy of some commercially available removable and nonremovable offloading systems might be comparable to that of TCCs [64, 65] (Fig. 12.48). More studies are being performed to confirm these findings.

Plantar ulcers can be surgically removed by a procedure called an ulcerectomy [66]. This procedure promotes faster healing (Fig. 12.49). Ulcerectomy may be performed concomitantly with an unloading osteotomy to reduce or completely remove a bone protrusion that is causing the overload and thus causing the consequent ulcer (Fig. 12.50). Appropriate offloading footwear must be worn until the surgical plantar suture is completely healed. Patients who undergo surgical removal of ulcers located in areas other than the plantar surface should be given walkers to contain

Fig. 12.48 *Left*. Offloading walker and insoles: Optima Diab (Salvatelli srl, Civitanova Marche Italy). *Right*. An offloading device for the heel when in bed (Heelift AFO, Darco Europe, Raisting, Germany)

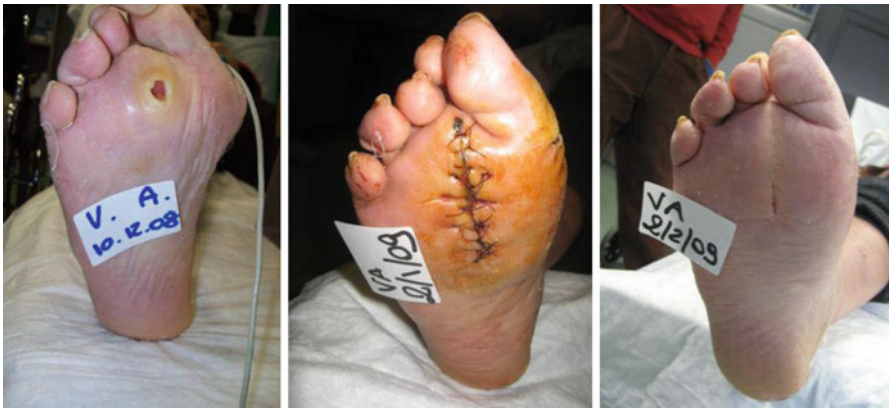

Fig. 12.49 Plantar ulcerectomy with concomitant correction of the valgus toe

and protect the foot with dressing. After healing, the use of proper footwear can prevent further ulcer formation [3].

12.6 Charcot Foot (Neuro-osteoarthropathy)

Charcot foot is a serious condition that is often overlooked, and its diagnosis and treatment can be challenging [67]. Little is known about its pathogenesis, and it is often referred to as "Charcot foot syndrome."

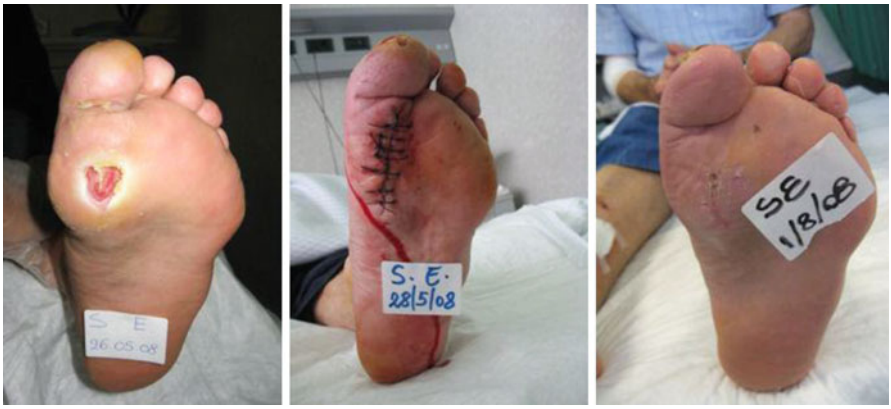

Fig. 12.50 Ulcerectomy with concomitant osteotomy. These procedures completely removed the protrusion of the first metatarsal head bone

12.6.1 Definition

According to a recent definition, Charcot foot syndrome is defined as "Charcot neuropathic osteoarthropathy" and is commonly referred to as "Charcot foot" [68]. Charcot foot is an insidious, destructive, and progressive pathological condition that affects the foot bones and leads to deformity that may cause ulcer formation and subsequent disability. The development of Charcot foot is characterized by subluxation and joint dislocation, osteolysis and bone fragmentation, and soft tissue edema.

12.6.2 Epidemiology

The epidemiological data for Charcot foot vary greatly, with the reported incidence ranging from 0.08 to 13 % of the population. This variation may be due to different definitions, such as the presence or absence of neuropathy, to different descriptions of patient characteristics, or to differences in data collection procedures. Charcot foot most often affects the midfoot, with the forefoot less frequently affected (Fig. 12.51). Ankle deformity occurs in less than 1 % of Charcot foot cases [69]. Neuropathy is a major risk factor for Charcot foot, and other risk factors include diabetes duration, overweight, and osteoporosis. The disease typically develops in patients in their 40s; however, patients who have type 1 diabetes for a long time may develop Charcot foot at an earlier age [70].

12.6.3 Etiopathogenesis

Genetic factors seem to contribute to the etiopathogenesis of Charcot foot. In particular, some studies found an association between osteoprotegerin G1181C and T245G polymorphisms and diabetic Charcot neuroarthropathy [71, 72]. Inflammation plays

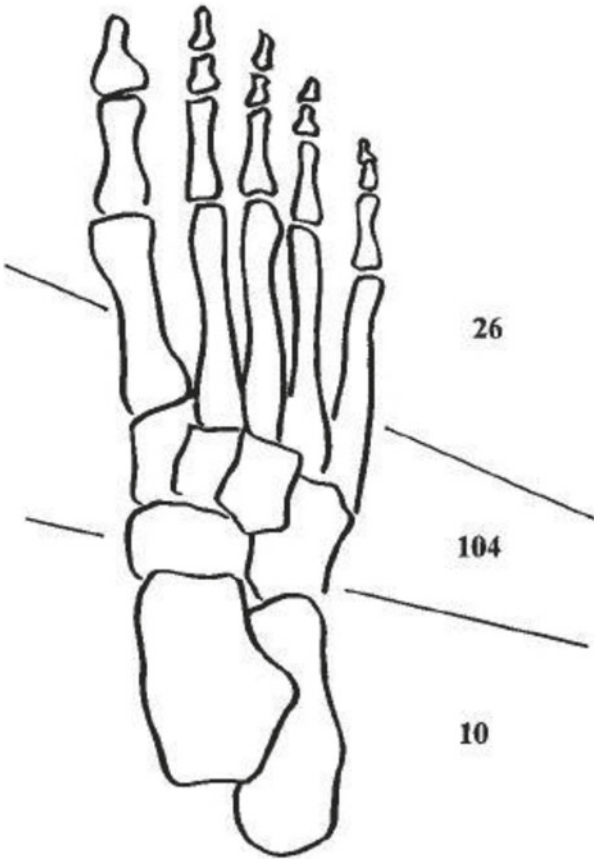

Fig. 12.51 Areas of the foot that may be affected by Charcot foot arthropathy

an important role during the acute phase of Charcot foot. Specifically, increased levels of inflammatory cytokines promote osteoblast differentiation, and increased levels of receptor activator of nuclear factor-κB (RANK) ligand (RANKL) increase osteoclast activity via the RANKL/RANK/ osteoprotegerin (OPG) signaling pathway and overcome the protective effect of OPG-mediated attenuation of osteoblast differentiation [73, 74]. One can speculate that genetic predisposing factors and chronic inflammation can shift the balance of bone remodeling toward osteolysis [75–77]. If not diagnosed promptly and treated effectively, Charcot foot may rapidly evolve and cause severe deformities that lead to the formation of nonhealing ulcers that eventually result in amputation (Fig. 12.52).

12.7 Diagnosis and Treatment of Charcot Foot

12.7.1 Acute Charcot Foot

Acute Charcot foot is characterized by rapid onset and by signs and symptoms that are typical of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (heat), *and*

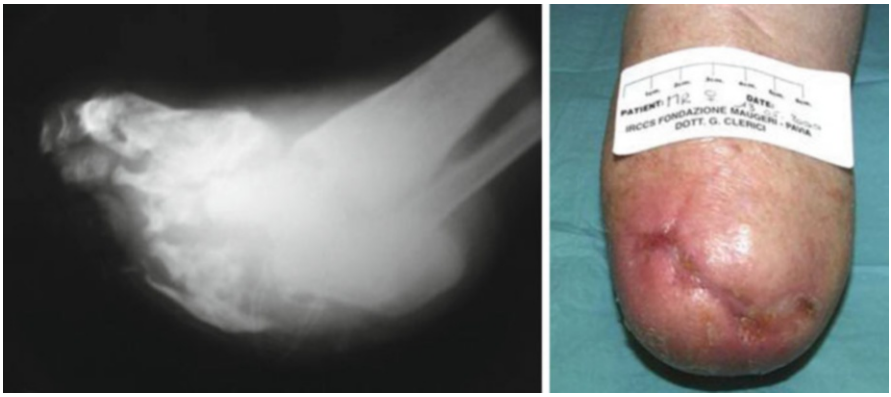

Fig. 12.52 A Charcot foot. In this case, the severe deformity required amputation

functio laesa (loss of function). Pain (*dolor*) is also a symptom of inflammation; however, pain may be reduced or absent due to concomitant sensory neuropathy. Usually pain onset occurs after walking or high-impact weight-bearing activities such as hiking, running, and dancing. During this phase, prompt treatment can halt the progression of bone degeneration and prevent foot deformity. Unfortunately, incipient Charcot foot is seldom diagnosed. Patients should not bear weight on the foot; however, some patients are mistakenly encouraged to walk more. The persistence of overpressure on the weight-bearing areas of foot increases bone resorption and, as a consequence, foot deterioration progresses. The bones fracture easily, and bone deposition becomes irregular, with alterations in the interosseous spaces and bone dislocations. Eventually, the bone architecture resembles a "bag of bones."

X-ray imaging of the foot is the first diagnostic approach for neuropathic patients presenting with suspected Charcot foot. However, X-ray imaging may not be performed until later in the development of Charcot foot, delaying the diagnosis. Assessing the cutaneous temperature is essential for diagnosis, with the skin temperature of the Charcot foot being increased by at least 2 °C compared to the non-affected contralateral side [17]. Figure 12.53 shows an example of acute Charcot foot with edema and increased temperature relative to the contralateral side; an X-ray reveals osteolysis at the bottom of the first metatarsal and the first cuneiform bones. Cutaneous thermometry provides information on the stage of Charcot foot: high temperatures indicate onset, and normal temperatures indicate a quiescent phase.

Magnetic resonance imaging (MRI) is a very sensitive technique that is useful in making a diagnosis of Charcot foot at its earliest stage, even before bone and joint changes become evident on X-rays [76–78]. Specifically, MRI can show alterations that are characteristic of Charcot foot, such as soft tissue swelling and bone and muscle edema [79]. Although MRI is not required for diagnosis when X-rays show signs of Charcot foot, it may be useful for surgery or to exclude the presence of osteomyelitis (in case of an evident or previous ulcer) [80].

Some nuclear techniques can be useful as diagnostic tools [81–85] but, as stated by the American Diabetic Association [68], these methods have some problems,

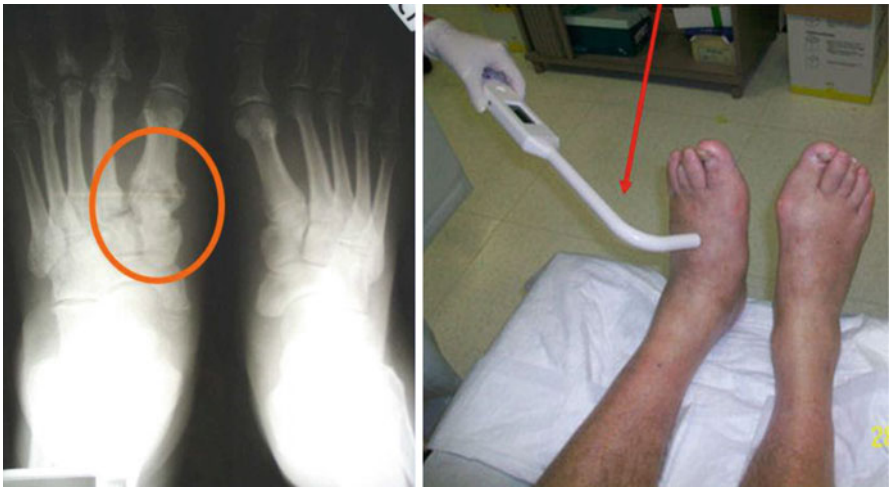

Fig. 12.53 X-ray imaging (*red circle*: bone changes) and assessment of cutaneous temperature (*arrow*: infrared thermometer) are used to diagnose an acute Charcot foot

including false negatives, low specificity, and a poor ability to discriminate between bone and soft tissue. Figure 12.54 shows technetium-99 m scintigraphy that reveals an increased signal on the first metatarsal head and metatarsocuneiform joint. This increased signal might be a sign of structural bone remodeling. Clearly, these diagnostic methods, and PET scans, are only used when a suspected acute Charcot osteoarthropathy cannot be diagnosed by traditional X-ray examination.

The treatment of acute Charcot is based on complete offloading plus the application of a total contact healing plaster cast [86, 87]. In patients with plantar ulcers, total contact casts allow mobility; in contrast, these casts are used to prevent ambulation in patients with Charcot foot. Plaster casts must be replaced as swelling decreases, typically every 7–10 days. With each change, the physician should assess cutaneous temperature and edema reduction as well as apply a new cast. These casts must be worn for prolonged periods (3–6 months). During this time, crutches or a wheelchair must be used to avoid any weight-bearing loads on the foot. Reduction of edema and a decrease in the cutaneous temperature are signs that strict immobilization of the foot has been successful [88] (Fig. 12.55).

Early recognition and treatment of acute Charcot foot can minimize the progression of foot deformity [89]. In contrast, delayed detection prevents prompt immobilization of the foot and may allow irreversible damage to occur [90].

12.7.2 Chronic Charcot Foot

Patients with chronic Charcot foot have characteristic foot deformities (Fig. 12.56). Progression to foot deformity occurs via the attenuation of inflammation and concomitant joint instability and dislocation accompanied by edema of the spongious bone. This phase is followed by erosion of the cartilage and by bone resorption;

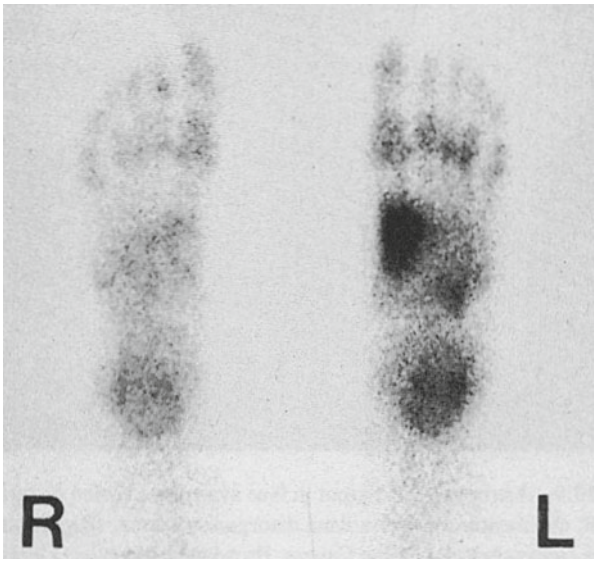

Fig. 12.54 A bone scan using technetium-99m shows a higher signal on the bottom of the first metatarsal bone and metatarsocuneiform joint

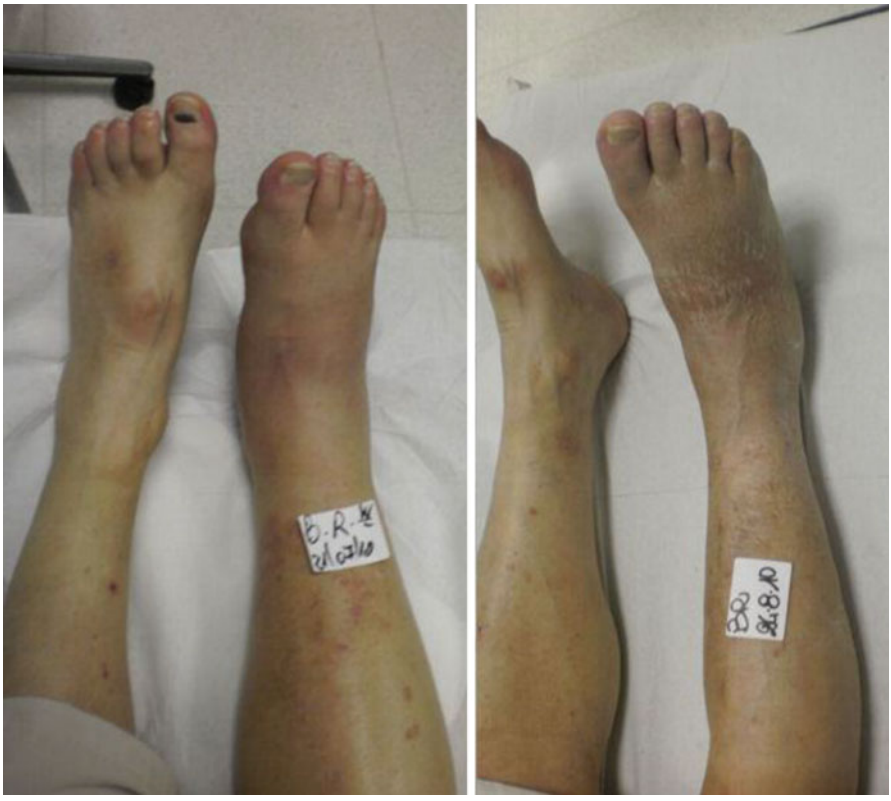

Fig. 12.55 Resolution of edema and redness in a Charcot foot after 5 weeks of immobilization in a plaster cast

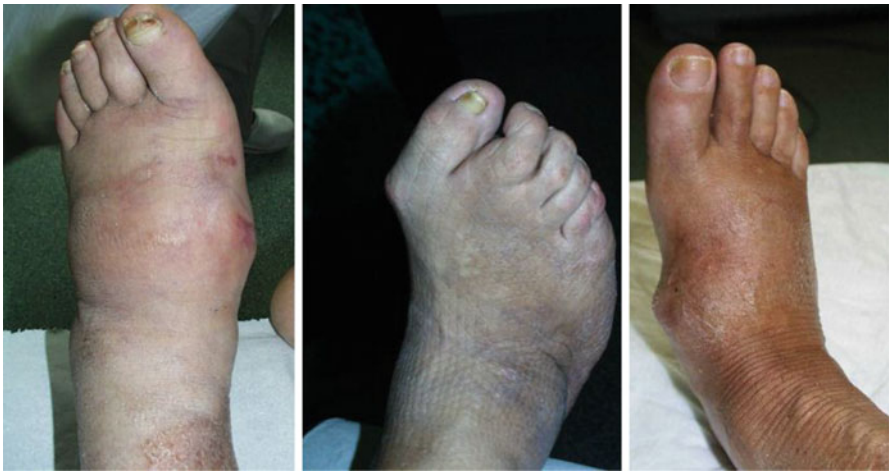

Fig. 12.56 Typical deformities of chronic Charcot foot

further bone fractures may occur, along with new bone resorption and deposition. Foot joint instability progresses and evolves into joint stiffness.

In 1966, Eichenholtz proposed a chronology of the disease that was divided into three stages [91]:

- Stage I (Development): patients present with acute inflammation. X-ray imaging reveals bony erosion or resorption or the presence of bone fragments. The duration ranges between 3 and 6 months.
- Stage II (Coalescence): heat, swelling, and redness increase. The foot becomes stable.
- Stage III (Reconstruction): X-ray imaging reveals remodeling of the bone structure, with new bone consolidation (healing), sclerosis, and increased bone density.

This classification system is useful for optimizing the timing of the surgical intervention. According to this classification, stage III is a phase in which bone destruction and bone consolidation result in distortion of bone architecture, thus causing a deformity (Fig. 12.57).

The hallmark deformity associated with chronic Charcot foot is midfoot collapse of the arch [92], described as a rocker-bottom deformity. As a consequence of this deformity, excessive weight-bearing forces are applied to bone protrusions, and persistence of these forces will eventually lead to formation of a plantar ulcer. Figure 12.58 shows a typical midfoot collapse of the arch with plantar ulceration.

Frykberg and Sanders later proposed a classification system to stage Charcot arthropathy according to the localization of the bone lesion, namely, metatarsophalangeal joint, midfoot, ankle, or heel [67]. Charcot foot treatment and prognosis are related to the extent of the foot deformity and to whether there is a plantar ulcer that can lead to osteomyelitis. Charcot foot without plantar ulceration can be protected using proper footwear and a sole that helps prevent ulcer formation. Prognosis of

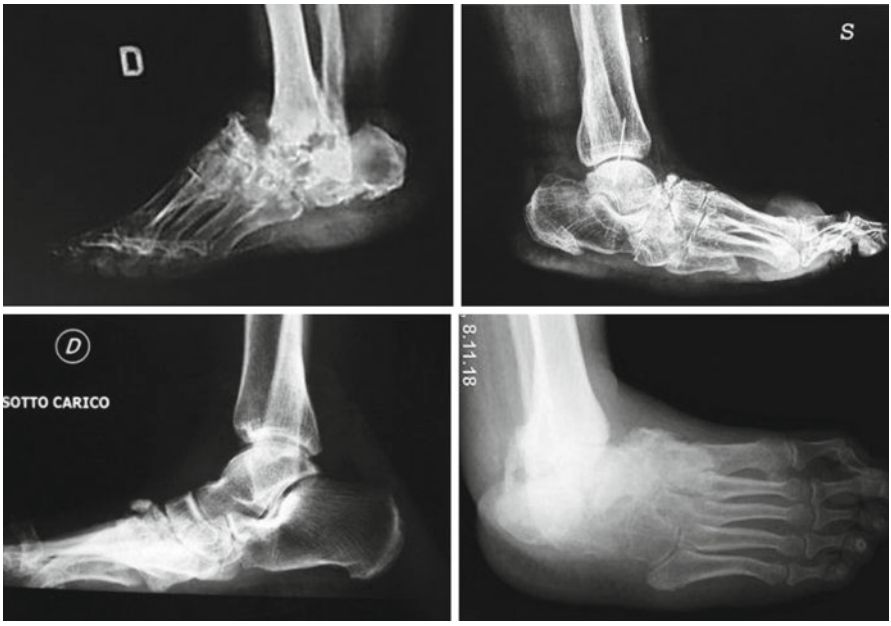

Fig. 12.57 Typical deformities of chronic Charcot foot by X-ray imaging

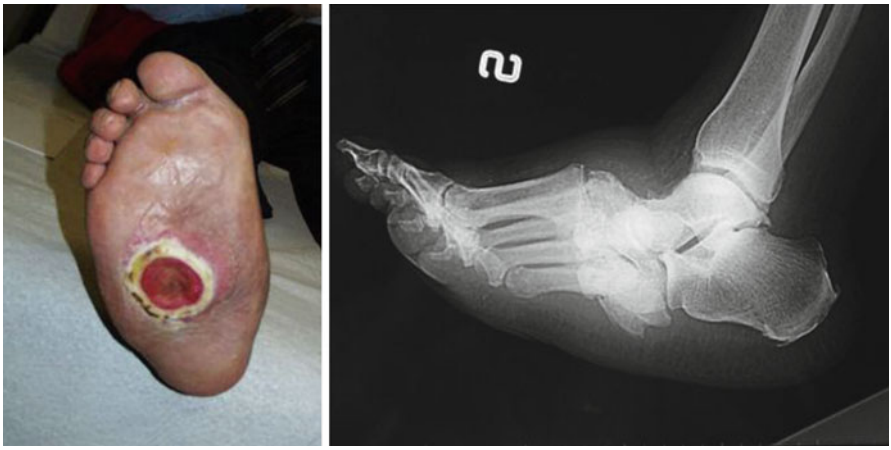

Fig. 12.58 Typical appearance of a rocker-bottom deformity with plantar ulceration.

Charcot in the forefoot is usually favorable, even in the presence of osteomyelitis of the metatarsal bones. Unfortunately, Charcot of the ankle is more likely to result in an above-the-ankle amputation.

Treatment of chronic Charcot foot aims to correct the deformity in order to prevent ulcer formation or to minimize the progression of foot deformity that may cause gait disturbances. If a custom foot orthosis cannot stop ulcers from forming, surgery may be needed to correct the deformity [93]. Surgical management of

Charcot foot is based primarily on expert opinion, and data regarding the most effective surgical techniques are still lacking [68]. Surgery is only performed in patients with Eichenholtz stage III Charcot arthropathy [94]. However, surgical treatment can be difficult and is associated with high failure rates (30–70 %) due to the risk of infection or failure of fixation [95, 96]. The presence of a long-lasting open ulcer is a major clinical challenge as the risk of concomitant osteomyelitis is extremely high.

The severity of Charcot foot depends on prompt recognition and localization of the deformity; deformities occurring near the tibiotarsal joint are associated with higher disease severity than Charcot foot deformities in more distal parts of the foot. Charcot of the heel represents an exception to this rule. Surgical treatment of these conditions must be performed in specialized diabetic foot centers by clinicians with expertise in Charcot foot management.

Finally, it is worth noting that patients with diabetes and Charcot syndrome have higher mortality compared to those with diabetes and neuropathy or with diabetes and neuropathic ulcer [97–99]. Treatment of Charcot foot with uncomplicated plantar ulcers is based on the same approaches used for the management of neuropathic plantar ulcers.

12.8 Ischemic Diabetic Foot Ulcers

For many years, it was thought that neuropathy was the major cause of foot ulceration in patients with diabetes. In fact, the diabetic foot was usually portrayed as having "mal perforans." More recently, arteriopathy was suggested to play an important prognostic role in "diabetic foot syndrome." This assumption was first proposed at the beginning of the 1990s by Pecoraro, who evaluated the relevance of ischemia in the prognosis of amputation, and by LoGerfo, who studied the features of lower limb arteriopathy in diabetes as well as the prognostic relevance of surgical revascularization [100, 101].

Both in diabetic and nondiabetic patients, peripheral artery disease (PAD) develops as a result of pathological deposition of atherosclerotic plaques that partially (stenosis) or completely (occlusion) obstruct one or more lower limb arteries. For this reason, PAD is also referred to as a peripheral occlusive arteriopathy. Although histologically similar to atherosclerosis in nondiabetics, atherosclerosis in patients with diabetes has some morphologically and clinically relevant differences. Compared with nondiabetic subjects, patients with diabetes usually present with more distal and bilateral atherosclerotic lesions; moreover, calcification of the artery walls is more common in diabetes, and occlusions are more frequent than stenoses [102]. All of these features pose challenges when performing revascularization and account for the role of lower limb ischemia as a prognostic determinant for major amputation.

12.8.1 Epidemiology

The incidence of PAD in the general population may be underestimated due to the lack of symptoms in its earliest phase. According to the National Health and

Nutrition Examination Survey (NHANES), more than half of adult PAD patients (>60 years of age) may be asymptomatic [103]. In patients with diabetes, the prevalence of PAD may be even more underestimated, since the perception of pain (both when moving and when at rest) may be attenuated or absent due to the presence of concomitant neuropathy [104]. Despite this confounding factor, the prevalence of PAD is higher in diabetic patients than in the nondiabetic population [105–109]. However, data on PAD prevalence varies according to the diagnostic criteria used [110].

The ankle-brachial index (ABI) is the most accurate, noninvasive method for diagnosing PAD. Using this method, the estimated prevalence of PAD in diabetic patients is 20 %, with some age-related variations [111, 112]. Recently, an Italian study found that PAD was present in 8 % of patients with newly diagnosed diabetes [113]. PAD not only occurs more frequently in diabetics than in nondiabetic subjects, but it may also develop at an earlier age and may affect women during their reproductive years [114]. The rapid progression of PAD in diabetes is of particular importance, with obvious clinical implications for the timing of surveillance [115, 116].

12.8.2 Diagnosis and Management of Ischemic Ulcer (Critical Limb Ischemia)

Assessment of lower extremity arterial occlusive disease is a very important step in managing diabetes [104]. Early detection and recognition may allow successful treatment [117]. Such an assessment should include objective foot assessment, palpation of pulses, and ABI determination.

The accuracy of foot examination for diagnosing PAD is considered insufficient [118]. In this respect, we agree with Mayfield et al., who stated, “The clinical exam remains an inexact art” [119]. Palpation of pulses is fundamental for diagnosing PAD: the absence of palpable pulses is a sign of occlusive disease, though it does not provide information regarding PAD severity or localization of the lesion [120]. Investigator variability may be a confounder for accurate pulse detection.

ABI determination is considered the most sensitive method [121] for diagnosing PAD and also gives good information about the severity of PAD. However, ABI does not provide information about the localization, length, or morphology of stenoocclusions or about run-in and runoff. Segmental pressure determination may provide the approximate lesion localization. Useful information may also be obtained by pulse volume waveform analysis using continuous wave Doppler techniques, but interpretation of the data is quite subjective.

The American Diabetes Association (ADA) considers ABI a “reproducible and reasonable accurate, noninvasive measurement for the detection of PAD and the determination of disease severity” [104]. The ABI is calculated by dividing the systolic blood pressure at the posterior tibial artery or dorsalis pedis artery by the systolic pressure at the humeral artery or radial artery. The ADA states that ABI values <0.91 are suggestive of PAD, and ABI values >1.30 are suggestive of calcification of the tunica media (Mönkeberg’s sclerosis). Other ABI values may provide information about the severity of PAD, as illustrated in Table 12.3.

Table 12.3 PAD severity based on ABI values according to the American Diabetes Association

ABI value	Severity of PAD
0.91–1.30	Normal
0.70–0.90	Mild
0.40–0.69	Moderate
<0.40	Severe

Notably, the incidence of Mönkeberg's sclerosis is higher in diabetic patients than in nondiabetic patients [122, 123]. Calcification of the tunica media is usually associated with neuropathy [124]. In our experience, calcification occurs in about 10 % of patients with early stage type 2 diabetes and in about 40 % of diabetic patients with critical limb ischemia (CLI) [125]. Recently, findings from a Belgian study support our skepticism regarding the accuracy of ABI and ankle pressure measurement, with the authors concluding, "In the diabetic foot, where lesions tend to be situated in BTK arteries (which lie parallel to each other), the pressure measured in one distal artery is less representative of atherosclerotic disease in the lower extremity" [126].

Calcification of the tunica media is responsible for hardening of the vessel, which then becomes incompressible and gives false high-pressure readings; in essence, calcification prevents accurate pressure measurement. An ABI value >1.3 is definitely not a reassuring one as it is suggestive of vascular calcification and a high risk of cardiovascular events [127]. Palpation of pulses and ABI determination can be performed in outpatient settings. These techniques may have some limitations; however, these limitations should not prevent their use.

Researchers have proposed some classification systems to stage PAD severity that may also help physicians select the most appropriate therapeutic approach. The Lèriche-Fontaine classification system and the Rutherford classification system, both of which are based on the presence of pain and ulceration, have been used for many years and are still used today by vascular surgeons. However, these systems should not be used to stage PAD in diabetic patients, as pain, both in motion and at rest, may be absent or attenuated by concomitant neuropathy. Moreover, gangrene can develop from a neuropathic ulcer irrespective of the presence of ischemia.

The Wagner wound classification system, which is well established and widely used, is based on ulcer depth but does not take the presence of arteriopathy into account [128]. The University of Texas classification system, proposed in 1988, includes assessments of wound depth, infection, and ischemia and provides information about the risk of major lower extremity amputation [129]. So far, this classification system is thought to provide the most accurate estimates of the risk of amputation in diabetic patients.

Afterward, the International Working Group on the Diabetic Foot developed the PEDIS classification for research purposes. According to this classification system, which is very similar to the Texas one, wounds are analyzed according to perfusion, depth, infection, and sensation (Table 12.4) [130]. However, none of these classification systems can identify patients at high risk of lower leg amputation based on PAD severity. Epidemiological studies showed that lower limb systolic blood pressure and transcutaneous oximetry at the dorsum of the foot are prognostic discriminants for amputation in subjects with peripheral arteriopathy. Therefore, these

Table 12.4 PEDIS classification provided by the IWGDF

Perfusion	**Grade 1** No symptoms or signs of PAD Palpable dorsal pedal and posterior tibial artery ABI 0.9–1.1 TBI > 0.6 $tcpO_2$ > 60 mmHg	**Grade 2** Symptoms and signs of PAD, but not of critical limb ischemia Presence of intermittent claudication ABI <0.9 and ankle pressure >50 mmHg TBI <0.6 and systolic toe blood pressure >30 mmHg $tcpO_2$ 30–60 mmHg	**Grade 3** Critical limb ischemia Systolic ankle pressure <50 mmHg Systolic toe blood pressure <30 mmHg cpO_2 < 30 mmHg	
Extent/size				
Depth/tissue loss	**Grade 1** Superficial full- thickness ulcer, not penetrating any structure deeper than dermis	**Grade 2** Deep ulcer, penetrating below dermis to subcutaneous structures, involving fascia, muscles, or tendons	**Grade 3** All subsequent layers of the affected foot, including bone and/or joint (exposed bone, probing to bone)	
Infection	**Grade 1** No symptoms or signs of infection	**Grade 2** Infection involving the skin and the subcutaneous tissue only (at least two of following items are present: Swelling Erythema > 0.5–2 cm Local tenderness Warmth Purulent discharge	**Grade 3** Erythema >2 cm plus one of following items: Swelling Tenderness Warmth Discharge	**Grade 4** Any foot infection with following signs of a systemic inflammatory response syndrome: Temperature >38° or <36 °C Heart rate > 90 beats/min Respiratory rate >20 breaths/min $PaCO_2$ < 32 mmHg WBC count >12,000 or <4000/cu mm
Sensation	**Grade 1** No loss of protective sensation	**Grade 2** Loss of protective sensation on affected foot		

parameters are used to identify the severity level at which a limb is at high risk of amputation within 6–12 months. Such a severity grade is referred to as CLI, and systolic blood pressure of the ankle or first toe and transcutaneous oximetry at the dorsum of the foot are used as diagnostic parameters.

In 2007, the second edition of the TASC guidelines proposed an ischemia severity classification system based on systolic blood pressure at the ankle or first toe and on transcutaneous oximetry [131]. However, the presence of calcification and the absence of tibial arteries may pose some problems.

Duplex scanning, which combines Doppler ultrasound with real-time ultrasound imaging of the arteries, is the gold standard noninvasive technique for assessing blood circulation [132, 133]. This is a highly sensitive method for diagnostic assessment of the major arteries of the thigh; however, sensitivity decreases if the test is used to assess below the knee calcified arteries. Unfortunately, as stated above, medial artery calcification is quite common in diabetics. It is worth noting that ankle arteries and arteries of the plantar arch can only be assessed with highly sophisticated instruments used by skilled professionals. Assessment of the peroneal artery can be difficult and, in our experience, is rarely reported in clinical records [9].

CT angiography and MRI angiography are excellent vascular diagnostic methods that produce informative images [134, 135]. However, these techniques may not be accurate for assessing more distal arteries, and the presence of calcification may be a confounder [136, 137]. The rapid development of new techniques is likely to allow the use of these methods to achieve excellent diagnostic results. However, the main issue is whether these diagnostic techniques are essential for determining the need for revascularization. Detection of CLI by transcutaneous oximetry and ankle pressure measurement, if feasible, provide a clear indication for the need for revascularization in the presence of a foot ulcer.

Digital angiography is the gold standard diagnostic tool for foot ulcers and can be used in diabetic patients to detect arterial lesions and to determine their length, localization, and morphology. Arteriography is associated with the risk of serious complications, such as contrast medium-induced nephrotoxicity (CIN). The risk of complications seems to be higher in diabetic patients than in nondiabetic patients; however, the use of pre- and post-examination hydration protocols can reduce the risk of nephrotoxicity to a very low level, even in people with diabetes [138–142]. It is unknown whether the protective effect is due to the substances used in these protocols, such as cysteine, bicarbonate, or to the hydration *sic et simpliciter* [143]. It is clear that in the absence of indications for revascularization, there is no need for arteriography as a diagnostic tool.

Vascular procedures (endoluminal or surgical) can restore direct flow to stenotic and occluded arteries. The only treatment that can significantly reduce the rate of major amputation is revascularization by peripheral transluminal angioplasty or peripheral bypass grafting [144–147]. Other therapeutic approaches, such as treatment with prostanoids, hyperbaric oxygen therapy, epidural stimulation, and ozone therapy, should only be used as adjunct therapies with specific indications, rather than as alternatives to direct revascularization [148–151].

We agree with the statement by Kenneth Ouriel in *The Lancet* that "Revascularization is unquestioned as appropriate therapy for patients with CLI

directed at the prevention of limb-loss and accompanying disability" [152]. Of particular importance is the emphasis that this is the optimal treatment for patients with CLI. This statement communicates a basic concept in the management of diabetic foot ulcers: revascularization is *necessary* for wound healing, but is not enough to *ensure* healing. Importantly, proper management of foot ulcers is required after revascularization for successful healing and to maximize the chances of limb salvage. Figure 12.59 shows an example of successful recanalization of the posterior tibial artery (a) and the use of the pedal-plantar loop technique (b); note that careful post-procedure care of the lesion (foot care) was required for limb salvage (c).

These techniques are essential for treating patients with symptoms of critical limb ischemia, such as rest pain and/or foot lesion. They are also needed to increase

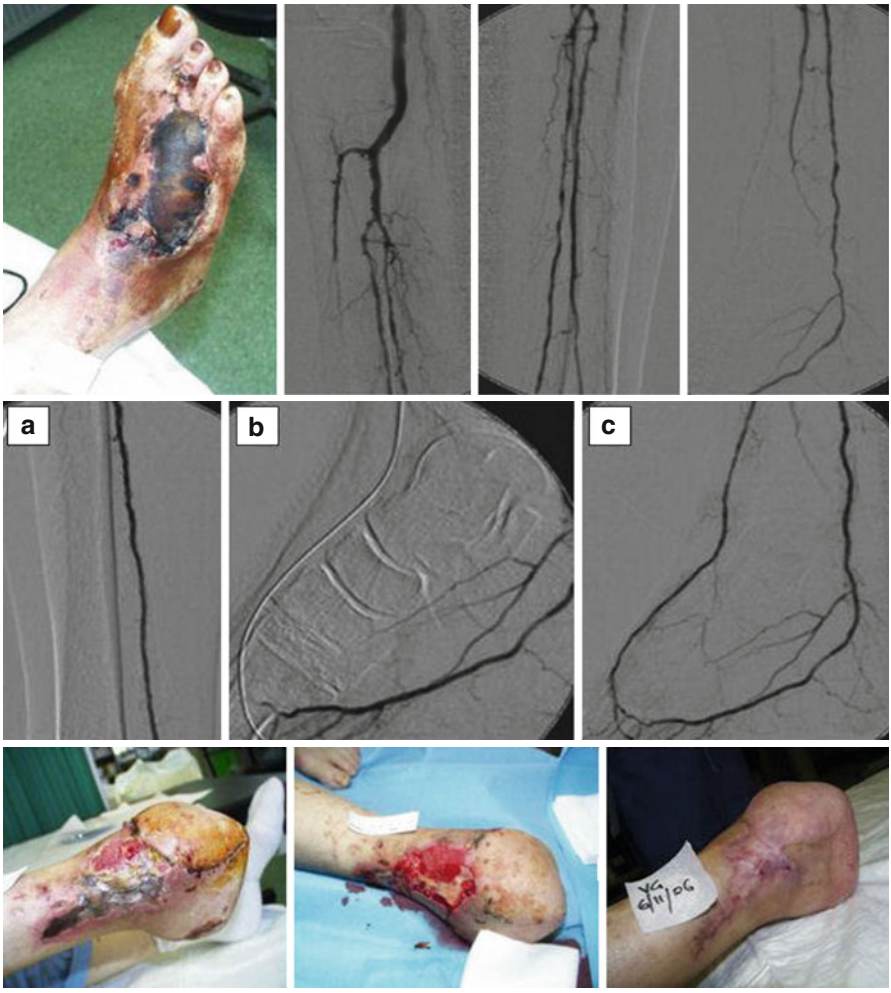

Fig. 12.59 Successful recanalization of (**a**) the posterior tibial artery and (**b**) pedal-plantar loop. (**c**) Limb salvage after revascularization plus wound care and surgery

the chances of successful debridement of gangrenous tissue in the feet of patients with CLI. In our opinion, medical malpractice may arise when clinicians opt for minor amputation without previous assessment of CLI and concomitant revascularization (if indicated).

12.8.3 Treatment of Ischemic Foot Ulcer After Revascularization

Revascularization is a necessary approach for wound healing but is not enough to ensure healing. Indeed, appropriate foot ulcer management is required after revascularization for successful healing and to maximize the chances of limb salvage. Revascularization may be enough to ensure the healing of superficial, noninfected ulcers (grade C1 according to the Texas wound classification system or grade 1 according to the Wagner classification); in such ulcers, the restoration of blood flow can help spontaneous healing. It is worth noting that Texas grade C1 ulcers account for just 20 % of all lesions; nevertheless, this is a surprisingly high percentage of ulcers that can, theoretically, heal easily.

Deep and/or infected ulcers may not heal easily [153]. Figure 12.60 shows the rates of amputation in patients with foot sepsis alone or combined with CLI. Notably, the presence of infection in the ulcers of ischemic patients is associated with a very high risk of amputation. Thus, with the aim of minimizing the chance of limb loss, revascularization must be combined with appropriate ulcer care. Figure 12.61a–e shows an example of a foot lesion that required appropriate care combined with revascularization to heal.

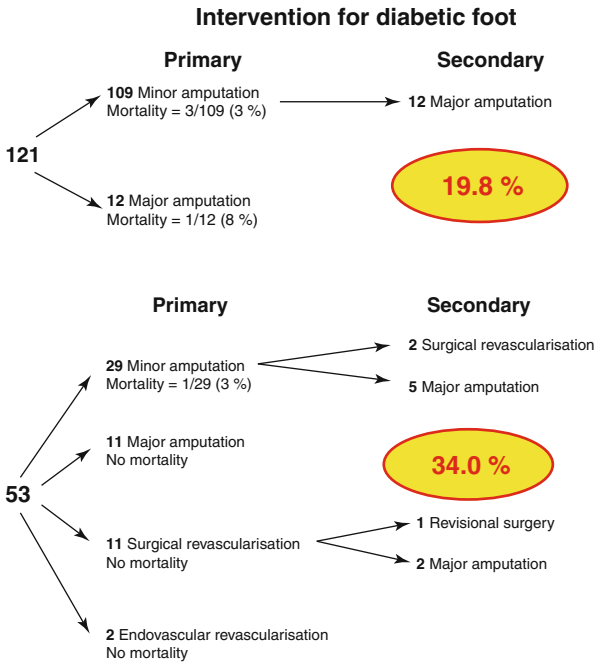

Fig. 12.60 Amputation rates in patients with sepsis alone or with combined critical lower limb ischemia (CLI) and sepsis

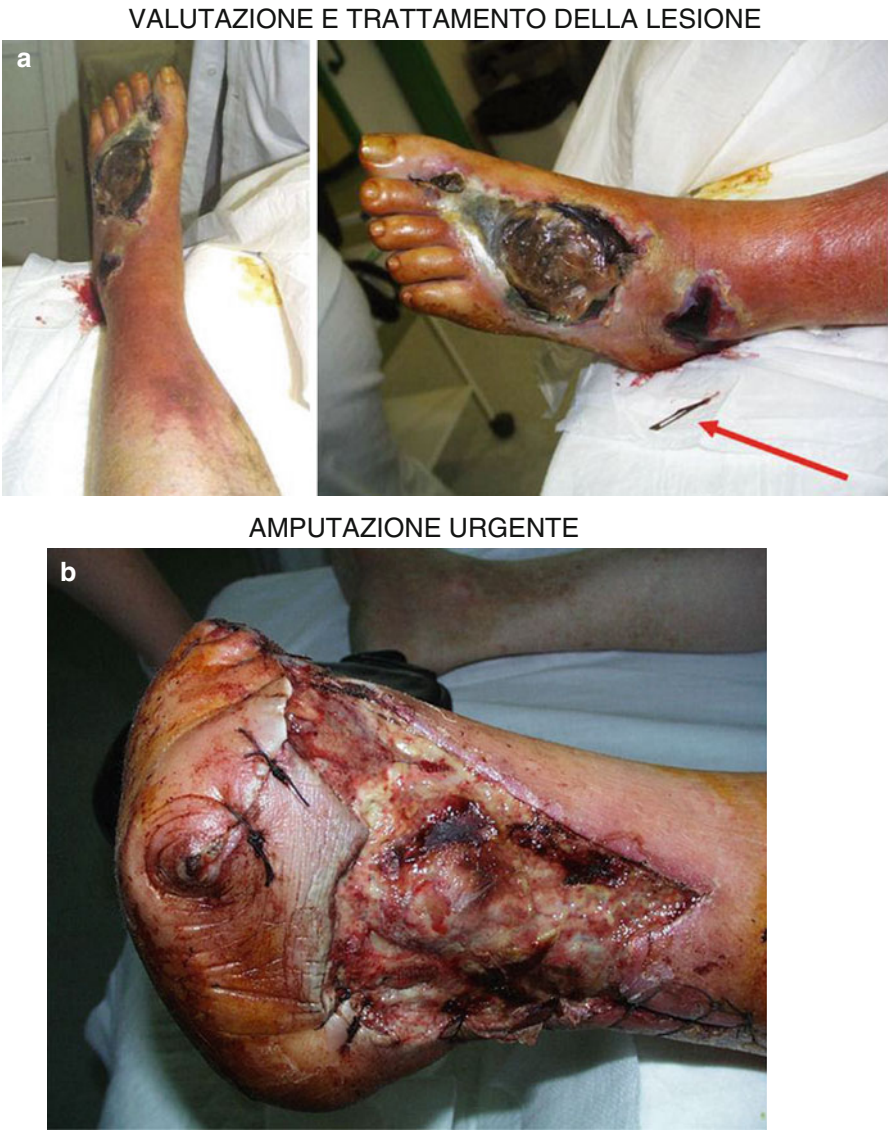

Fig. 12.61 (**a**) A patient presented with a deep abscess on the midfoot and fasciitis extending beyond the ankle. After surgical incision, collection of pus on the forefoot became evident. (**b**) The patient underwent Chopart-level amputation in an emergency room. The abscess was removed surgically, and extensive surgical debridement of the suprafacial tissue (up to the ankle) was performed. (**c**) The day after surgery, percutaneous transluminal angioplasty revascularization was performed, with recanalization of the completely occluded posterior tibial artery and the stenotic anterior tibial artery. (**d**) The wound bed appearance on day 5 after revascularization. (**e**) Wound healing after dermo-epidermal skin grafting

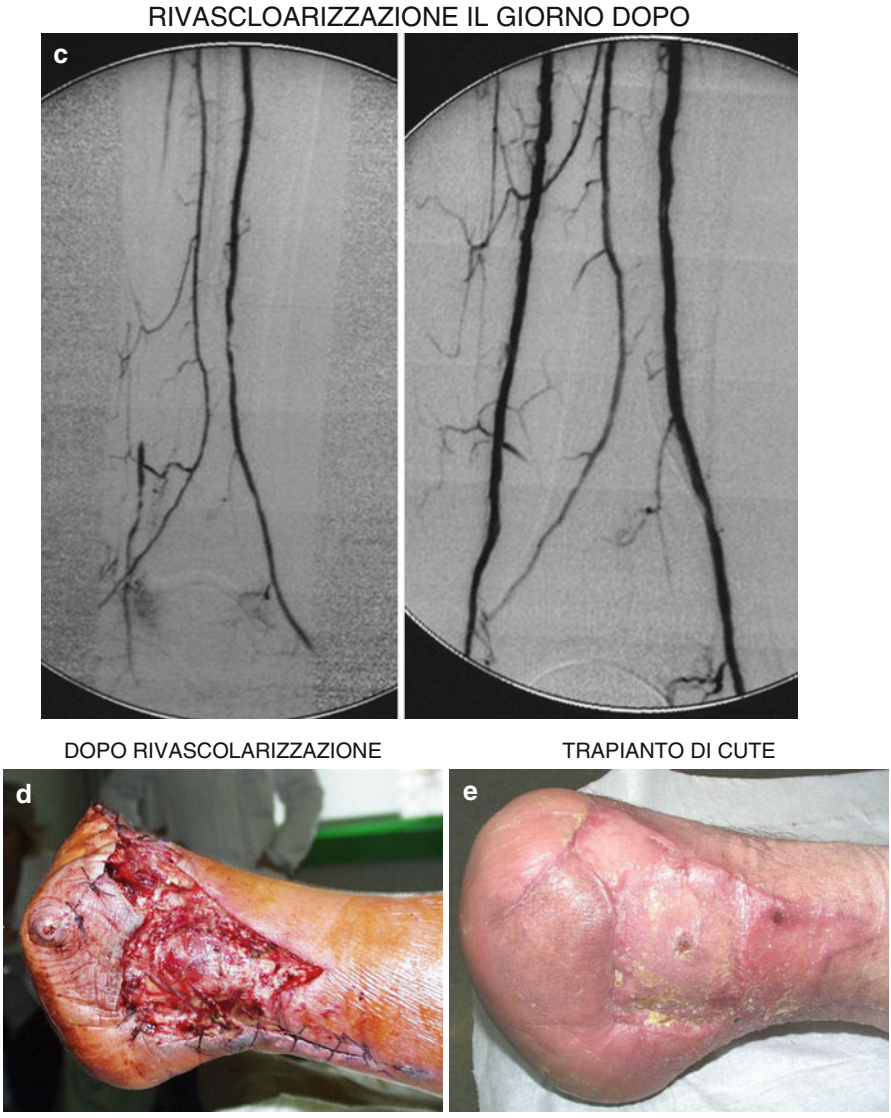

Fig. 12.61 (continued)

Conclusions

Diabetic foot may be referred to as a "syndrome" rather than as a "disease," and treatment strategies should be based on this concept of the condition as a group of different clinical findings. Establishing a differential diagnosis between neuropathic and neuroischemic foot is the first step toward appropriate care. Offloading is the gold standard treatment for noninfected neuropathic ulcers, and

revascularization is the cornerstone of treatment of neuroischemic ulcers, since it minimizes the chance of lower limb amputation. However, if not combined with proper wound care (conservative or surgical), revascularization alone is not enough to ensure wound healing and to prevent the development of gangrenous infection. Finally, treatment of Charcot foot can be difficult. Early detection and recognition can minimize its progression to severe deformity. Customized shoes and insoles may be indicated in less serious conditions, while severe deformities may require corrective surgery. Multidisciplinary approaches and multimodal treatment of diabetic foot ulcers are key strategies for successful outcomes, namely, minimizing amputation and maximizing patient survival.

References

1. Boyko EJ, Ahroni JH, Smith DG, Davignon D. Increased mortality associated with diabetic foot ulcer. Diabet Med. 1996;13:967–72.
2. Chammas NK, Hill RL, Foster AV, Edmonds ME. Is neuropathic ulceration the key to understanding increased mortality due to ischaemic heart disease in diabetic foot ulcer patients? A population approach using a proportionate model. J Int Med Res. 2002;30: 553–9.
3. Uccioli L. Advances in the treatment of peripheral vascular disease in diabetes and reduction of major amputations. Int J Low Extrem Wounds. 2011;10:72–4.
4. Vamos EP, Bottle A, Edmonds ME, Valabhji J, Majeed A, Millett C. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care. 2010;33:2592–7.
5. Li Y, Burrows NR, Gregg EW, Albright A, Geiss LS. Declining rates of hospitalization for nontraumatic lower-extremity amputation in the diabetic population aged 40 years or older: U.S., 1988–2008. Diabetes Care. 2012;35:273–7.
6. Centers for Disease Control and Prevention (CDC). Hospital discharge rates for nontraumatic lower extremity amputation by diabetes status–United States, 1997. MMWR Morb Mortal Wkly Rep. 2001;50:954–8.
7. Sanders LJ, Robbins JM, Edmonds ME. History of the team approach to amputation prevention: pioneers and milestones. J Vasc Surg. 2010;52(Suppl):3S–16.
8. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Barbano P, et al. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. J Diabetes Complications. 1998;12:96–102.
9. Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes in Italy: 2001–2010. PLoS One. 2014;9(1):e86405.
10. Faglia E, Clerici G, Mantero M, Caminiti M, Quarantiello A, Curci V, Morabito A. Incidence of critical limb ischemia and amputation outcome in contralateral limb in diabetic patients hospitalized for unilateral critical limb ischemia during 1999–2003 and followed-up until 2005. Diabetes Res Clin Pract. 2007;77:445–50.
11. Edmonds ME. Progress in the care of diabetic foot. Lancet. 1999;354:270–2.
12. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care. 2003;26:491–4.
13. Rathur HM, Boulton AJ. The neuropathic diabetic foot. Nat Clin Pract Endocrinol Metab. 2007;3:14–25.
14. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes Care. 1999;22:1029–35.

15. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D, Ragnarson Tennvall G, Reike H, Spraul M, Uccioli L, Urbancic V, Van Acker K, van Baal J, van Merode F, Schaper N. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia. 2007;50:18–25.
16. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, Jirkovska A, Piaggesi A, Ragnarson-Tennvall G, Reike H, Spraul M, Van Acker K, Van Baal J, Van Merode F, Ferreira I, Huijberts M. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia. 2008;51:747–55.
17. American Diabetes Association/American Academy of Neurology: report and recommendations of the San Antonio Conference on diabetic neuropathy. Diabetes Care. 1988;11:592–7.
18. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P, Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33:2285–93.
19. Bril V, England JD, Franklin GM, Backonja M, Cohen JA, Del Toro DR, Feldman EL, Iverson DJ, Perkins B, Russell JW, Zochodne DW, American Academy of Neurology, American Asociation of Neuromuscular and Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy–report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation. Muscle Nerve. 2011;43:910–7.
20. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care. 2004;27:1458–86.
21. Maser RE, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab. 2005;90:5896–903.
22. Spallone V, Morganti R. Neuropatia diabetica. In: Uccioli L, editor. Il piede diabetico. Società Editrice Universo. Roma; 2008. p. 53–106.
23. Dyck PJ. Severity and staging of diabetic polyneuropathy. In: Gries FA, Cameron NE, Low PA, Ziegler D, editors. Textbook of diabetic neuropathy. Stuttgart: Thieme; 2003. p. 170–5.
24. Boulton AJ. Guidelines for diagnosis and outpatient management of diabetic peripheral neuropathy. European Association for the Study of Diabetes, Neurodiab. Diabetes Metab. 1998;24 Suppl 3:55–65.
25. Nather A, Neo SH, Chionh SB, Liew SC, Sim EY, Chew JL. Assessment of sensory neuropathy in diabetic patients without diabetic foot problems. J Diabetes Complications. 2008;22:126–31.
26. Modawal A, Fley J, Shukla R, Rudawsky D, Welge J, Yang J. Use of monofilament in the detection of foot lesions in older adults. J Foot Ankle Surg. 2006;45:76–81.
27. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. J Vasc Surg. 2009;50:675–82.
28. Van Deursen RW, Sanchez MM, Derr JA, Becker MB, Ulbrecht JS, Cavanagh PR. Vibration perception threshold testing in patients with diabetic neuropathy: ceiling effects and reliability. Diabet Med. 2001;18:469–75.
29. Manivannam M, Periyasamy R, Narayanamurtty VB. Vibration perception threshold and the law of mobility in diabetic mellitus patients. Prim Care Dibetes. 2009;3:17–21.
30. Reulen JP, Lansbergen MD, Verstraete E, Spaans F. Comparison of thermal threshold tests to assess small nerve fiber function: limits vs. levels. Clin Neurophysiol. 2003;114:556–63.
31. Bagavathiappan S, Philip J, Jayakumar T, Raj B, Rao PN, Varalakshmi M, Mohan V. Correlation between plantar foot temperature and diabetic neuropathy: a case study by using an infrared thermal imaging technique. J Diabetes Sci Technol. 2010;4:1386–92.
32. Ziegler D, Mayer P, Wiefels K, Gries FA. Evaluation of thermal, pain, and vibration sensation thresholds in newly diagnosed type 1 diabetic patients. J Neurol Neurosurg Psychiatry. 1988;11:1420–4.

33. Sosenko JM, Kato M, Soto R, Bild DE. Comparison of quantitative sensory threshold measures for their association with foot ulceration in diabetic patients. Diabetes Care. 1990;13:1057–61.
34. Miralles-García JM, de Pablos-Velasco P, Cabrerizo L, Pérez M, López-Gómez V, Sociedad Española de Endocrinología y Nutrición. Prevalence of distal diabetic polyneuropathy using quantitative sensory methods in a population with diabetes of more than 10 years' disease duration. Endocrinol Nutr. 2010;57:414–20.
35. Zinman LH, Bril V, Perkins BA. Cooling detection thresholds in the assessment of diabetic sensory polyneuropathy: comparison of CASE IV and Medoc instruments. Diabetes Care. 2004;27:1674–9.
36. Ziegler D, Siekierka-Kleiser E, Meyer B, Schweers M. Validation of a novel screening device (NeuroQuick) for quantitative assessment of small nerve fiber dysfunction as an early feature of diabetic polyneuropathy. Diabetes Care. 2005;28:1169–74.
37. Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. Diabetes Care. 2002;25:1444–50.
38. Bus SA, Maas M, Cavanagh PR, Michels RP, Levi M. Plantar fat-pad displacement in neuropathic diabetic patients with toe deformity: a magnetic resonance imaging study. Diabetes Care. 2004;27:2376–81.
39. Cavanagh PR, Ulbrecht JS, Caputo GM. Biomechanical aspects of diabetic foot disease: aetiology, treatment and prevention. Diabet Med. 1996;13 Suppl 1:517–22.
40. Schnider SL, Kohn RR. Glucosylation of human collagen in aging and diabetes mellitus. J Clin Invest. 1980;66:1179–81.
41. Giacomozzi C, D'Ambrogi E, Uccicoli L, Macellari V. Does the thickening of Achilles tendon and plantar fascia contribute to the alteration of diabetic foot loading? Clin Biomech (Bristol, Avon). 2005;20:532–39.
42. Carrington AL, Shaw JE, Van Schie CH, Abbott CA, Vileikyte L, Boulton AJ. Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? Diabetes Care. 2002;25:2010–5.
43. Kanji JN, Anglin RE, Hunt DI, Panju A. Does this patient with diabetes have large -fiber peripheral neuropathy? JAMA. 2010;303:1526–32.
44. Freeman R. Autonomic peripheral neuropathy. Lancet. 2005;365:1259–70.
45. Tentolouris N, Voulgari C, Liatis S, Kokkinos A, Eleftheriadou I, Makrilakis K, Marinou K, Katsilambros N. Moisture status of the skin of the feet assessed by the visual test neuropad correlates with foot ulceration in diabetes. Diabetes Care. 2010;33:1112–4.
46. Quattrini C, Jeziorska M, Tavakoli M, Begum P, Boulton AJ, Malik RA. The Neuropad test: a visual indicator test for human diabetic neuropathy. Diabetologia. 2008;51:1046–50.
47. Spallone V, Morganti R, Siampli M, Fedele T, D'Amato C, Cacciotti L, Maiello MR. Neuropad as a diagnostic tool for diabetic autonomic and sensorimotor neuropathy. Diabet Med. 2009;26:686–92.
48. Tentolouris N, Marinou K, Kokotis P, Karanti A, Diakoumopoulou E, Katsilambros N. Sudomotor dysfunction is associated with foot ulceration in diabetes. Diabet Med. 2009;26:302–5.
49. Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, Melga P, Viviani GL, Esposito K, Morganti R, Cortelli P, Diabetic Neuropathy Study Group of the Italian Society of Diabetology. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis. 2011;21:69–78.
50. Stevens MJ, Edmonds ME, Douglas SLE, Watkins PJ. the influence of neuropathy on the microvascular response to local heating in the human diabetic foot. Clin Sci. 1991;80:249.
51. Hamady MS, Yu DF, Sayer GL, Edmonds ME, Walters HL, Sidhu PS. Lower limb arteriovenous communications in diabetes mellitus: a potential reason for aggravation of ischemic symptoms. Cardiovasc Intervent Radiol. 2006;29:745–51.
52. Wheeler SG, Ahroni JH, Boyko EJ. Prospective study of autonomic neuropathy as a predictor of mortality in patients with diabetes. Diabetes Res Clin Pract. 2002;58:131–8.

53. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. Diabetes Care. 2006;29:334–9.
54. Delbrigde L, Ctercteko GC, Fowler C. The aetioligy of neuropathic ulceration in the diabetic foot. Br J Surg. 1985;72:1–6.
55. Boulton AJ. Diabetic neuropathy: classification, measurement and treatment. Curr Opin Endocrinol Diabetes Obes. 2007;14:141–5.
56. Caputo GM, Ulbrecht JS, Cavanagh PR. The total contact cast: a method for treating neuropathic diabetic ulcers. Am Fam Physician. 1997;55:605–11.
57. Boulton AJ, Bowker JH, Gadia M, Lemerman R, Caswell K, Skyler JS, Sosenko JM. Use of plaster casts in the management of diabetic neuropathic foot ulcers. Diabetes Care. 1986;9:149–52.
58. Nabuurs-Fransenn M, Sleegers R, Huijberts MSP, Wijnen W, Sanders AP, Walenkamp G, Schaper NC. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. Diabetes Care. 2005;28:243–7.
59. Sinacore DR. Total contact casting for diabetic neuropathic ulcers. Phys Ther. 1996;76: 296–301.
60. Caravaggi C, Faglia E, De Giglio R, Mantero M, Quarantiello A, Sommariva E, Gino M, Pritelli C, Morabito A. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care. 2000;23:1746–51.
61. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001;24:1019–22.
62. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, Mizel MS, Boulton AJ. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005;28:555–9.
63. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vasc Surg. 2010;52(3 Suppl):37S–43.
64. Piaggesi A, Macchiarini S, Rizzo L, Palumbo F, Tedeschi A, Nobili LA, Leporati E, Scire V, Teobaldi I, Del Prato S. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. Diabetes Care. 2007;30:586–90.
65. Faglia E, Caravaggi C, Clerici G, Sganzaroli A, Curci V, Vailati W, Simonetti D, Sommalvico F. Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. Diabetes Care. 2010;33:1419–23.
66. Piaggesi A, Schipani E, Campi F, Romanelli M, Baccetti F, Arvia C, Navalesi R. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabet Med. 1998;15:412–7.
67. Sanders LJ, Frykberg RG. Charcot neuroarthropathy of the foot. In: Bowker JH, Pfeifer MA, editors. Levin and O'Neal's the diabetic foot. 6th ed. St. Louis: Mosby; 2001. p. 439–65.
68. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, Van GH, Hartemann A, Game F, Jeffcoate W, Jirkovska A, Jude E, Morbach S, Morrison WB, Pinzur M, Pitocco D, Sanders L, Wukich DK, Uccioli L. The Charcot foot in diabetes. Diabetes Care. 2011;34:2123–9.
69. Fabrin J, Larsen K, Holstein PE. Long-term follow-up in diabetic Charcot feet with spontaneous onset. Diabetes Care. 2000;23:796–800.
70. Petrova NL, Foster AV, Edmonds ME. Difference in presentation of charcot osteoarthropathy in type 1 compared with type 2 diabetes. Diabetes Care. 2004;27:1235–6.
71. Pitocco D, Zelano G, Gioffrè G, Di Stasio E, Zaccardi F, Martini F, Musella T, Scavone G, Galli M, Caputo S, Mancini L, Ghirlanda G. Association between osteoprotegerin G1181C and T245G polymorphisms and diabetic charcot neuroarthropathy: a case-control study. Diabetes Care. 2009;32:1694–7.

72. Korzon-Burakowska A, Jakóbkiewicz-Banecka J, Fiedosiuk A, Petrova N, Koblik T, Gabig-Cimińska M, Edmonds M, Małecki MT, Węgrzyn G. Osteoprotegerin gene polymorphism in diabetic Charcot neuroarthropathy. Diabet Med. 2011;29(6):771–5.
73. Ndip A, Williams A, Jude EB, Serracino-Inglott F, Richardson S, Smyth JV, Boulton AJ, Alexander MY. The RANKL/RANK/OPG signaling pathway mediates medial arterial calcification in diabetic Charcot neuroarthropathy. Diabetes. 2011;60:2187–96.
74. Mabilleau G, Petrova NL, Edmonds ME, Sabokbar A. Increased osteoclastic activity in acute Charcot's osteoarthropathy: the role of receptor activator of nuclear factor-kappaB ligand. Diabetologia. 2008;51:1035–40.
75. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood. 2012;119:651–65.
76. Toledano TR, Fatone EA, Weis A, Cotten A, Beltran J. MRI evaluation of bone marrow changes in the diabetic foot: a practical approach. Semin Musculoskelet Radiol. 2011;15:257–68.
77. Gaeta M, Mileto A, Mazzeo A, Minutoli F, Di Leo R, Settineri N, Donato R, Ascenti G, Blandino A. MRI findings, patterns of disease distribution, and muscle fat fraction calculation in five patients with Charcot-Marie-Tooth type 2 F disease. Skeletal Radiol. 2011;41(5):515–24.
78. Zampa V, Bargellini I, Rizzo L, Turini F, Ortori S, Piaggesi A, Bartolozzi C. Role of dynamic MRI in the follow-up of acute Charcot foot in patients with diabetes mellitus. Skeletal Radiol. 2011;40:991–9.
79. Chantelau E, Richter A, Ghassem-Zadeh N, Poll LW. "Silent" bone stress injuries in the feet of diabetic patients with polyneuropathy: a report on 12 cases. Arch Orthop Trauma Surg. 2007;127:171–7.
80. Ledermann HP, Morrison WB. Differential diagnosis of pedal osteomyelitis and diabetic neuroarthropathy: MR Imaging. Semin Musculoskelet Radiol. 2005;9:272–83.
81. Palestro CJ, Mehta HH, Patel M, Freeman SJ, Harrington WN, Tomas MB, Marwin SE. Marrow versus infection in the Charcot joint: indium-111 leukocyte and technetium-99m sulfur colloid scintigraphy. J Nucl Med. 1998;39:346–50.
82. Tomas MB, Patel M, Marwin SE, Palestro CJ. The diabetic foot. Br J Radiol. 2000;73:443–50.
83. Palestro CJ, Love C. Nuclear medicine and diabetic foot infections. Semin Nucl Med. 2009;39:52–65.
84. Pickwell KM, van Kroonenburgh MJ, Weijers RE, van Hirtum PV, Huijberts MS, Schaper NC. F-18 FDG PET/CT scanning in Charcot disease: a brief report. Clin Nucl Med. 2011;36:8–10.
85. Höpfner S, Krolak C, Kessler S, Tiling R, Brinkbäumer K, Hahn K, Dresel S. Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. Foot Ankle Int. 2004;25:890–5.
86. Frykberg RG, Eneroth M. Principles of conservative management. In: Frykberg RG, editor. The diabetic Charcot foot: principles and management. Brooklandville: Data Trace Publishing Company; 2010. p. 93–116.
87. Jostel A, Jude EB. Medical treatment of Charcot neuroosteoarthropathy. Clin Podiatr Med Surg. 2008;25:63–9. vi–vii.
88. Armstrong DG, Todd WF, Lavery LA, Harkless LB, Bushman TR. The natural history of acute Charcot's arthropathy in a diabetic foot specialty clinic. Diabet Med. 1997;14:357–63.
89. Giurini JM, Chrzan JS, Gibbons GW, Habershaw GM. Charcot's disease in diabetic patients. Correct diagnosis can prevent progressive deformity. Postgrad Med. 1991;89:163–9.
90. Chantelau E. The perils of procrastination: effects of early vs. delayed detection and treatment of incipient Charcot fracture. Diabet Med. 2005;22:1707–12.
91. Eichenholtz SN. Charcot joints. Springfield: Charles C Thomas; 1966.
92. Parhouse N, Le Quesne PM. Impaired neurogenic vascular response in patients with diabetic and neurogenic foot lesions. N Engl J Med. 1989;39:346–50.
93. Mittlmeier T, Klaue K, Haar P, Beck M. Should one consider primary surgical reconstruction in charcot arthropathy of the feet? Clin Orthop Relat Res. 2010;468:1002–11.

94. Pinzur MS. Surgical management: history and general principles. In: Frykberg RG, editor. The diabetic Charcot foot: principles and management. Brooklandville: Data Trace Publishing Company; 2010. p. 165–88.
95. Johnson AR, Yoon P. Limb salvage in an unstable ankle fracture of a diabetic patient with Charcot arthropathy. Foot Ankle Spec. 2010;3:184–9.
96. Sohn MW, Stuck RM, Pinzur M, Lee TA, Budiman-Mak E. Lower-extremity amputation risk after charcot arthropathy and diabetic foot ulcer. Diabetes Care. 2010;33:98–100.
97. Iversen MM, Tell GS, Riise T, Hanestad BR, Østbye T, Graue M, Midthjell K. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag Health Study, Norway. Diabetes Care. 2009;32:2193–9.
98. Gazis A, Pound N, Macfarlane R, Treece K, Game F, Jeffcoate W. Mortality in patients with diabetic neuropathic osteoarthropathy (Charcot foot). Diabet Med. 2004;21:1243–6.
99. Sohn MW, Lee TA, Stuck RM, Frykberg RG, Budiman-Mak E. Mortality risk of Charcot arthropathy compared with that of diabetic foot ulcer and diabetes alone. Diabetes Care. 2009;32:816–21.
100. Pecoraro E, Reiber E, Burges M. Pathways to diabetic limb amputation. Diabetes Care. 1990;3:513–5.
101. LoGerfo FW, Gibbons GW, Pomposelli Jr FB, Campbell DR, Miller A, Freeman DV, Quist WC. Trends in the care of the diabetic foot. Expanded role of arterial reconstruction. Arch Surg. 1992;127:617–20.
102. Pomposelli FB, Campbell DR. Vascular surgery for the diabetic foot. In: Veves A, Giurini JM, LoGerfo FW, editors. The diabetic foot. Humana Press; 2002. p. 411–28. Totowa, NJ.
103. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;19: 1317–24.
104. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003;26:333–41.
105. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc. 1985;33:13–8.
106. Abbot RD, Brand FN, Kannel WB. Epidemiology of some peripheral arterial findings in diabetic man and women: experiences from the Framingham Study. Am J Med. 1990;88: 376–81.
107. 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;55:583–9.
108. Walters DP, Gatling W, Mullee MA, Hill RD. The prevalence, detection, and epidemiological correlates of peripheral vascular disease: a comparison of diabetic and non-diabetic subjects in a English community. Diabetic Med. 1992;9:710–5.
109. Donahue RP, Orchard TJ. Diabetes mellitus and macrovascular complications. An epidemiological perspective. Diabetes Care. 1992;15:1141–55.
110. Hiatt RH, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation. 1995;91:1472–9.
111. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes-a review. Diabet Med. 2010;27:4–14.
112. Elhadd TA, Robb R, Jung RT, Stonebridge PA, Belch JJF. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. Practical Diabetes Int. 1999;16:163–6.
113. Faglia E, Caravaggi C, Marchetti R, Mingardi R, Morabito A, Piaggesi A, Uccioli L, Ceriello A, SCAR (SCreening for ARteriopathy) Study Group. Screening for peripheral arterial disease by means of the ankle-brachial index in newly diagnosed Type 2 diabetic patients. Diabet Med. 2005;22:1310–4.

114. Walters DP, Gatling W, Mullee MA, Hill RD. The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. Diabet Med. 1992;9:354–8.
115. Kallio M, Forsblom C, Groop PH, Groop L, Lepantalo M. Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. Diabetes Care. 2003;26:1241–5.
116. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. J Am Coll Cardiol. 2008;18:1736–42.
117. McDermott MM, Kerwin DR, Liu K, Martin GJ, O'Brien E, Kaplan H, Greenland P. Prevalence and significance of unrecognized lower extremity peripheral arterial disease in general medicine practice. J Gen Intern Med. 2001;16:384–90.
118. Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA. 2006;295:536–46.
119. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach M. Preventive foot care in people with diabetes. Diabetes Care. 1998;21:2161–77.
120. Brearley S, Shearman CP, Simms MH. Peripheral pulse palpation: an unreliable physical sign. Ann R Coll Surg Engl. 1992;74:169–71.
121. Caruana MF, Bradbury AW, Adam DJ. The validity, reliability, reproducibilily and extended utility of ankle to brachial pressure index in current vascular surgical practice. Eur J Vasc Endovasc Surg. 2005;29:443–51.
122. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. Diabetologia. 1988;31:16–23.
123. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. Diabetologia. 1993;36:615–21.
124. Jeffcoate WJ, Rasmussen LM, Hofbauer LC, Game FL. Medial arterial calcification in diabetes and its relationship to neuropathy. Diabetologia. 2009;52:2478–88.
125. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five- year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg. 2006;32:484–90.
126. Aerden D, Massaad D, von Kemp K, van Tussenbroek F, Debing E, Keymeulen B, Van den Brande P. The ankle-brachial index and the diabetic foot: a troublesome marriage. Ann Vasc Surg. 2011;25:770–7.
127. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004;109:733–9.
128. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle. 1981;2:64–122.
129. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998;21:855–9.
130. Peters EJ, Lavery LA, International Working Group on the Diabetic Foot. Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diabetes Care. 2001;24:1442–7.
131. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR on behalf of the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(Suppl):S73–108.
132. Ramaswami G, Al-Kutoubi A, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, et al. The role of duplex scanning in the diagnosis of lower limb arterial disease. Ann Vasc Surg. 1999;13:494–500.
133. Bradbury AW, Adam DJ. Diagnosis of peripheral arterial disease of the lower limb. BMJ. 2007;334:1229–30.

134. Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, Berry E, Gough M, Kleijnen J, Westwood M. 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;11:1–184.
135. Heijenbrok-Kal MH, Kock MC, Hunink MG. Lower extremity arterial disease: multidetector CT angiography meta-analysis. Radiology. 2007;245(2):433–9. Epub 2007 Sep 11.
136. Kreitner KF, Kalden P, Neufang A, Düber C, Krummenauer F, Küstner E, Laub G, Thelen M. Diabetes and peripheral arterial occlusive disease: prospective comparison of contrast-enhanced three-dimensional MR angiography with conventional digital subtraction angiography. AJR Am J Roentgenol. 2000;174:171–9.
137. Meyer BC, Werncke T, Foert E, Kruschewski M, Hopfenmüller W, Ribbe C, Wolf KJ, Albrecht T. Do the cardiovascular risk profile and the degree of arterial wall calcification influence the performance of MDCT angiography of lower extremity arteries? Eur Radiol. 2010;20:497–505.
138. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. N Engl J Med. 1989;320:143–9.
139. Amini M, Salarifar M, Amirbaigloo A, Masoudkabir F, Esfahani F. N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: a randomized clinical trial. Trials. 2009;29:10–45.
140. Sterner G, Nyman U, Valdes T. Low risk of contrast-medium-induced nephropathy with modern angiography techniques. J Intern Med. 2001;250:429–34.
141. Zaytseva NV, Shamkhalova MS, Shestakova MV, Matskeplishvili ST, Tugeeva EF, Buziashvili UI, Deev AD, Dedov II. Contrast-induced nephropathy in patients with type 2 diabetes during coronary angiography: risk-factors and prognostic value. Diabetes Res Clin Pract. 2009;86 Suppl 1:S63–9.
142. Pannu N, Wiebe N, Tonelli M, Alberta Kidney Disease Network. Prophylaxis strategies for contrast-induced nephropathy. JAMA. 2006;21(295):2765–79.
143. Holt S. Radiocontrast media-induced renal injury–saline is effective in prevention. Nephron Clin Pract. 2003;93:C5–6.
144. Eickhoff JH. Changes in the number of lower limb amputations during a period of increasing vascular surgery activity. Results of a nation-wide study, Denmark, 1977–1990. Eur J Surg. 1993;159:469–73.
145. Muhs BE, Gagne P, Sheehan P. Peripheral arterial disease: clinical assessment and indications for revascularization in the patient with diabetes. Curr Diab Rep. 2005;5:24–9.
146. Hallett Jr JW, Byrne J, Gayari MM, Il Strup DM, Jacobsen SJ, Gray DT. Impact of arterial surgery and balloon angioplasty on amputation: a population-based study of 1155 procedures between 1973 and 1992. J Vasc Surg. 1997;25:29–38.
147. Abou-Zamzam Jr AM, Gomez NR, Molkara A, Banta JE, Teruya TH, Killeen JD, et al. A prospective analysis of critical limb ischemia: factors leading to major primary amputation versus revascularization. Ann Vasc Surg. 2007;21:458–63.
148. Wunderlich RP, Peters EJ, Lavery LA. Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. Diabetes Care. 2000;23:1551–5.
149. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care. 2010;33:998–1003.
150. The ICAI. Study Group Prostanoids for chronic critical leg ischemia. A randomized, controlled, open-label trial with prostaglandin E1. Ischemia Cronica degli Arti Inferiori. Ann Intern Med. 1999;130:412–21.
151. Petrakis IE, Sciacca V. Epidural spinal cord electrical stimulation in diabetic critical lower limb ischemia. J Diabetes Complications. 1999;13:293–9.
152. Ouriel K. Peripheral arterial disease. Lancet. 2001;358:1257–64.
153. Adam DJ, Raptis S, Fitridge RA. Trends in the presentation and surgical management of the acute diabetic foot. Eur J Vasc Endovasc Surg. 2006;31:151–6.

Neuropathic Ulcers

13

Agbor Ndip, Kathyn Sadler, and Nicholas Lower

13.1 Introduction

The most common cause of neuropathic ulceration to the lower limb is diabetes mellitus [1]. Primary neurological conditions (including multiple sclerosis and paraplegia), renal failure, chronic liver disease, alcohol excess, nutritional deficiencies, HIV, trauma, and surgery can also lead to peripheral neuropathy and hence to ulceration. Less common conditions that can result in neuropathic ulcers include chronic leprosy, spina bifida, syringomyelia, tabes dorsalis, poliomyelitis, and hereditary sensory and motor neuropathy (HSMN) commonly called Charcot-Marie-Tooth (CMT) disease [2, 3].

13.2 Epidemiology

Due to the heterogeneity of causes, it is difficult to provide an estimate of the prevalence of neuropathic ulcers in general; however, the prevalence of diabetic foot ulcers has been reported. The chance of an individual with diabetes developing a foot ulcer at sometime during their life has been estimated at 1 in 4 [4]. The prevalence of diabetes is increasing in every country, and it has been estimated that by 2030 there will be more than 550 million people with diabetes globally. In 2013 more than 3 million people in the UK had a diagnosis of diabetes [5], and it has been estimated that by 2030 over 550 million people globally will have diabetes.

Lower-limb ulcers are chronic, complex wounds which can be very debilitating and adversely affect patients' quality of life, often leaving them unable to work

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[6, 7]. Lower-limb ulcers also have massive economic effects on healthcare services. A European study conducted between 2003 and 2004 found that the total cost of treatment of a diabetic foot ulcer ranged from £3500 for noninfected neuropathic ulcers to £13,000 for infected ischemic ulcers [8]. In England, foot complications account for 20 % of the total National Health Service spend on diabetes care, which is around £650 million per year [9]. Not uncommonly, foot ulcers can be complicated by infection and/or need for lower-limb amputation [10]. In fact, foot ulcers precede amputation in 85 % of all non-traumatic lower-limb amputations [11]. Individuals who develop a diabetic foot ulcer are at greater risk of premature death, myocardial infarction, and fatal stroke than those without a history of diabetic foot ulceration [12].

13.3 Pathophysiology

Peripheral neuropathy may affect sensory and/or motor nerves. The sensory modalities implicated in neuropathic ulceration include pain, pressure, proprioception, temperature, and heat/cold. These sensory modalities transmit stimuli to the brain resulting in sensory awareness that enables the individual to relate to their environment, identify nociceptive stimuli responsible for local tissue injury, and respond to these by taking appropriate protective actions. Therefore, in sensory nerve damage, there is loss of protective sensation (LOPS) leading to injuries [13].

In the absence of pain sensation, foot injuries occur without the individual taking much notice [14]. Their weight exerts strain on the same foot site with relatively little discomfort resulting in repetitive mechanical forces and callous formation, followed by tissue breakdown, and eventually chronic ulceration [15]. It is not uncommon for a patient with a neuropathic ulcer to walk into the clinic without limping – they simply cannot feel pain to allow them adapt their gait/walking to prevent further injury.

Similarly, loss of pressure sensation results in individuals exerting a lot of pressure at one spot under the foot when they walk, building up a callus at that site without causing much discomfort. The pressure can become so high that it eventually leads to breakdown of tissues and ulceration. Sensory neuropathy also allows mechanical and thermal trauma with small cuts or punctures going unnoticed. Over time these may progress to ulcers. There are anecdotal reports of “holiday ulcers” where people have walked barefoot on hot sandy beaches and developed blisters and ulcers due to lack of temperature sensation.

Peripheral neuropathy can also affect motor nerves, leading to wasting of the small intrinsic muscles of the foot. This results in an imbalance between the flexor and extensor muscles [16], in turn leading to deformities and creating additional pressure points exposed to the risk of ulceration. The reduced muscle bulk also reduces the amount of soft tissue padding, therefore exposing the skin to high mechanical forces between the underlying bone and the walking surface. Autonomic neuropathy reduces sweating, consequently reducing hydration, causing the skin to be less elastic and so more vulnerable to mechanical stress [16].

13.4 Assessment of Patients with Neuropathic Ulcers

When assessing a patient with a foot ulcer, it is important to take a full history from the patient, considering both intrinsic and extrinsic factors.

Intrinsic factors include the presence of any underlying cause of neuropathy, predisposing medical conditions, diabetes, or symptoms to suggest diabetes if not yet diagnosed. A medication history [17], smoking history, and alcohol intake history are also important. Any previous history of ulcers should also be noted. A description of the ulcer itself including onset, chronicity, appearance, pain, and discharge (exudates or slough) should be elicited. Extrinsic factors include any trauma that the patient is aware of, pressure points, and their footwear. The patient's shoes should be inspected. Shoes that are too worn or too tight (too narrow or too short) for the patient are likely to lead to rubbing, blistering, and callous formation [18]. (Figs. 13.1, 13.2, and 13.3).

Neuropathic ulcers are usually painless unless an arterial component or infection is present. The wound margins tend to display callus buildup, a useful clue to the underlying high pressure load. Pedal pulses are usually present unless there is a vascular component. Foot temperature is usually normal. Despite even a large plantar ulcer, the patient may walk normally, without a limp, highlighting their lack of sensation.

Other aspects of abnormal foot pressures and neuropathy including limited joint mobility (LJM), dry skin, and various deformities (pes cavus, flattened plantar arch, hallux rigidus, hammer toes, claw toes, etc.) should also be elicited [18, 19].

13.5 Multidisciplinary Foot Teams

In many Western centers, diabetic patients with foot ulcers are managed in specialist foot clinics run by a multidisciplinary foot team (MDFT). This may include a combination of diabetes physicians, specialist nurses, podiatrists, vascular surgeons,

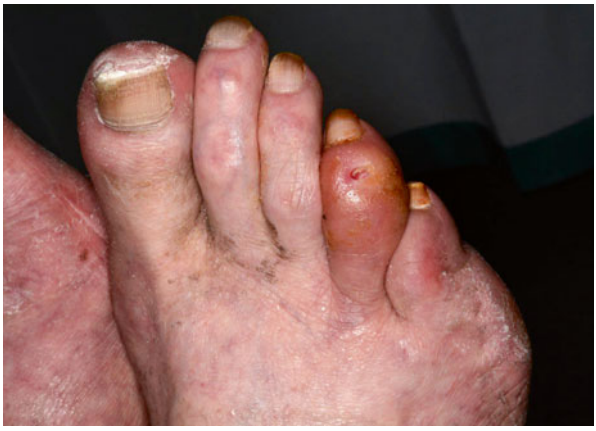

Fig. 13.1 Sausage-shaped right 4th toe with surrounding erythema; ulcer over the DIPJ probes to bone suggestive of osteomyelitis. Note the dry skin with toe deformity and callus buildup around the tip of the hallux and lateral border of the 5th toe – neuropathic ulceration from tight shoes

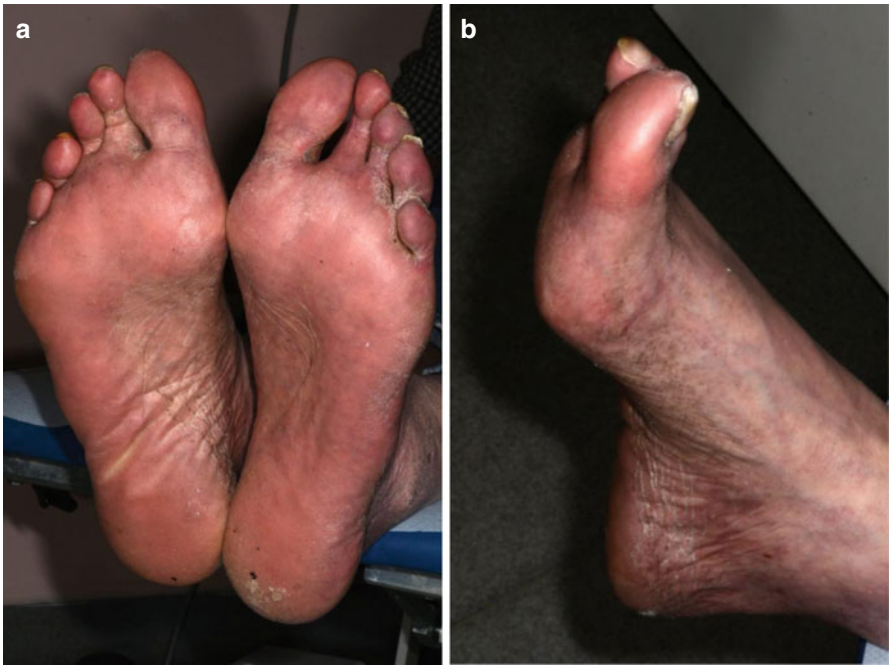

Fig. 13.2 Neuropathic foot. Note the dry skin (**a**, **b**), dystrophic nails (**b**), raised plantar arch (**b**), and distended foot veins (from autonomic shunting)

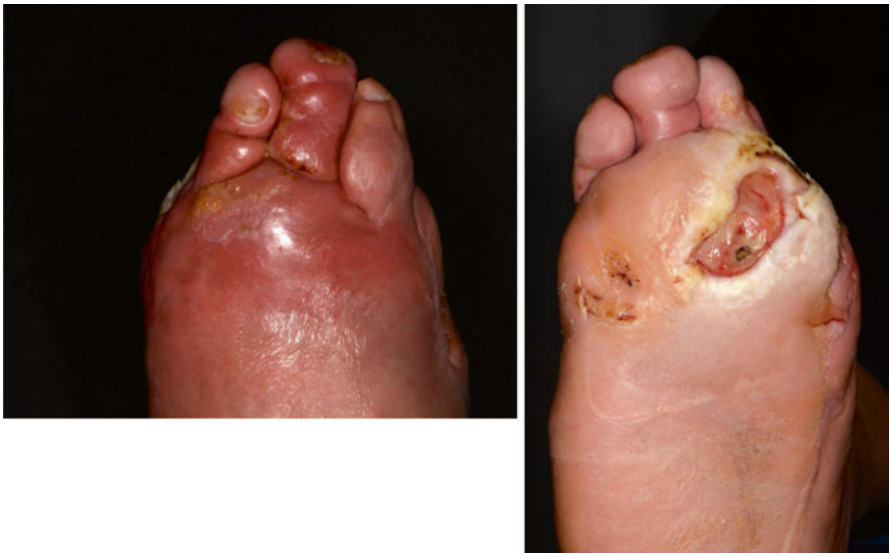

Fig. 13.3 Neuropathic ulceration in a patient with previous right hallux and 5th toe ray amputation. Like underlying infection. Not the hypertrophic callus rim around the ulcer due to inadequate offloading

orthopedic surgeons, orthotists, or psychologists. Patients with new ulcerations, swelling, or discoloration should be referred to these services promptly from primary care for urgent assessment and management. In the presence of severe infection, they may require prompt hospitalization for intravenous antibiotics. Evidence supports the role of the MDFT with one study finding that the total number of amputations fell by 70 % over 11 years following improvements in foot care services and implementation of an MDFT. [20]. The National Institute for Healthcare and Care Excellence (NICE) recommends that hospitals should have a care pathway for patients with diabetic foot problems, which should be managed by an MDFT, consisting of healthcare professionals with specialist skills and competencies [21].

13.6 Identification and Treatment of Infection

Diagnosis of infection in diabetic foot ulcers can be difficult as signs one would expect to find locally (pain, erythema, swelling, and raised temperature) may not be present [8]. Systemic signs may only be present in severe infections such as osteomyelitis or septicemia. Infection in a diabetic foot wound can produce signs such as poor blood glucose control, increased slough/exudate, pus, foul smell or change in smell, pain, and warmth. Although diagnosing infection at an early stage can be challenging, it is crucial in preventing progression of the infection and thereby preventing necrosis, gangrene, and amputation [22]. More than half of all diabetic foot ulcers will become infected at sometime so a high index of suspicion is vital [23]. The following factors increase the likelihood of an infection developing [24]: a positive probe-to-bone test, ulcer present for more than 30 days, a history of recurrent DFUs, a traumatic foot wound, the presence of peripheral arterial disease in the affected limb, a previous lower-extremity amputation, loss of protective sensation, the presence of renal insufficiency, and a history of walking barefoot.

Signs of severe infections include widespread inflammation, crepitus, bullae, necrosis, or gangrene. If a wound appears infected, appropriate cultures should be sent (soft tissue, secretions, or bone if osteomyelitis is suspected). All open wounds will be colonized with pathogens so superficial swabs are unlikely to culture the specific pathogen responsible for the infection. Empirical antibiotics should be prescribed in accordance with local microbiology advice while awaiting culture results and sensitivities. Other useful investigations include a full blood count, C reactive protein, renal function and liver function. Evidence does not support antibiotic therapy for ulcers that do not appear infected. Topical antibiotics may be useful in cases where there is poor vascular supply leading to reduced antibiotic tissue penetration, but the evidence base supporting their use is thin.

Diabetic patients with signs of infected ulceration should have a radiograph of their foot to detect any evidence of osteomyelitis. Signs of osteomyelitis on a radiograph include focal destruction of cortical bone, periosteal new bone formation, soft tissue swelling secondary to inflammation around the area, and focal osteoporosis caused by hyperemia. Conventional radiographs may not display any signs of osteomyelitis for up to 10 days so other types of imaging such as MRI should be used,

where available, if clinical suspicion remains despite a normal radiograph [25]. If MRI is contraindicated or unavailable, a labeled leukocyte imaging scan can be performed instead. Radiography can also be used to exclude a foreign body in tissues which is common with plantar neuropathic ulcers.

13.7 Identification of Deformities

As described previously, deformities of the feet can result from neuropathic changes, and these deformities create extra pressure points which are at high risk of ulceration. Feet should be inspected for common deformities including hammer toes (a fixed flexion deformity of the proximal interphalangeal joint), claw toes (flexion at the distal and proximal interphalangeal joints with dorsiflexion at the metatarsophalangeal joint), prominent metatarsal heads, and pes cavus (high arch).

13.8 Management of Neuropathic Ulcers

The basic aims of management are wound closure with prompt healing and prevention of the development of further ulcers.

These management goals can be achieved through a variety of measures including: local wound care (debridement), infection control, ensuring adequate blood supply, VAC therapy, adjunctive therapies, pressure offloading, treating underlying factors (intrinsic and extrinsic), patient education, temperature self-assessment, fat pad augmentation, and specialist shoes.

13.8.1 Debridement

This is the removal of devitalized, damaged, or infected tissue from an ulcer and hence exposure of healthy tissue. Exposure of the healthy tissue aids the healing process, and removal of devitalized tissue reduces the risk of infection. Debridement may be a single procedure, or it may need to be ongoing for maintenance of a clean wound bed [26].

Sharp debridement can be done in an outpatient setting by a podiatrist or foot specialist. A scalpel, scissors, or forceps are used to remove devitalized tissue. This procedure can be painful so adequate analgesia is essential. Assessment of the vascular supply to the feet is important before undertaking extensive sharp debridement. Patients requiring revascularization should not undergo sharp debridement due to the risk of trauma to tissues that are vascularly compromised.

Surgical debridement should be considered in cases of extensive necrotic tissue or localized fluctuance indicating pus or gas in the surrounding soft tissue. This involves excision or wider resection of both nonviable and healthy tissue from wound margins until a healthy bleeding wound bed is achieved.

Autolytic debridement is a process by which the body attempts to shed devitalized tissue with the use of moisture. If tissue is kept moist, it will degrade naturally

and deslough from the underlying healthy tissues. The presence of matrix metalloproteinases (MMPs) enhances this process. These are enzymes produced by damaged tissue, acting to disrupt the proteins that bind the dead tissue to the body. Autolytic debridement uses the body's own enzymes and moisture to rehydrate, soften, and liquify hard dead tissue and slough using semiocclusive or occlusive dressings (e.g., hydrogels, hydrocolloids) to maintain a moist environment and enhance the body's natural debridement process. This technique can be used when there is a small amount of nonviable tissue, if other methods of debridement are unsuitable, or for maintenance debridement. It is a slow process which increases the risk of infection and maceration.

Maggot debridement therapy involves applying sterile larvae of the green bottle fly to a neuropathic ulcer. This technique can achieve rapid digestion of necrotic tissue and pathogens and therefore promote granulation. Larval therapy is not recommended to be used as the only method of debridement in neuropathic ulcers as calluses cannot be removed by the larvae [27]. It is also not recommended for use in ulcers with an ischemic component as the process can cause or aggravate severe pain.

Hydrosurgical debridement uses a high-energy saline beam as a cutting implement to remove devitalized tissue [28]. The benefits of this technique include a short treatment time and the ability to remove most, if not all, dead tissue from the wound bed. Disadvantages include the need for specialist and expensive equipment.

13.8.2 Infection Control

Steps that can be taken to prevent infection developing in an ulcer include debridement of devitalized tissue, tight diabetic control (hyperglycemia leads to an increased risk of infection and also impairs healing in an established wound infection), care with footwear (checking for objects inside socks and shoes), and not walking barefoot to avoid any pathogens entering any wounds.

13.8.3 Ensuring Adequate Blood Supply

As previously described, neuropathic ulcers are commonly complicated by a degree of ischemia. Poor blood supply to the foot will impair its healing capacity. If the blood supply is good and recurrent insults are avoided, the ulcer should heal well. However, there may also be a vascular component that requires attention from surgical colleagues. It is important to recognize vascular deficits and refer early to vascular surgeons.

13.8.4 Vacuum-Assisted Closure (VAC) Therapy

VAC is an active wound therapy that applies subatmospheric or negative pressure (minus 125 mmHg) to the wound bed via a foam dressing. Applying negative pressure via a VAC pump aims to remove excess exudate and provide a moist,

wound-healing environment. It also reduces edema in the surrounding tissues that may impede local blood flow and impair healing. It also promotes increased angiogenesis and granulation tissue. VAC can be used on what is initially a complex wound to transform it into a simple wound that is then easier to close surgically. However, two Cochrane reviews of studies investigating the use of VAC in the management of diabetic foot wounds have concluded that the current evidence base is only supported by a limited number of underpowered, poorly designed studies.

13.8.5 Adjunctive Therapies

Platelet-derived growth factor (PDGF) is a protein involved with regulating cell growth and division. It has a significant role in angiogenesis. When a tissue injury occurs, platelets aggregate as part of the hemostatic mechanism, and they release PDGF which is powerfully chemotactic for inflammatory cells including macrophages. These migrate to the wound and remove necrotic tissue and fibrin. In the epidermis PDGF promotes the progression of basal epithelial cells through the cell proliferation cycle. It acts to move cells from G0 (resting phase) to G1. In the dermis PDGF stimulates proliferation of myofibroblasts. Studies have shown that treatment with PDGF significantly increases the chance of complete wound healing compared to placebo. PDGF treatment also significantly decreases the time to complete healing by 30 % [29].

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor required for the proliferation and differentiation of hematopoietic precursors of neutrophil granulocytes. G-CSF also enhances the antimicrobial functions of mature neutrophils. A meta-analysis examining the impact on rates of infection, cure, and wound healing of G-CSF in addition to normal care in diabetic patients with foot infection found that G-CSF did not significantly affect the chance of wound healing or resolution of infection. However, the addition of G-CSF was associated with fewer surgical interventions, including amputations. Addition of G-CSF was also found to reduce length of hospital stay, but it did not affect the length of systemic antibiotic therapy.

Honey has been used in the healing of leg ulcers for centuries. One theory is that honey may facilitate autolytic debridement; another theory proposes antimicrobial properties. However, there is a lack of data to support the routine use of honey in the management of neuropathic ulcers.

There is some evidence to suggest that systemic hyperbaric oxygen therapy (HBOT) may reduce the incidence of major amputations in patients with diabetic foot ulcers [30, 31].

13.8.6 Pressure Offloading

Reducing and redistributing pressures from high-risk areas to an even share throughout the foot is an important step in the management of neuropathic ulcers [32]. The gold standard method for pressure offloading is a total contact cast. This is a minimally padded cast which is molded to the foot and lower leg. It redistributes

pressure evenly across the whole of the plantar surface of the foot. It is not easy for the patient to remove so the total contact cast (TCC) has much higher compliance rates, and in turn higher success rates, compared to removable devices. In patients with a unilateral, uncomplicated plantar ulcer, using a TCC can reduce healing time by approximately 6 weeks [33]. TCCs are not suitable for patients with infected ulcers or osteomyelitis as wounds cannot be inspected regularly, allowing infection to spread without being noticed. They are also contraindicated in patients with ischemia due to the risk of inducing further ulcers. The application and removal of TCCs requires specially trained personnel [34]. If fitted by unskilled staff, ulcers can develop inside the cast. Other devices used if a TCC is either contraindicated or not tolerated by the patient include removable cast walkers, Scotchcast boots, healing sandals, crutches, walkers, and wheelchairs.

13.8.7 Treating Underlying Factors

The underlying cause of the peripheral neuropathy should be managed accordingly to prevent further deterioration. In cases of neuropathic ulcers secondary to diabetes, tight glycemic control is imperative to improve healing, reduce the risk of infection, and reduce the risk of further ulceration. Blood pressure, cholesterol, and weight also need to be controlled. Smoking cessation advice and support should be offered to all current smokers. Malnutrition should be corrected when present.

Other comorbidities that have been shown to impair wound healing must be considered and addressed. These include renal dialysis or transplant in patients with end-stage renal disease [4]. Uremia can impair white cell function and hence increase the risk of infection and impede wound healing. These patients are also likely to have peripheral edema which can adversely affect microcirculation. Anemia should be corrected and adequate nutritional support should be provided, especially in patients with low albumin.

Extrinsic factors which cause trauma and hence ulceration should be addressed. Those patients at high risk of falling should be identified. The patient's footwear should be examined for fit and presence of any foreign bodies, such as small stones, which may initiate skin damage. Those with inappropriate footwear should receive footwear education and referred to an orthotist or a shoemaker experienced in providing footwear to people with neuropathy.

13.8.8 Patient Education

The patient must be educated about the origin of neuropathic ulcers. Pain serves a purpose; it warns the individual that something is wrong and therefore alerts them to remove the stimulus. One of the leading pioneers on the management of neuropathic ulcers – Dr. Paul Brand – once said: "pain is God's greatest gift to mankind!" With impaired sensation this protective pain mechanism is lost. Patients with neuropathy should be educated and advised to check their feet regularly including

before going to bed at night. Attention to socks and shoes is important. Patients may not notice small stones or objects in their shoes because of neuropathy. Patients should be advised to check the temperature of bath water with their elbow before stepping in to avoid thermal trauma to their feet. They should also avoid electric blankets, hot water bottles, and sitting too close to a fire or heater. Patients should also be warned not to walk around the house with bare feet. Well-fitting comfortable footwear is important, as is good nail care.

Patients should be educated regarding the importance of prompt detection and treatment of ulcers. They should be advised to report any changes in current ulcers, or the surrounding skin, such as swelling, change in color, or discharge to a health-care professional.

In patients with diabetes, the importance of glycemic control needs to be highlighted. Patients should also be informed of the benefits of blood pressure, cholesterol, and weight control as well as smoking cessation.

13.8.9 Temperature Self-Assessment

High-temperature gradients between feet have been shown to precede the onset of neuropathic ulceration. The incidence of ulceration can be significantly reduced by daily at-home patient self-monitoring of foot temperatures [29].

13.8.10 Fat Pad Augmentation

Injectable silicone oil has been used in attempts to increase the thickness of tissue on the plantar surface of the foot and reduce peak foot pressures [29]. There is currently no evidence to prove that fat pad augmentation improves outcomes such as ulceration or amputation.

13.8.11 Specialist Shoes

An orthotist or specialist shoemaker should be available to assess and/or provide suitable footwear for patients with neuropathic foot ulcers. The footwear should protect the foot from trauma while ensuring that blood flow to the foot is not compromised.

13.8.12 Amputation

Surgical amputation may become necessary if there is overwhelming infection of the limb or the limb is deemed unsalvageable.

Other indications for amputation include uncontrollable neuropathic pain; a debilitating, non-healing, long-term ulcer; or a useless or disabling infected foot.

Approximately 50 % of patients who have an amputation will develop an ulcer on the contralateral foot within 18 months of the amputation [22].

Conclusion

The presence of peripheral neuropathy reduces the body's sensation of painful stimuli, while autonomic neuropathy erodes some of the natural defenses, further contributing to the insult on the integrity of the skin. The result is slow ulceration, most commonly over pressure points, where these stresses are accentuated. Diabetes mellitus is the most commonly implicated disease in the development of neuropathic foot ulcers. Of those with the condition, 25 % will go on to develop an ulcer. This has huge implications for both the patient and the financial pressures on a resource-constrained health system especially with the rising prevalence of diabetes worldwide.

An appreciation of both intrinsic and extrinsic factors is essential in the assessment of any ulcer in a diabetic patient and allows differentiation between neuropathic, arterial, or venous ulcers. Further attention to signs of infection is important in determining their severity and any complications that may be contributing to their presentation, such as osteomyelitis.

Optimal management is achieved by a multifaceted multidisciplinary approach including education, debridement, infection control, improving diabetic control, and reducing risk factors. Severe cases may require amputation. Adjunctive therapies are relatively new developments, and evidence for their efficacy will become clearer with their increasing use.

References

1. London NJ, Donnely R. ABC of arterial and venous disease. Ulcerated lower limb. BMJ. 2000;320:1589–91.
2. Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. Semin Intervent Radiol. 2009;26(4):286–95.
3. Khachemoune A, Kauffman C. Diagnosis of leg ulcers. Internet J Dermatol. 2001;1(2):1–7.
4. Ndip A, Rutter MK, Vileikyte L, Vardhan A, Asari A, Jameel M, Tahir HA, Lavery LA, Boulton AJM. Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. Diabetes Care. 2010;33:1811–6.
5. Diabetes UK. State of the nation 2012 – England. [Internet] London: Diabetes UK; 2012. http://www.diabetes.org.uk/About_us/What-we-say/Improving-services--standards/State-of-the-Nation-2013/. Accessed May 2013.
6. Haria JM, Singh VK, Jain SK. Life with diabetic foot ulcer – a cross sectional study. Int J Sci Study. 2014;1(6):33–5.
7. Abetz L, Sutton M, Brady L, et al. The diabetic foot ulcer scale: a quality of life instrument for use in clinical trials. Pract Diab Int. 2002;19:167–75.
8. Ndip A, Jude EB. Emerging evidence for neuroischaemic diabetic foot ulcers: model of care and how to adapt practice. Int J Low Extrem Wounds. 2009;8(2):82–94.
9. Kerr M. Foot care for people with diabetes: the economic case for change. Newcastle-upon-Tyne: NHS Diabetes; 2012. www.diabetes.org.uk/Documents/nhs-diabetes/footcare/footcare-for-people-with-diabetes.pdf. Accessed May 2014.
10. Leslie CA, Sapico FL, Ginunas VJ, Adkins RH. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes Care. 1988;11(2):111–6.

11. Bloomgarden ZT. Clinical diabetic neuropathy. Diabetes Care. 2005;28(12):2968–74.
12. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia. 2012;55(11):2906–12.
13. Reiber GE, Viliekyte L, Boyko EJ. Causal pathways for incident lower extremity ulcers in patients with diabetes from two settings. Diabetes Care. 1999;22(1):157–62.
14. American Diabetes Association. Consensus Development Conference on diabetic foot wound care. Diabetes Care. 1999;22:1354–60.
15. Edmonds ME, Foster AVM. ABC of wound healing, diabetic foot ulcers. BMJ. 2006;332:407–10.
16. Shaw JE, Boulton A. The pathogenesis of diabetic foot problems: an overview. Diabet Med. 1996;13 Suppl 1:812–6.
17. Mulder G, Armstrong D, Seaman S. Standard, appropriate, and advanced care and medical-legal considerations: part one — diabetic foot ulcerations. Wounds. 2003;15(4):92–106.
18. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment. Diabetes Care. 2008;31:1679–85.
19. Mueller MJ, Hastings MK, Commean PK, Smith KE, Pilgram TK, Robertson D, Johnson J. Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. J Biochem. 2003;36:1009–17.
20. Krishnan S, Nash F, Baker N, et al. Reduction in diabetic amputations over 11 years in a defined UK population: benefits of multidisciplinary team work and continuous prospective audit. Diabetes Care. 2008;31(1):99–101.
21. National Institute for Health and Clinical Excellence. Diabetic foot problems: inpatient management of diabetic foot problems. Clinical guideline 119. London: NICE; 2011. http://publications.nice.org.uk/diabetic-foot-problems-cg119. Accessed May 2014.
22. International Best Practice Guidelines. Wound management in diabetic foot ulcers. Wounds International; 2013. www.woundsinternational.com.
23. Wu S, Driver VR, Wrobel JS, et al. Foot ulcers in the diabetic patient, prevention and treatment. Vasc Health Risk Manag. 2007;3(1):65–76.
24. Lipsky BA, Berendt AR, Cornia PB. Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. IDSA guidelines. Clin Infect Dis. 2012;54(12):132–73.
25. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004;39:885–910.
26. Wounds UK. Effective debridement in a changing NHS: a UK consensus. London: Wounds UK; 2013. www.wounds-uk.com. Accessed May 2014.
27. Gottrup F, Jorgensen B. Maggot debridement: an alternative method for debridement. Eplasty. 2011;11:e33.
28. Haycock S, Chadwick P. Debridement of diabetic foot wounds. Nurs Stand. 2012;26(24):51–8.
29. Ndip A, Ebah L, Mbako A. Neuropathic diabetic foot ulcers – evidence-to-practice. Int J Intern Med. 2012;5:129–34.
30. Hinchliffe RJ, Valk GD, Apelqvist J, et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev. 2008;24 Suppl 1:S119–44.
31. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2004;2:CD004123.
32. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vasc Surg. 2010;52:37s–43.
33. Scottish Intercollegiate Guidelines Network. Management of diabetes. A national clinical guideline. Guideline no 116. Edinburgh: SIGN; 2010. http://www.sign.ac.uk/pdf/sign116.pdf. Accessed May 2014.
34. Armstrong DG, Lavery LA, Nixon BP, et al. It's not what you put on, but what you take off: techniques for debriding and off-loading the diabetic foot wound. Clin Infect Dis. 2004;39 suppl 2:S92–9.

Vasculitis and Ulceration

14

Pinjala Ramakrishna

14.1 Introduction

Leg ulcers refer to full-thickness skin loss on the leg or foot due to any cause. Leg ulcers may be acute or chronic. Acute ulcers are sometimes defined as those that follow the normal phases of healing and show signs of healing in less than 4 weeks. Chronic ulcers are those that persist for more than 4 weeks and are often of complex poorly understood origin [1] (Fig. 14.1).

The etiology of leg ulcers may be venous, arterial, or neuropathic. In some patients different types of inflammatory vascular disorders (vasculitides) are also known to be associated with painful non-healing ulcers in the foot and leg. It is very important to determine the etiology of the ulcers as this has crucial implications for management to heal them and prevent recurrence. However, it is not uncommon to have a venous ulcer in the presence of vasculitis or arterial, and this complicates matters. Rheumatoid arthritis can produce a vasculitis ulcer. It is typically deep, well demarcated, and punched out on the dorsum of the foot or calf. The patients of rheumatoid arthritis may also have venous disease due to poor mobility, neuropathy, and possibly impaired healing due to use of steroids [2].

14.2 Pathophysiology

Vasculitis is defined as an inflammation that compromises or destroys the vessel wall leading to local hemorrhagic or ischemic events. Vasculitis accounts for the presence of lower-extremity ulcers in fewer than 20 % of patients. Lower-extremity ulcers are associated with antiphospholipid antibodies, either as a manifestation of

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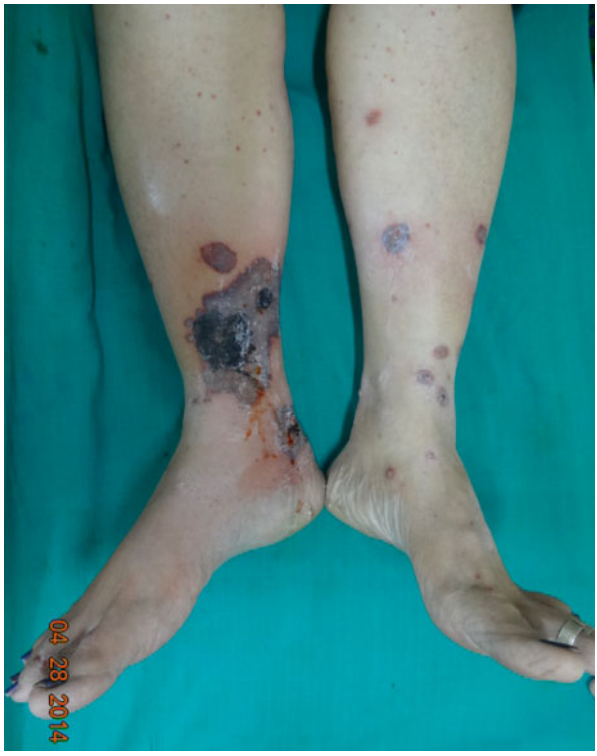

Fig. 14.1 Cutaneous vasculitis ulcerations

the primary antiphospholipid syndrome or secondary to the underlying connective tissue disease. Skin biopsies are gold standard for the diagnosis of cutaneous vasculitis. Cutaneous vasculitis can manifest as urticaria, infiltrative erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, punched-out ulcers, and digital gangrene. The morphology depends on the size of the vessels and extent of the vascular bed affected. The involvement can range from a vasculitis affecting few superficial, small vessels in petechial eruptions to extensive pan-dermal small-vessel vasculitis in hemorrhagic bullae to muscular vessel vasculitis in lower-extremity nodules with livedo racemosa. Skin biopsy, with subcuticular tissue taken from the earliest, most symptomatic, reddish, or purpuric lesion, is crucial for obtaining accurate and representative diagnostic sample. Vasculitis can be classified based on the size of vessels affected and the dominant immune cell mediating the inflammation (e.g., neutrophilic, granulomatous, lymphocytic, or eosinophilic). The inflammatory process results in the disruption of small-vessel inflammatory cells with deposition of fibrin within the lumen, vessel wall coupled with nuclear debris. This picture allows the confident recognition of neutrophilic vasculitis (also known as leukocytoclastic vasculitis) involving mostly small vessels. If muscular vessels are affected by vasculitis, then one can see infiltration of its wall by inflammatory cells abundantly. Extravasation of red blood cells resulting in formation of the purpura and necrosis is usually considered to be

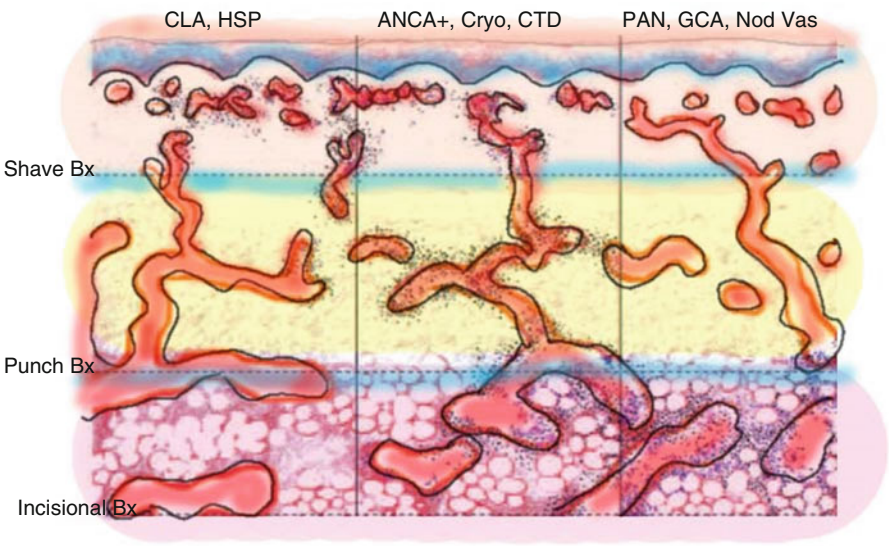

Fig. 14.2 Cutaneous vasculitis can be classified based on the size of vessel affected and extent of skin and subcutaneous tissue involvement. Superficial, intermediary, and deep layers involved in different types of vasculitis (CLA, HS/ANCA, Cryo, CTD/PAN, GCA, Nod Vas)

supportive, but not diagnostic of vasculitis as they can also be seen in hemorrhagic, vaso-occlusive disorders (pseudovasculitis). Vasculitic foci associated with extravascular granulomas, tissue eosinophilia, or tissue neutrophilia signal the risk of coexistence of systemic disease. The histological information coupled with special studies (direct immunofluorescence and antineutrophil cytoplasmic data) and clinical findings prompts us more precise and accurate diagnosis of localized and systemic vasculitis syndromes (Fig. 14.2).

In patients with different types of systemic vasculitis, there can be multiple leg ulcers which are necrotic and deep. There can be atypical distribution of the vasculitis ulcerative lesions such as nail fold infarcts and splinter hemorrhages.

Patients with rheumatoid arthritis (RA) are predisposed to developing chronic leg ulcers. In one study 9 % of patients with RA had a leg ulcer at some time, and 0.6–8 % of inpatients with RA had an active leg ulcer. This compared to 1 % prevalence in the general adult population [3–5].

Clinical manifestations arise because of the systemic inflammatory response resulting from release of chemical mediators from the inflamed blood vessels. The chemical mediators give rise to nonspecific systemic manifestations. They include fever, night sweats, malaise, weight loss, arthralgia, myalgia, and laboratory features such as normocytic and normochromic anemia, leukocytosis, thrombocytosis, and raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Some patients, especially early in the course of their illness, present with isolated systemic manifestations and pose a diagnostic challenge. Conversely, systemic inflammatory response is not seen in most patients with localized forms of vasculitis. More

specific manifestations from involvement of various organ systems arise from one or both of the following mechanisms. Thinning of the vessel wall is seen secondary to inflammatory cell infiltration. This leads to increased vascular permeability or vessel wall rupture. Hemorrhage occurs into the affected organ.

14.3 Types of Vasculitis

Generally vasculitis is divided in to three groups depending on the types of vessels involved, that is: (1) large-vessel vasculitis, (2) medium-vessel vasculitis, and (3) small-vessel vasculitis (Table 14.1) [6]. Histological findings of vasculitis in different stages are dependent on the timing of biopsy. Early lesions of LCV and those of urticarial vasculitis (UV) show a sparse infiltrate of neutrophils and nuclear debris around a postcapillary venule. Mature lesions of LCV show variable amounts of fibrin and nuclear debris around a disrupted small-vessel wall. Old, waning lesions of LCV will have scant nuclear debris and fibrin deposits in and around vessels, more numerous mononuclear infiltrates, and abundant extravasated red blood cells.

There are several classification systems for vasculitis, and they include the American College of Rheumatology classification, which comprises two subcategories: (1) cutaneous small-vessel vasculitis and (2) large-vessel necrotizing vasculitis criteria. The Chapel Hill Consensus Criteria (CHCC) proposes three subcategories: (1) large-vessel vasculitis, which includes giant cell arteritis and Takayasu's arteritis (skin lesions are uncommon); (2) medium-sized vessel vasculitis, which includes classic polyarteritis nodosa and Kawasaki's disease (associated with mucocutaneous lymph node syndrome); and (3) small-vessel vasculitis, which encompasses Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (polyarteritis), Henoch-Schönlein purpura, essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic vasculitis. Unfortunately, current vasculitis classification systems do not provide consensus for research, clinical diagnosis, and management of cutaneous vasculitis. While most practitioners appear to favor the CHCC for classifying vasculitis, there is an apparent lack of agreement of specific disorders and an overlap among primary vasculitides when the various classification systems are adopted [7].

Table 14.1 Vasculitis

Large-vessel vasculitis
Giant cell arteritis/Takayasu's arteritis
Medium-vessel vasculitis
Polyarteritis nodosa/Kawasaki's disease
Small-vessel vasculitis
ANCA-associated vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis)
Henoch-Schonlein purpura
Cutaneous leukocytoclastic angiitis
Cryoglobulinemic vasculitis

14.4 Predisposing Factors

Predisposing factors for vasculitis include infection, certain medications, and contact with allergens. A wide variety of bacterial, viral, fungal, protozoan, and helminthic organisms have been implicated in the development of vasculitis. Similarly, a wide range of medications have been implicated in causing vasculitis in some individuals, and these include insulin, penicillin, hydantoins, streptomycin, aspirin, sulfonamides, thiazides, phenothiazines, vitamins, phenylbutazone, quinine, streptokinase, tamoxifen, anti-influenza vaccine, and serum oral contraceptives. Contact with chemical agents such as insecticides, petroleum products, and food allergens (milk proteins and gluten) can also predispose susceptible individuals to vasculitis. Individuals with non-healing leg ulcers need to be referred to a specialist for appropriate diagnoses and management as vasculitis can "mimic" other disorders.

14.5 Clinical Presentation

These ulcers pose a therapeutic challenge and are often resistant to treatment. Generally the ulcer wounds are taken care by adequate wound cleaning and non-sticky dressings, along with pain relief and anti-infective measures. These patients' vasculitis ulcers usually require more attention for the pain relief.

There are five important questions to be asked when faced with a patient with possible vasculitis ulcerations depending on clinical presentation:

1. Is this a condition that could mimic the presentation of vasculitis?
2. Is there a secondary underlying cause?
3. What is the extent of vasculitis?
4. How do I confirm the diagnosis of vasculitis?
5. What specific type of vasculitis is this?

Clinical presentation depends on site of involvement. If only cutaneous venules are involved, red cell transudation or hemorrhage occurs within the skin presenting with palpable purpura. If pulmonary capillaries are involved, presentation could be more dramatic with hemorrhage occurring into alveoli presenting with breathlessness and hemoptysis and narrowing or complete occlusion of affected vessel because of vascular intimal proliferation and intraluminal thrombus formation. This leads to ischemia or infarction of affected organs. Examples of presenting manifestations are necrotic skin ulcers, mononeuritis multiplex, or infarction of a major organ depending on site of involvement. Thus, vasculitis should be suspected in patients with unexplained ischemia (which occurs in the absence of risk factors for atherosclerotic vascular disease) or multisystem disease especially in the presence of systemic inflammatory response or features such as palpable purpura, mononeuritis multiplex, or glomerulonephritis. Depending on type of blood vessel affected and extent of involvement, clinical presentation could range from isolated benign and self-limiting cutaneous vasculitis to life-threatening widespread internal organ involvement [8]. Common signs and symptoms associated with small- and

medium-vessel cutaneous vasculitis include palpable purpura, necrosis, livedo reticularis, and microlivedo. Small-vessel disease results in smaller and more regular lesions, whereas medium-vessel disease results in irregular lesions due to vascular anastomosis.

14.6 Differential Diagnosis

The different types of vasculitic disorders include systemic lupus erythematosus (SLE), scleroderma, polyarteritis nodosa, or Wegener's granulomatosis. In the diabetic patients, the ulcer is typically on the foot over a bony prominence. The neuropathic, arterial, and venous components can contribute to the formation of ulcers in diabetes. Hypertensive ulcer, due to arteriolar occlusion, is a very painful ulcer with necrotic edges. The hypertension-associated ulcers are usually on the lateral aspect of the lower leg over the lateral malleolus. Sometimes vasculitic ulcers may mimic the malignant ulcers such as basal cell carcinoma, squamous cell carcinoma, malignant melanoma, or Bowen's disease. They are rare but must be considered if ulceration does not respond to treatment. Similarly metabolic and hematological disease can also give rise to ulcers which should be excluded from the differential diagnosis before confirming the diagnosis of vasculitis ulceration (Table 14.2).

14.7 Laboratory Studies

Investigations aimed at eliminating other etiologies and obtaining a definitive diagnosis of vasculitis include complete blood profile, hepatitis profile due to the strong association with hepatitis C, serological testing for streptococcal infection, serum protein electrophoresis, HIV testing for high-risk patients, chest x-ray, symptom-directed workup for autoimmune disease, and underlying malignance with age-appropriate screening and multiple tissue biopsies.

Whenever we suspect the vasculitis as the cause for the ulceration in the initial clinical examination, the following tests should be considered before the special tests can be performed to confirm the diagnosis. Hemoglobin, ESR, platelets, white cell count, C-reactive protein, and serum proteins abnormalities may be associated with vasculitis. Tests such as rheumatoid factor, antinuclear antibody, complement, and anti-neutrophil cytoplasmic antibodies (ANCA) will be considered as specific immunological studies to differentiate the types of vasculitis underlying the ulcerations (Table 14.3).

Cutaneous polyarteritis nodosa (CPAN) is a rare form of cutaneous vasculitis that involves small- and medium-sized arteries of the dermis and subcutaneous tissue without systemic vessel involvement. It presents with tender subcutaneous nodules, digital gangrene, livedo reticularis, and ulcerations extending up to the subcutaneous tissues. The diagnosis is confirmed by the skin biopsy. The characteristic pathological feature is a leukocytoclastic vasculitis in the small- to medium-sized arterioles of the dermis. Generally after treatment with steroids, the lesions resolve

Table 14.2 Conditions which can mimic cutaneous vasculitis (differential diagnosis)

Mechanism	Disorder	Frequency
Haemorrhage (blood vessel incompetence, coagulation-fibrinolytic disorders)	Pigmented purpuric dermatitis	Common
	Solar/senile purpura	Common
	Scurvy	Less frequent than vasculitis
	Idiopathic thrombocytopenic purpura	Rare
	Some viral, drug, and arthropod-induced eruptions	Less frequent than vasculitis
Infection	Infective endocarditis	Common
	Septic vasculitis (septic vasculopathy)	Less frequent than vasculitis
	Lucio's phenomenon (endothelial swelling due to mycobacteria leprae)	Rare
Embolism	Atrial myxoma	Rare
	Cholesterol embolus	Common
Thrombosis	Antiphospholipid antibody syndrome (APS)	Common
	Thrombotic thrombocytopenic purpura	Less frequent than vasculitis
	Livedo vasculopathy	Common
	Warfarin (coumarin)-induced skin necrosis	Common
	Purpura fulminans	Common
	Disseminated intravascular coagulation	Common
	Monoclonal gammopathy (1° cryoglobulins)	Less frequent than vasculitis
	Sickle cell disease	Rare
Vasospasm (drug induced)	Ergot derivatives	Rare
	Methysergide	Rare
	Cocaine	Rare
Vascular trauma	Hypothenar hammer syndrome	Less frequent than vasculitis
Vessel wall pathology	Calciphylaxis	Rare
	Amyloidosis	Rare
	Radiation arteriopathy	Rare
	Primary hyperoxaluria	Rare

Table 14.3 Laboratory tests for vasculitis

Hemoglobin
ESR
C-reactive protein
Platelets
White cell count
Serum proteins
Rheumatoid factor
Antinuclear antibody
Complement
Antineutrophil cytoplasmic antibody

completely over a period of 1 month. The etiopathogenesis of cutaneous polyarteritis nodosa remains unclear. The diagnosis is based on skin biopsy, as there are no specific serological tests. The treatment with steroids, cyclophosphamide, or other immunomodulators helps in healing of these ulcers in addition to the wound care as there are no other effective definitive therapies available [9].

Familial atrophie blanche: This is an uncommon condition. It is characterized by white atrophic patches of skin on the lower extremities as a result of fibrinoid vasculitis of superficial and mid-dermal vessels. This progresses to end up in necrosis and ulceration of the epidermis. There seems to be familial or genetic predisposition of underlying the development of this disease and some called it Georgian ulcers due to that reason. This term was first used in Milan in 1929 to painful ulcers in the atrophic skin of legs in women. Initially it was mistaken for tuberculosis and syphilis. But later it was considered as a variant of stasis dermatitis. In 1966 Gray et al. showed that it was clearly unrelated to stasis dermatitis and he established this as a distinct clinical entity [10, 11].

Mixed connective tissue disease (MCTD) and polyarteritis nodos a (PAN) are characterized by microvascular impairments of small- and medium-sized vessels presented as intimal proliferation, medial hypertrophy, intravascular thrombus formation, and occlusion accompanied by hypercoagulation tendency (high titers of D-dimers, high factor VIII, elevated fibrinogen level, high titers of anticardiolipin antibodies). Reported high prevalence of medium-sized vessel occlusions in patients with MCTD may need angiographic studies. Prominent vascular changes justify aggressive therapy with anticoagulants, aspirin, and iloprost. The anticoagulation therapy has been reported to be beneficial in MCTD associated with leg ulcer, arterial thrombosis, pulmonary hypertension, Budd-Chiari syndrome, and pulmonary thromboembolism. A number of double-blind placebo-controlled studies of IV Iloprost infusion have shown benefit in Raynaud's syndrome and digital ulcers healing. In addition to its vasodilatory and antiplatelet effects, prostaglandin therapy has been shown to downregulate lymphocyte adhesion to the endothelium. Iloprost was shown to restore the innate antioxidant system in patients with Raynaud's phenomenon secondary to systemic sclerosis. Iloprost is the first choice for patients with critical digital ischemia or ulceration. It can produce benefit lasting for between 6 weeks and 6 months in most patients [12].

14.8 Treatment

Treatment will depend on the type, nature, and severity of the vasculitis. The goal of initial treatment is to induce remission of the disease. Once this has been accomplished, the drug dose is lowered to reduce side effects; in proven serious vasculitis conditions, aggressive therapy is indicated. In initial stages, high-dose oral steroid

is generally initiated and may be accompanied by 2–6 weekly pulses of intravenous cyclophosphamide, an immunosuppressant drug. It is important not to ignore the potential side effects of these agents [13]. Complications of steroid therapy are well documented. Careful monitoring of opportunistic infection, bone marrow suppression, and hemorrhagic cystitis is necessary. There needs to be awareness of the potential for the subsequent development of bladder tumor and increased risk of other neoplasia. Mortality data suggests that while early deaths in vasculitis are the result of the active disease, late deaths may be caused by the complications of therapy. Low-dose oral steroid, azathioprine, and methotrexate have been used in less severe forms of vasculitis and as maintenance therapy after remission has been induced [14]. The necessary constituent of successful treatment was aggressive immune-suppressive therapy for vasculitis with cyclophosphamide and methyl prednisolone pulse therapy, followed by high PR doses, and addition of cyclosporin A.

It is obvious that there is a need to treat local infection with effective local antibiotic long-term therapy according to microbial susceptibility up to complete wound healing. Wound infections often are responsible for the unhealed ulcers and be an origin for microbial dissemination [15]. Besides its antibiotic properties, ciprofloxacin has been reported as an activator of interleukin-3 production, granulocyte-macrophage colony-stimulating factor, and hematopoiesis, which are important for wound healing (tissue regenerator). It is also considered as an inhibitor of antiphospholipid antibodies. A high dose of ciprofloxacin has been reported to inhibit TNF-a production, lymphocyte blast transformation, and synthesis of immunoglobulins. There is three-phasic regeneration in wound healing. The first initial phase is very slow (first month) as is associated with treatment of the affecting factors interfering with normal regeneration: infection, inflammation, vascular damage, and thrombosis. The second period (1–2 months) was associated with rapid wound regeneration, which was followed by the third period (after 2 months) of slower healing due to phenomenon of contact cell inhibition. These periods may be much longer due to active, not neutralized, affecting factors.

Conclusion

In conclusion, ulcerations due to vasculitis and connective tissue disorders are extremely resistant to accepted conventional treatments. They often are complicated with severe local (osteomyelitis, abscess) or general (sepsis) infections that should be treated aggressively with broad-spectrum antibiotics for a long time. The multimodal approach leads to early diagnosis and appropriate treatment with the effective use of immunosuppression, vasodilators, anticoagulants, antiaggregants, wound debridement (surgical or biological), hyperbaric oxygenation, the use of regeneration activators (ciprofloxacin), and skin grafting. Patients and medical team patience will be appreciated when these hopeless and debilitating conditions will be cared by combined and persistent efforts of the multidisciplinary team.

References

1. Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. Health Qual Life Outcomes. 2007;5:44.
2. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol. 2005;27:504–28.
3. Thurtle OA, Cawley MI. The frequency of leg ulceration in rheumatoid arthritis: a survey. J Rheumatol. 1983;10(3):507–9.
4. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. Br J Dermatol. 2002;147:905–13.
5. Mongan ES, Cass RM, Jacox RF, Vaughen JH. A study of the relation of seronegative and seropositive rheumatoid arthritis to each other and to necrotizing vasculitis. Am J Med. 1969;47(1):23–35.
6. Fries JF, Hunder GG, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum. 1990;33:1135–6.
7. Acland KM, Darvay A, Wakelin SH, Russell-Jones R. Livedoid vasculitis: a manifestation of the antiphospholipid syndrome? Br J Dermatol. 1999;140(1):131–5.
8. Suresh E. Diagnostic approach to patients with suspected vasculitis. Postgrad Med J. 2006;82:483–8.
9. Chen KR. Cutaneous polyarteritis nodosa: a clinical and histopathological study of 20 cases. J Dermatol. 1989;16(6):429–42.
10. Milstone LM, Braverman IM, Lucky P, Fleckman P. Classification and therapy of atrophie blanche. Arch Dermatol. 1983;119(12):963–9.
11. Jetton RL, Lazarus GS. Minidose heparin therapy for vasculitis of atrophie blanche. J Am Acad Dermatol. 1983;8(1):23–6.
12. Della Bella S, Molteni M, Mocellin C, et al. Novel mode of action of iloprost: *in vitro* down-regulation of endothelial cell adhesion molecules. Prostaglandins Other Lipid Mediat. 2001;65:73–83.
13. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med. 1984;76(3):377–84.
14. Lapraik C, Watts R, Scott DG. Modern management of primary systemic vasculitis. Clin Med. 2007;7(1):43–7.
15. Takeuchi A, Hashimoto T. Oral prostaglandin E1 as a therapeutic modality for leg ulcers in Behcet's disease. Int J Clin Pharmacol Res. 1987;7(4):283–9.

Lymphatic Ulcer of Lower Limb

15

Waldemar L. Olszewski

15.1 Introduction

Lymphedema of the limbs is characterized by obstruction of limb collecting lymphatics by inflammation or mechanical obstruction after trauma or oncological surgery and irradiation. Lack of natural tissue fluid drainage pathways is followed by its accumulation in the interstitial space leading to expansion of tissues called clinical edema. The stagnant tissue edema fluid contains proteins, recirculating immune cells, and cellular debris. Moreover, bacteria penetrating the sole of the skin cannot be evacuated due to lack of outflow pathways to the regional lymph nodes. Among the complications of lymphedema, the most frequent are dermatolymphangioadenitis (DLA), skin fibrosis, deposition of fat tissue in the subcutis, and skin ulcers.

15.2 Pathology

Ulcer development is one of the late complications of chronic lymphedema. Although not frequent, it is a very serious condition of advanced stages [1] (Figs. 15.1 and 15.2). Ulcers are usually formed in the lower parts of the calf or on the dorsum of the foot. Their location is not limited to the internal aspect of the calf as it is the case with venous ulcers. Various locations are dependent on where skin injuries mostly take place. Shoe abrasions are common. Moreover, the large hanging dependent swollen skin fragments often touch the surface, and the epidermis is damaged followed by lymph leakage. Subsequently, the denuded skin surface is colonized by skin flora. Oozing of lymph precludes covering of the surface by edge keratinocytes. In addition, microbes present in the lymphedematous tissues and

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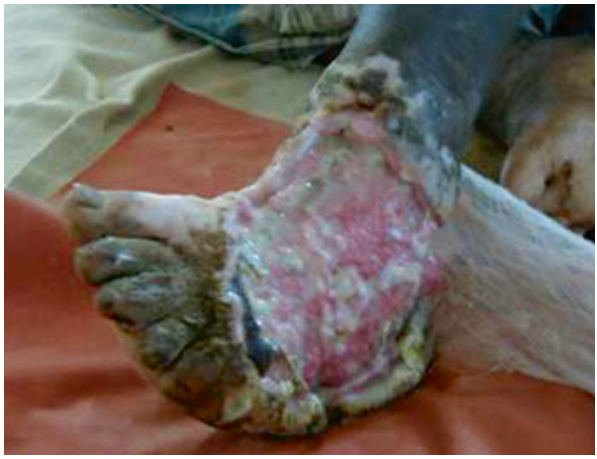

Fig. 15.1 Large foot ulcer in lymphedema of the lower limb stage IV. This ulcer requires debridement and long-term topical therapy concurrently with procedures for decrease of edema of the whole limb

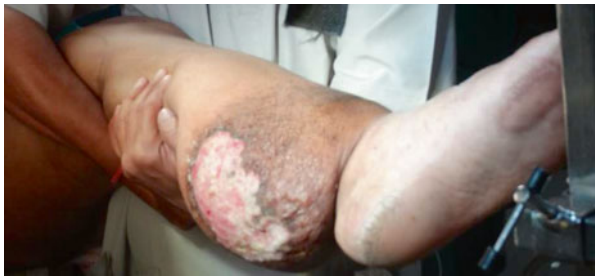

Fig. 15.2 Lymphedema with ulcer

lymph enhance the local host immune reaction [2, 3]. Infiltrating granulocytes phagocytize bacteria and granulation tissue debris and release enzymes preventing the covering of the ulcer surface by keratinocytes. Lymphedema skin ulcers are shallow with smooth edges in contrast to venous ulcers. However, in advanced stage of lymphedema and elephantiasis, necrosis of tissue may occur and tendons and fascia can be seen in the ulcer bottom.

What is specific for obstructive lymphedema is presence of large accumulated mass of bacteria in the swollen tissues deprived of lymphatic outflow [3]. This is predisposed to local inflammation and subsequently ulcer formation. Moreover, patients with obstructive lymphedema suffer from recurrent attacks of dermato-lymphangioadenitis (DLA) caused by bacteria present in a dormant state in the stagnant tissue fluid and lymph [2, 4, 5]. This microflora is, together with microbes colonizing from the environment, responsible for non-healing of ulcers and poor healing after the debulking surgery. Interestingly, the detected bacteria are in vitro sensitive to most antibiotics but not penicillin; however, penicillin is clinically most effective [2]. This means that there are other non-defined non-culturable bacterial strains responding to penicillin, which may be responsible for non-healing.

15.3 Role of the Lymphatic System in Ulcer Healing

Wound healing should not be considered as a process limited to the damaged tissues. It is always accompanied by an intensive response of the regional and, in advanced stages, the systemic lymphatic (immune) system (Fig. 15.3). Penetration of microorganisms through the epidermis and cellular changes caused by tissue injury are almost immediately recognized in the local lymphatic system irrespective of the topography of tissue. Blood immune cells and plasma humoral factors extravasate by the process of chemotaxis and increased capillary permeability. The migrating immune cells incorporate the microbial antigens as well as self-antigens from the apoptotic disintegrated tissue parenchymal cells and migrate via initial and collecting lymphatics to the regional lymph nodes. There, the elimination of antigens and raising of antigen-specific lymphocytes take place.

Intensive transport of microbial and self-antigens along lymphatic to lymph nodes and cellular reaction in the lymphoid tissue result in the formation of antigen-specific cohorts of cytotoxic lymphocytes. It remains so far unknown whether these cells migrate back from the bloodstream to the ulcer and, if so, whether they participate in the healing process. The effect of homing lymphocytes may be pro- and anti-inflammatory as well as lymphatic pro- and antiangiogenic. Lymph nodes are sites for quick reaction to bacteria resulting in their elimination. They may also be sites for raising tolerance to own antigens from wound cellular debris. Maybe in delayed wound healing, the low level tolerance is not sufficient to overcome an

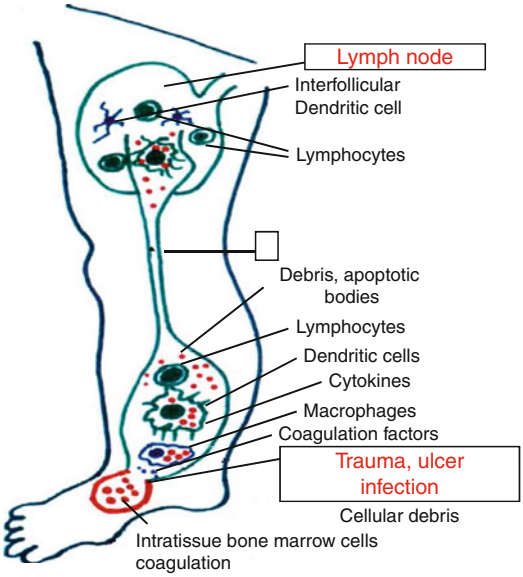

Fig. 15.3 Schematic presentation of how pathological events in the limb evoke reaction of the lymphatic system: lymphatics and nodes

excessive mass of self-antigens. It may then be suggested that in the non-healing ulcers, the aggressive lymph node-derived cells may prevent healing by attacking own granulation cells. Around 20 % of long-lasting venous ulcers are complicated by systemic allergic reactions. An open question remains whether there is a closed functional loop "wound-regional lymph node-blood circulation-wound" and what may be the tasks of the lymphocytes and precursors of dendritic cells circulating in this loop. The hypothetical loop is "wound-afferent lymphatics-lymph node-efferent lymphatics-blood-wound": antigens are transported from the wound via afferent lymphatics to the lymph node; once there, a processing of the antigen takes place followed by proliferation of antigen-specific lymphocytes; these cells are released and transported along efferent lymphatic via the thoracic duct to the blood circulation; some of them are trapped in the liver, gut, bone marrow, and spleen and inform local lymphoid tissue about penetration of the body by microbes and release of own cellular debris; these antigen-specific cells are further extracted from blood at the wound site; there, they participate in the healing and reconstruction processes and, however, may also attack own granulation cells in the autoimmune process. Debris help additional colonization by bacteria. This may explain delayed wound healing and systemic allergic reaction seen in some 20 % patients with long-lasting ulcers. Scintigraphy may help in the localization of the pathology (Fig. 15.4).

15.4 Treatment of Lymphatic Ulcers

Treatment is directed at (a) decrease of lymphedematous limb volume and (b) local procedures for healing.

15.4.1 Conservative Procedures in Lymphedema

Conservative therapy includes intermittent pneumatic compression, bandaging or stocking, and penicillin prophylaxis against recurrent attacks of DLA.

15.4.2 Surgical Procedures in Lymphedema (Figs. 15.5 and 15.6)

Surgical revision of the groin and inguinal lymph nodes is the first pre-debulking step. Enlarged lymph node may be anastomosed to the great saphenous vein according to the technique described by the author [6, 7]. In case the lymph nodes were found fibrotic but afferent lymphatic still patent, the latter should be implanted into the saphenous vein. In case of total fibrosis of nodes and afferent vessels, the inguinal fossa should be cleansed without ligation of any afferent vessels to allow fluid to leak to the wound [8]. Leakage stops within days.

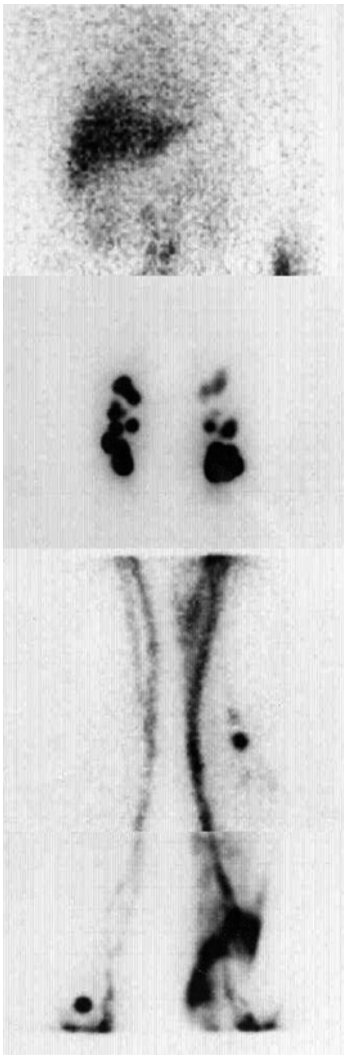

Fig. 15.4 Lymphoscintigram of the left lower limb with calf ulcer. Dissemination of tracer at and around the ulcer, dilated afferent lymphatic collectors, and enlarged lymph nodes

15.4.3 Treatment of Ulcer

The ulcer should be treated as any other ulcer by debridement, topical antiseptics, and nanosilver dressings. Results are often not satisfactory. Then debulking of the fragment of ulcerated tissue should be done. Systemic antibiotics should be given perioperatively and for as along as wound healing is not completed. Thereafter, long-term penicillin (Penidure) should be given in a dose of 1,200,000 u., i.m.,

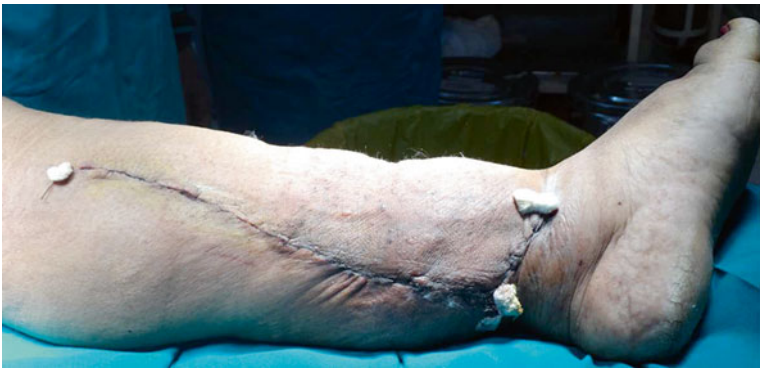

Fig. 15.5 Debulking of tissues with ulcer immediately after surgery

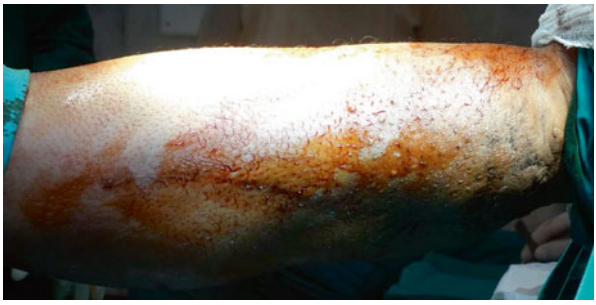

Fig. 15.6 Three months after debulking, just prepared for debulking on the lateral side

every 3 weeks for 1 year or longer, to prevent recurrence of ulceration and DLA attacks. Postoperative compression with elastic bandages and stockings is mandatory. When operative wounds are healed up, intermittent pneumatic compression is highly recommended every day for 1 h at 80–120 mmHg pressures, followed by immediate wrapping of the limb to prevent edema fluid reaccumulation [9, 10].

References

1. Karnasula MV. Management of ulcers in lymphoedematous limbs. Indian J Plast Surg. 2012;45(2):261–5.
2. Olszewski WL, Jamal S. Skin bacterial factor in progression of filarial lymphedema. Lymphology. 1994;27:148–9.
3. Olszewski WL, Jamal S, Manokaran G, Pani S, Kumaraswami V, Kubicka U, Łukomska B, Dworczyński A, Swoboda E, Meisel-Mikołajczyk E. Bacteriologic studies of skin, tissue fluid, lymph, and lymph nodes in patients with filarial lymphedema. Am J Trop Med Hyg. 1997;57:7–15.
4. Olszewski WL. Prevention of lymphangitis in lymphedema with long-term penicillin: a proposed study. Lymphology. 1994;27:201–5.

5. Olszewski WL. Episodic dermatolymphangioadenitis (DLA) in patients with lymphedema of the lower extremities before and after administration of benzathine penicillin: a preliminary study. Lymphology. 1996;29:126–31.
6. Olszewski WL. Surgical lymphovenous shunts in treatment of lymph stasis (in Polish). Proc Congress Polish Surgical Society. 1966;1:69–70.
7. Nielubowicz J, Olszewski WL. Surgical lymphovenous shunts in patients with secondary lymphedema. Br J Surg. 1968;55:440–4.
8. Olszewski WL. Excision of fibrotic inguinal lymph nodes is indicated in lymphedema patients with no- lymph-flow in the groin. Lymphology. 2002;35:430–2.
9. Olszewski WL, Jain P, Ambujam G, Zaleska M, Cakala M, Gradalski T. Tissue fluid pressure and flow during pneumatic compression in lymphedema of lower limbs. Lymphat Res Biol. 2011;9(2):77–83.
10. Olszewski WL. A concise compendium on lymphology. Physiological Principles of Physiotherapy. In: Lee BB, Rockson S, Bergan J, editors. Springer; 2011. p. 219.

Infective Leg Ulcers

16

Rahul Khanna, Ram Niwas Meena, M. Venkat Mukunda, and Seema Khanna

16.1 Introduction

In the UK alone which has a population of 50 million, there are about 400,000 patients with leg ulcer disease of which at any given time 100,000 have open leg ulcers requiring treatment [1]. By simple extrapolation, India with a population of 1200 million should have a leg ulcer burden of approximately 10,000,000. It is a leading cause of morbidity especially in the elderly population. Treatment of the underlying cause is the mainstay of therapy, but the role of good nursing care especially at the community level is of paramount importance.

Leg ulcers are almost always secondary to a preexisting medical disease (Table 16.1). Although the list of causes is long, the most common etiological factors for leg ulcers in the West and now in urban India are venous ulcers (70 %), arterial (5 %), and mixed venous and arterial (20 %). However, this is not representative of the entire Indian subcontinent, and infective ulcers constitute a major share in tropical Asia and Africa.

Several studies have implicated infectious causes for lower-limb ulceration. However, there is no large cumulative experience, and the literature on infectious ulcers is composed of mostly of small series or case reports. Most infectious ulcers are bacterial although viruses, parasites, and fungi have been reported as causative agents mainly in the immunocompromised patients. A list of likely pathogens is included in Table 16.2.

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Table 16.1 Causes of leg ulcers

1. Vascular
(a) Venous
(b) Arterial
(c) Mixed
2. Neuropathic
(a) Diabetes
(b) Tabes
(c) Syringomyelia
(d) Spinal injury
(e) Leprosy
3. Metabolic
(a) Diabetes
(b) Gout
4. Hematological
(a) Sickle cell disease
(b) Cryoglobulinemia
5. Trauma
(a) Injury
(b) Pressure
(c) Burns
6. Tumors
(a) Basal cell carcinoma
(b) Squamous cell carcinoma
(c) Sarcoma
7. Infection
(a) Bacterial
(b) Fungal
(c) Protozoal
8. Panniculitis
(a) Necrobiosis lipoidica
(b) Fat necrosis
9. Pyoderma gangrenosum
10. Autoimmune ulcers
11. Hypertensive ulcers

16.1.1 Mixed Etiology

Most ulcers have more than one etiology. Ulcers of any primary origin such as ischemic, venous, or neurotropic ultimately get infected as well. Though the dominant disease process must be treated first, the superimposed infections require treatment also.

Table 16.2 Infectious causes of limb ulcers

Disease	Pathogen
Erysipelas (bullosa)	*Streptococcus pyogenes*
Fasciitis necroticans	*Streptococcus hemolyticus*
Ulcerating pyoderma	*Staphylococcus aureus*
Gas gangrene	Clostridium
Ecthyma gangrenosum	Pseudomonas
Septic embolism	Meningococcus and others
Anthrax	Bacillus anthracis
Diphtheria	Corynebacterium diphtheria
Osteomyelitis	Several microorganisms
Herpes, CMV, Lues maligna	HSV, CMV, *Treponema pallidum*
Tularemia	*Francisella tularensis*
Tropical ulcer	Bacteroides, *Borrelia vincenti*
Maduramycosis (eumycetoma/mycetoma), *Exophiala jeanselmei*	*Nocardia brasiliensis*
Chondroblastomycosis, coccidioidomycosis	Several bacteria
Histoplasmosis	*Histoplasma capsulatum*
Bacillary angiomatosis	*Bartonella henselae*
Ulcerating cutaneous tuberculosis	Mycobacterium tuberculosis
Amebiasis	*Entamoeba histolytica*
Leishmaniasis	*Leishmania donovani* complex
Leprosy	*Mycobacterium leprae*

Taken from Spentzouris and Labropoulos [2]

16.1.2 Pyoderma Gangrenosum

This is a misnomer because these ulcers are noninfected and are an important cause of non-healing ulcers of the leg. Ulcers of pyoderma gangrenosum may be associated with inflammatory bowel disease, inflammatory arthropathy, or myeloproliferative disorders [3]. Half of these ulcers are associated with chronic disease and the remainder are idiopathic. Lesions of the lower limb start as painful pustules which progress to necrosis and ulceration. These ulcers may be single or multiple with raised purple serpiginous undermined borders. Besides antibiotics, immunosuppressive therapy forms the mainstay of treatment.

16.1.3 Mycobacteria-Associated Leg Ulcers

Chronic ulceration due to atypical mycobacteria is a rare but important cause of non-healing leg ulcers. The organisms implicated are *Mycobacterium ulcerans*, *Mycobacterium marinum*, and *Mycobacterium chelonae*. The ulcers may start as a subcutaneous nodule and later transform into an undermined ulcer with an areola. The diagnosis is established by polymerase chain reaction-based identification of

the organism. Treatment is with oral clarithromycin and topical silver sulfadiazine with hyperthermia [4]. The therapy needs to be continued for several months, and additional antibiotics may be required for secondary bacterial infection.

Tubercular vasculitis secondary to mycobacterium tuberculosis infection has been reported as a cause of leg ulcers with distal ischemia and occasionally peripheral gangrene [5]. The patients typically present with fever, lymphadenitis, and foot or leg ulceration. Diagnosis is confirmed by lymph node biopsy and CT angiography will demonstrate vasculitis. Conventional antitubercular therapy for 6–9 months is curative.

16.2 Leprosy Ulcer

In an epidemiological study of ulcers in India, leprosy was the most common cause of leg ulceration [6]. The predisposing cause of plantar ulcers in leprosy is nerve damage. This nerve damage results in loss of sensation, motor paralysis, and loss of autonomic nerve function which could lead to the loss of the ability to sweat. The weight-bearing points on the plantar aspect of the foot chiefly over the metatarsal heads and the heel tend to be subjected to excessive pressure because of the body weight. This in turn leads to the plantar skin and subcutaneous fat to be squeezed and temporarily deprived of blood supply. The tissues can stand this ischemia for about half an hour. If this continues for longer, reversible metabolic changes leading to blister formation or hematoma can occur, and if this continues for even longer, after 2 h, irreversible metabolic changes occur in this tissue, leading to infarction and gangrene of these compressed tissues. Blisters and hematoma can break down to form ulcers or lead to abscess formation and then ulcers and raw areas or spreading cellulitis. Patchy areas of infarcted and necrotic tissue separate out leaving behind ulcers. Corns and calluses act to increase pressure in a concentrated area and thus can cause hematoma and abscesses under them in anesthetic feet. These break down to form ulcers. They act like a stone within a shoe in a person with normal sensation, except that the person with normal sensation will remove the shoe, remove the stone, and move on. A corn, in such a person, will cause the person to either have the corn removed or limp, to avoid pressure and pain over the area. A person with loss of sensation continues to walk on the corn or callous and develops a blister or hematoma and maybe an abscess. Blisters and hematoma could also occur because of shearing stresses and later lead to abscess formation. Fissures or cracks occur because of dry skin, which in turn is because of loss of sweating. This leads to open wounds and infections. Prevention of plantar ulcers in leprosy therefore involves minimizing pressure, reducing force, reducing shearing stresses, looking for and taking care of direct trauma as soon as it occurs, looking for and treating pre-ulcerative conditions, and compensating the skin for loss of moisture. To heal such an ulcer requires rest. Absence of irritating pressure and shearing stresses will permit healing to take place. To rest a plantar ulcer requires that a person should not bear weight on the affected limb. Needless to say that in the Indian context, where most of our patients are from the unorganized labor sector, they cannot afford rest

as it interferes with their livelihood. They need to be provided with a method of "healing, while walking."

The patient has to be kept on medical treatment of leprosy. Various types of flap procedures may be required to heal the ulcer [7, 8].

16.2.1 Buruli Ulcer

This is a necrotizing cutaneous infection caused by mycobacterium ulcerans. It is the second most frequent mycobacterial disease in humans after tuberculosis [9]. It has been reported in parts of Africa, Australia, South East Asia, China, Central America, and South America. There are large lesions which progress to scarring, contractual deformity, disabilities, and sometimes amputation. The environmental mycobacterium is found in rivers, swamps, wetlands, areas of deforestation, dam construction, and agriculture. Buruli ulcer is also referred to as mysterious disease because the mode of transmission remains uncertain.

16.3 Leg Ulcer Infection

When the virulence factors of the microorganisms outweigh the natural host immune defense, infection with invasion of microorganisms into surrounding tissues will occur. The progression of an ulcer to an infected state involves multiple factors such as type, site, size, and depth of ulcer; presence of nonviable contaminants; level of blood perfusion; the immune status of the host; the microbial load; and the combined level of virulence of various microorganisms. Most leg ulcers harbor mixed population of aerobic and anaerobic organisms. The frequency of anaerobic bacteria in noninfected and infected leg ulcers is 36 % and 49 %, respectively [10].

16.4 Acute Soft Tissue Infections of the Leg

These include cutaneous abscesses, traumatic wounds, and necrotizing infections. The single most common organism found is *Staphylococcus aureus* which is present in 30 % of cutaneous abscesses and traumatic injuries and 47 % of necrotizing soft tissue infection of the leg have polymicrobial aerobic-anaerobic microflora [11].

Necrotizing soft tissue infections involve skin, subcutaneous tissue, and sometimes muscle tissue. It can vary in degree of severity and speed of progression. Although *S. aureus* remains the single most common pathogen, other organisms isolated include *Clostridium perfringens* and *Streptococcus pyogenes* predominantly. Associated organisms present could be *Peptostreptococcus* sp., *B. fragilis*, *E. coli*, and *Prevotella* sp. Potentiation of infection by microbial synergistic partnership between aerobes such as *S. aureus* and *S. pyogenes* and nonsporing anaerobes

has been reported in various types of non-clostridial cellulitis and necrotizing fascitis [12].

The treatment of necrotizing soft tissue infections requires early diagnosis, aggressive and repeated debridement, and appropriate antibiotic therapy. From a therapeutic view point, it is necessary to differentiate between pure clostridial myonecrosis which involves muscle invasion and is associated with a higher mortality rate from other non-muscle-associated soft tissue infections. The use of hyperbaric oxygen is controversial although it is believed to facilitate wound healing [13].

16.5 Diabetic Foot Infections

Mixed microflora infects plantar ulcers which are common in diabetic patients. The common organisms isolated are *S. aureus*, *S. epidermidis*, *Streptococcus* spp., *P. aeruginosa*, *Enterococcus* spp., and coliform bacteria. Anaerobes such as peptostreptococcus, Bacteroides, and Prevotella spp. can be isolated in 95 % of diabetic wounds [14]. Because of the polymicrobial infection, repetitive culture is not required, and treatment of infection should be based on an understanding of the general microbiology of these wounds.

16.6 Venous and Pressure Ulcer Infections

Both venous and pressure ulcers of the leg harbor polymicrobial microflora and anaerobes in 30 % as well. Aerobic-anaerobic synergistic interactions are more crucial than specific microorganisms in such infections. About 25 % of decubitus ulcers have underlying osteomyelitis, and bacteremia is common in such patients [15]. Management of infections in both these ulcers requires aggressive debridement and broad-spectrum antimicrobial agents.

16.7 Targeted Antibiotic Therapy

Accurate identification of pathogens rather than colonizing bacteria is a prerequisite for targeted antibiotic therapy for infective leg ulcers [16]. Although wound swab is the easiest and most commonly used sampling technique, a better technique is procurement of a tissue biopsy specimen from the wound bed. Mere presence of bacteria within a wound is not sufficient to diagnose infection because normal skin flora and sometimes opportunistic colonizing bacteria are present in all chronic wounds and skin surface. Infection is a clinical diagnosis made on the presence of fever, pus, pain or tenderness, erythema, warmth, and induration. These findings represent a significant shift in balance in favor of the bacteria over the host's defense with consequent destruction of host tissue.

Antibiotic therapy for infected ulcers is usually started empirically leading to overuse of broad-spectrum antimicrobials and increasing antibiotic resistance.

Culture and sensitivity results may take several days during which the patients usually receive broad-spectrum antibiotics. This may result in significant changes in the wound flora between the time of procurement of the sample and availability of the culture report. Quicker techniques for microbiological analyses such as DNA fingerprinting and PCR assay have been shown to be effective in rapid detection of causative organism and reduce the delay in institution of appropriate antimicrobial therapy.

The accuracy of culture information depends on an appropriate specimen. It should not be contaminated by the adjacent normal flora. Delay in transportation of the specimen and inoculation on culture plates can lead to loss of the pathogen as proliferation of contaminating organisms occur. Poor sensitivity (failure to identify a pathogen) and poor specificity (identifying a colonizer as a pathogen) can result in wrong antibiotic selection. As compared to a tissue specimen, the sensitivity of a superficial swab has been reported to be 79 % for detection of infection. Thus, swab is likely to miss one in five wound infections diagnosed by punch biopsy.

16.8 Factors Promoting Microbial Proliferation in Leg Ulcers

Wounds with good blood perfusion, oxygen, and nutrient delivery and good immune status are resistant to microbiological colonization. If the tissue oxygen tension is greater than 40 mmHg, ulcer infection is unlikely, while in tissues with an oxygen tension less than 20 mmHg, ulcers are invariably going to be infected [17]. The redox (oxidation-reduction) potential of tissues around ulcers is also important. A low redox potential (Eh) favors the proliferation of anaerobic bacteria. Ulcers with low oxygen tension and a low redox potential promote development of polymicrobial aerobic-anaerobic organisms.

Conclusion

Infective ulcers are relatively rare. Usually infection occurs secondary to some primary pathology, but sometimes primary cause may be the infection and in such cases specific treatment has to be offered like antitubercular treatment in tuberculous ulcers.

References

1. Sarkar PK, Ballaatyne S. Management of leg ulcers. Postgrad Med J. 2000;76:674–82.
2. Spentzouris G, Labropoulos N. The evaluation of lower extremity ulcers. Semin Intervent Radiol. 2009;26:286–95.
3. Khachemoune A, Kauffman CL. Diagnosis of leg ulcers. Internet J Dermatol. 2001;1(2):1–8 www.ispulo.com.
4. Mm K, Kurokawa I, Ito Y, Yamanaka K, Yamazaki T, Mizutani H. Leg ulcer caused by mycobacterium ulcerans ssp. Shinshuense infections. Int J Dermatol. 2009;48(12):1330–3.
5. Yao Y, Liu B, Wang JB, Li H, Liang HD. Tuberculosis should not be ignored in patients with peripheral gangrene. J Vasc Surg. 2010;52(6):1662–4.

6. Gupta N, Gupta SK, Shukla VK, Singh SP. An Indian community based epidemiological study of wounds. J Wound Care. 2004;13:323–5.
7. Joshua J, Chakraborthy V. Wound coverage of plantar metatarsal ulcers in leprosy using a Toe web flap. Indian J Plast Surg. 2005;38(2):123–7.
8. World Health Organisation; Weekly Epidemiological Record WER, 88, No.35 30 August 2013: Global leprosy: update on the 2013 situation. http://www.who.int/wer/2013/wer8835.pdf?ua=1.
9. Merritt RW, Walker ED Small PLC, Wallace JR, Johnson PDR, BenbowME, Boakye DA. Ecology and transmission of Buruli Ulcer disease: a systematic review. PLoS Negl Trop Dis. 2010;4(12):e911. www.plosntds.org.
10. Bowler PG, Davies BJ. The microbiology of infected and noninfected leg ulcers. Int J Dermatol. 1999;38:101–6.
11. Elliot DC, Kufera JA, Myers RAM. Necrotising soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg. 1996;224:672–83.
12. Brook I. Aerobic and anaerobic microbiology of infections after trauma in children. J Acccid Emerg Med. 1998;15:162–7.
13. Pizzorno R, Borini F, Donelli A, Stubinski R, Medica M, Carmigani G. Hyperbaric oxygen therapy in the treatment of Fournier's disease in 11 male patients. J Urol. 1997;158:837–40.
14. Karchmer AW, Gibbons GW. Foot infections in diabetics: evaluation and management. Curr Clin Top Infect Dis. 1994;14:1–22.
15. Brown DL, Smith DJ. Bacterial colonization/infection and the surgical management of pressure ulcers. Ostomy Wound Manage. 1999;45:1195–205.
16. Nelson EA, Backhouse MR, Bhogal MS, Wright-Hughes A, Lipsky BA, Nixon J, Brown S, Gray J. Concordance in diabetic foot ulcer infection. BMJ Open. 2013;3:e2370.
17. Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev. 2001;14:244–69.

Necrotizing Soft Tissue Infection

17

Ajay Kumar Khanna, Parameswaran Sundaran, and Soumya Khanna

17.1 Introduction

Necrotizing fasciitis (NF) better called as necrotizing soft tissue infection (NSTI) is infrequent but highly lethal infections. Necrotizing soft tissue infections (NSTIs) are fulminant infections of any layer of the soft tissue compartment associated with widespread necrosis and systemic toxicity. Delay in diagnosing and treating these infections increases the risk of mortality. Early and aggressive surgical debridement with support for the failing organs significantly improves the survival. These infections were first described by Jones in 1871, and at that time they were termed "hospital gangrene" [1]. According to Martin et al., necrotizing fasciitis (NF) is essentially a "severe inflammation of the muscle sheath that leads to necrosis of the subcutaneous tissue and adjacent fascia" that is difficult to diagnose early and even more difficult to manage effectively. Early clinical suspicion, appropriate antimicrobials, and surgery are key to improving survival. The problem is that it is difficult to diagnose as in one survey, the correct diagnosis was initially suspected in only 2 % of admissions [2, 3].

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17.2 History

The description of NF by Hippocrates in the fifth century BC, and that of a Confederate physician in the American civil war, is no different from the presentation of today: "A purple or blue spot is first perceived … the skin in the affected spot melts away in 24 hr whilst a deep blue and purple, almost black, areola surrounding the dead mass, spreads rapidly in ever increasing circles." In Peking, a missionary surgeon reported similar presentations among opium addicts in 1924: "A chill may usher in the general symptoms. Irregular patches, dusky hue, blisters or large bullae develop, may break and discharge a dark serous fluid." In the days before the advent of antimicrobials, NF was treated successfully with 'bear-claw scratch debridement' and Carrel's tubes irrigating the tissues with Dakin's solution of chlorinated soda [4–6].

17.2.1 Types

Four types of NF have been described (Table 17.1).

17.2.1.1 Type I NF (Polymicrobial/Synergistic)

Type I is found in 80 % of cases where it results from synergistic mixture of anaerobic, aerobic, and facultatively anaerobic bacteria (e.g., *E. coli*, *Pseudomonas* spp., and *Bacteroides* spp.). Type I NF particularly affects the immunocompromised or those with underlying abdominal pathology. The common aerobic species isolated from these infections are *Streptococci, Staphylococci, Enterococci*, and the family of Gram-negative rods. *Bacteroides* species are the most common anaerobes involved [7–9].

17.2.1.2 Type II NF

Type II is found in about 20 % of cases, which is usually monomicrobial and due to Gram-positive organisms, and the commonest type II NF is caused most frequently by group A *β-hemolytic streptococcal* alone or occasionally with *Staphylococcus aureus*. It carries a very high mortality of 43–58 %. Historically, monomicrobial *S. aureus* NF is uncommon, but occurs in neonates.

17.2.1.3 Type III NF

The commonest Gram-negative causes of NF remain *Vibrio* spp., such as *V. damselae* and *V. vulnificus*, which were responsible for 0.53 cases per 100,000 in Hong Kong in the late 1990s. *V. vulnificus*, associated with raw oyster ingestion, is the commonest cause of seafood-related deaths in the USA, particularly affecting patients with liver disease and iron overload. Wound contamination with seawater accounts for 25 % of cases. Virulence factors and digestive enzymes contribute to the high mortality of 30–40 % despite prompt diagnosis and aggressive therapy [10].

Table 17.1 Types of necrotizing fasciitis

Types of NF	Etiology	Organism(s)	Clinical progress	Mortality
Type I (70–80 % cases)	Polymicrobial/synergistic, often bowel flora derived	Mixed anaerobes and aerobes	More indolent, better prognosis, easier to recognize clinically	Variable; depends on underlying comorbidities
Type II (20–30 % cases)	Often monomicrobial, skin or throat derived	Usually group A β-hemolytic streptococcus (GAS), occasionally ± *S. aureus*	Aggressive, protean presentations easily missed	>32 %. Depends if associated myositis or toxic shock
Type III (commoner in Asia)	Gram-negative, often marine-related organisms	*Vibrio* spp. mainly	Seafood ingestion or water contamination wounds	30–40 %
Type IV (fungal)	Usually trauma associated, immunocompetent patients	*Candida* spp. immunocompromised patients; *Zygomycetes* immunocompetent patients	Aggressive with rapid extension especially if immunocompromised	>47 % (higher if immunocompromised)

17.2.1.4 Type IV NF: Fungal

Rarely NF can be caused by *Candida*, especially in immunocompromised patients. In contrast, zygomycotic necrotizing infections (*Mucor* and *Rhizopus* spp.) affect immunocompetent patients after severe trauma and are responsible for nearly 32 % of NF cases in some countries. Fungal invasion most commonly follows traumatic wounds or burns, and aspergillus or zygomycetes may be isolated [11].

17.3 Pathophysiology

NSTI is the condition where the microbial virulence overweighs the host defense system. Impaired host immunity or local tissue hypoxia as in atherosclerosis, burns, cancer or other immunocompromised states, chronic alcoholism, corticosteroid use, diabetes mellitus, hypoalbuminemia, intravenous drug abuse, malnutrition, obesity, occult diverticulitis, peripheral vascular disease, postoperative infection, and trauma predispose to NSTI. The pathogenesis of the development of NF depends on the causative organism(s). Synergistic NF is a comparatively slow process, evolving over days. Often, following complicated abdominal surgery and ischiorectal or perineal abscesses, synergistic NF develops particularly where gut flora breaches the mucosa, entering tissue planes. A slowly evolving bruise on the abdominal wall or perineal infection may reflect underlying malignancy. Gas-forming organisms and anaerobic infection may produce crepitus. Surgically, classical "dishwater fluid" due to lysis of polymorphs and serous discharge, together with macroscopic fascial necrosis, myositis, or myonecrosis, may be demonstrated. "Crescendo" pain, necessitating progressively stronger analgesia, is typical as occlusion of perforating nutrient vessels, and infarction of the nerves produces progressive skin ischemia and pain. Muscle hypoxia and swelling alter oxygen tension, increasing intracompartmental pressures, sometimes resulting in compartment syndrome [12]. Type II is initially more insidious than type I, but progresses far more rapidly. The disease may appear to have arisen spontaneously with no obvious focus. In such cases, hematogenous infection from many foci, including the throat, ascending vaginitis, primary peritonitis, or necrotizing proctitis, reaches the fascial layer. Hence, initial symptoms are ascribed to influenza, gastroenteritis, or muscle strain. This mechanism may explain the association of streptococcal infection with seemingly minor sporting injuries in athletes. The streptococcal capsule and protein M, protein F, streptolysin O, hyaluronidase, streptokinase, and pyrogenic exotoxins have their specific roles to play in the pathogenesis of streptococcal infections. Direct inoculation of GAS though wounds or associated with surgery is less common: examples include injection sites, caesarean section, plastic surgery, and even minor cosmetic procedures [13]. Hence the earliest clinical feature common to all types of NF is exquisite, agonizing pain, quite out of proportion to any external signs. The degree of pain may be lessened in diabetic neuropathy or following powerful analgesia. It is common to find patients prescribed with narcotic analgesics for "severe cellulitis" before the true diagnosis is suspected. As nerves supplying the necrotizing areas of skin die, the central areas become anesthetic, while laterally, the tissues overlying the deep spreading fascial infection

remain tender. Infection in the deeper layers finally ascends, producing edema of the epidermal and dermal layers (peau d'orange) and a "woody" firmness of the tissues. Hemorrhagic bullae progress to cutaneous gangrene, with sensory and motor deficits resulting from fascial and nerve destruction [14]. Fifty percent of type II NF cases are associated with toxic shock syndrome leading to a mortality of 40–67 % with up to half of patients needing amputation [15].

17.4 Clinical Features

Perhaps the biggest hurdle in early diagnosis and management of an NSTI is how to make the diagnosis. The commonly involved sites are the extremities (36–55 %), trunk (18–64 %), and perineum (up to 36 %). Events commonly predisposing patients to NSTIs include mild trauma, insect bites, drug reactions, illicit drug injections, perirectal abscesses, major traumas, and surgical procedures. Although patients may have an underlying risk factor, 30 % of the NSTIs do occur in healthy individuals [16]. The initial nonspecific signs such as tenderness, swelling, erythema, and pain at the affected site mimic nonsevere soft tissue infections such as cellulitis and erysipelas. The initial nonspecific signs are tenderness. Symptoms are much more than signs in initial phase, but by the time patients present, appearances are usually those of late NF, with visible bruising, bullae, and cutaneous necrosis due to progress of the necrotizing process. A thorough history should suggest the causative organisms in most cases. Goh et al. analyzed nine case series with a total of 1463 patients [17]. Diabetes mellitus was a comorbidity in 44.5 % of patients. Contact with marine life or ingestion of seafood in patients with liver disease was risk factors in some parts of Asia. The top three early presenting clinical features were swelling (80.8 %), pain (790.0 %), and erythema (70.7 %). These being nonspecific features, initial misdiagnosis was common and occurred in almost three-quarters of patients. Clinical features that helped early diagnosis were pain out of proportion to the physical findings, failure to improve despite broad-spectrum antibiotics, presence of bullae in the skin, and gas in the soft tissue on plain X-ray. Specific enquiries should be made about minor trauma; soft tissue injury penetrating lesions including insect or human bites, recent surgery, skin infection, or ulcers; injection sites; and illicit intravenous drug usage. Many cases, however, remain idiopathic [18]. Fever (>38 °C) is found in around 44 % of the cases, and tachycardia (>100 beats/min) is usually found in 59 % cases. Infected sites have erythema (80 %), induration (66 %), tenderness (54 %), fluctuance (35 %), skin necrosis (23 %), and bullae (11 %) [19].

We analyzed our patients of necrotizing fasciitis of the lower limb. The study reviewed 118 cases (78 males and 40 females) with mean age of 45 + 16.5 years (range 12–95 years) of lower limb necrotizing fasciitis admitted to the Department of Surgery, BHU in India between 1995 and 2007. Most patients ($n = 97$) presented with fever. Other presenting symptoms included painful swelling, bullae, erythema, ulcer, and necrosis. Comorbid conditions such as diabetes, tuberculosis,

malignancy, and immunosuppressive therapy were associated in 72 (61 %) cases. Amputations were done in 24 patients. Thirty-one patients developed septic shock. Renal dialysis was done in 16 patients, and ventilatory support was needed in 12 patients. The most common organism identified was beta-hemolytic streptococci ($n=42$). Eighteen patients died, a mortality of 15 %. The authors consider early diagnosis and aggressive surgical intervention to be crucial for the successful treatment of the disease [20] (Figs. 17.1, 17.2, and 17.3).

Type III may be associated with raw seafood ingestion or wound exposure to seawater justifies culture for *Vibrio* spp. A history of tonsillitis, close contacts with impetigo, or recent nonsteroidal anti-inflammatory drug (NSAID) usage suggests streptococcal infection. Patients present with fever and myalgia, severe pain, nausea, vomiting, and diarrhea. Diagnosis in initial phases is particularly difficult, since patients seen earlier in the infection were more easily misdiagnosed with muscle strains or viral illnesses. Other common misdiagnoses include gastroenteritis, sunburn, or an "allergic rash." A widespread macular "toxic erythema" may be present in a minority of patients. Misdiagnosis of NF is particularly common in children as it is rare and then usually associated with recent varicella zoster. Despite severe pain and appearing quite unwell, some patients initially have only a mild erythema, cellulitis, or swelling overlying the affected area. Since lymphatic channels are obstructed early, lymphangitis and lymphadenitis are rare. Overall, an exquisitely tender area evolves into a smooth, swollen area of skin with distinct margins progressing to dusky blue/purple, "bruising" violaceous plaques and finally full-thickness necrosis with hemorrhagic bullae [21]. Later on patients present with gangrenous patches, and the patients are very toxic and may involve various organs with hypotension, tachycardia, renal shutdown, respiratory problems, etc.

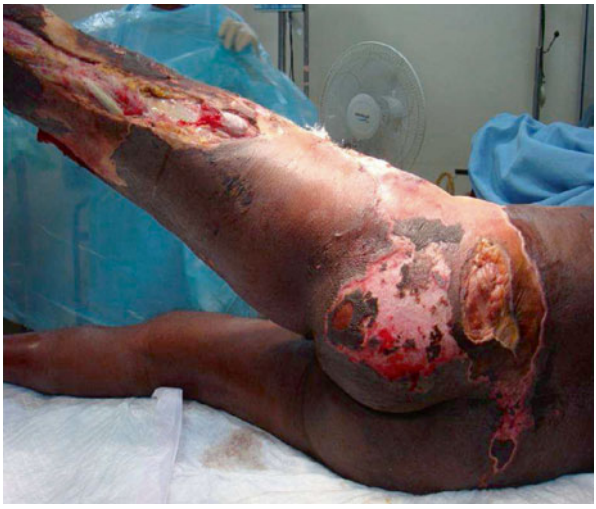

Fig. 17.1 Necrotizing fasciitis after thorn prick

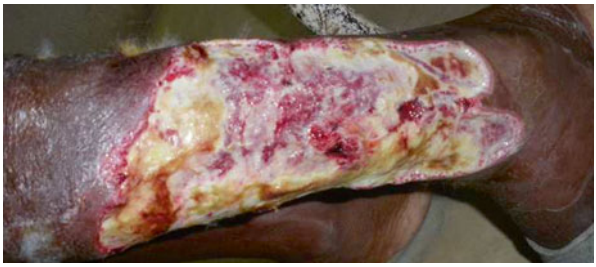

Fig. 17.2 Necrotizing fasciitis of the leg

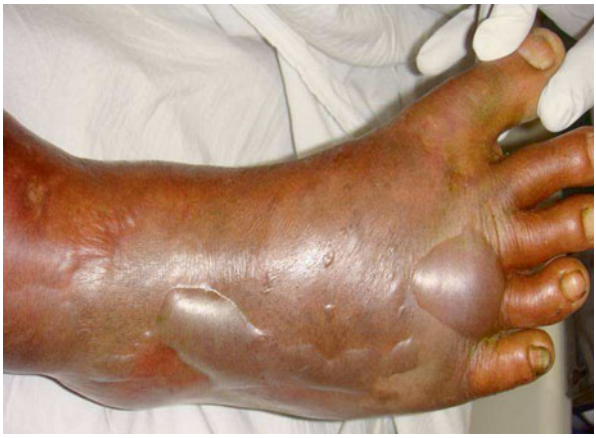

Fig. 17.3 Initial presentation with bullae

17.4.1 Investigations

17.4.1.1 Hematology

Disseminated intravascular coagulation and thrombocytopenia are common in any severe sepsis. A rapidly falling hemoglobin in the presence of a stable hematocrit may suggest intravascular hemolysis. The leukocyte count is less helpful for diagnosis. Although leukocytosis is common in type II, leukopenia is commoner in association with toxic syndrome. Infection with leukotoxin-producing organisms, e.g., Panton–Valentine leukocidin (PVL)-producing *S. aureus* or GAS, often leads to lymphopenia [22].

17.4.1.2 Biochemistry

Acute renal failure is quite common in severe sepsis, and dosing of renally excreted antimicrobials should be adjusted accordingly. Bacterial infection, inflammation, thrombosis, and necrosis all increase serum C-reactive protein (CRP). A very high CRP level is common. CRP levels of >16 mg/dL, with a sensitivity of 89 % and specificity of 90 %, have been reported in type II [23]. Raised serum creatinine kinase (CK) indicates myositis or myonecrosis, as well as the effects of circulating toxins or ischemia. Involvement of adjacent muscle raises CK and is not present in all cases of NF, but CK levels of 600 U/L gave a sensitivity of 58 % and a specificity of 95 % for cases of NF. One-third of patients with type II are hypocalcemic on

admission, due to calcium precipitation with fat necrosis [24]. Hypocalcaemia may also be a sign of severity in synergistic NF. Hypoalbuminemia and hyponatremia are common: in a series of 21 matched, consecutive cases, a serum sodium level of <135 mmol/L was found to be significantly associated with NF [25]. Severe metabolic acidosis may be found in NF. A high serum lactate combined with low sodium levels may be predictive of mortality. With serum lactate levels ≥6 mmol/L, the mortality was 32 %, whereas a lactate of <6 mmol/L and a serum sodium of <135 mg/L were associated with a mortality of 19 % [26].

17.4.1.3 Culture

Blood cultures are positive in 11–60 % of patients in type II, but the yield in type I synergistic fasciitis is lower. Routine culture of throat and vaginal swabs may be useful to establish a primary focus. Blister fluid is often sterile. Percutaneous needle aspiration of the advancing edge is painful. A tissue biopsy is the investigation of choice. Fungal cultures, especially in immunosuppressed or trauma patients, and enrichment cultures are useful, especially where patients have had recent antibiotic treatment [27].

17.4.1.4 Radiological

Plain X-ray of the area may show gas. Ultrasound may also show gas, but it mainly shows the edema and collection. The computed tomography scan findings suggestive of NSTI include the extent of abnormal soft tissue gas dissecting along the fascial planes, fascial stranding, and asymmetric thickening of fascial planes. The sensitivity of CT to identify NSTI is 100 %, specificity is 81 %, positive predictive value is 76 %, and negative predictive value is 100 % [28]. Magnetic resonance imaging (MRI) with gadolinium can differentiate necrotic and inflamed or edematous tissue. T2-weighted images on MRI are probably the best radiological adjunctive investigation, but are more sensitive than specific [29]. Chest X-ray may reveal early changes of fluid overload or changes of adult respiratory distress syndrome. Radiology of the affected areas is generally unhelpful, although occasionally MRI of the suspected area of fasciitis may be helpful, but should not delay surgery.

17.4.1.5 Histology

The characteristic findings include subcutaneous necrosis, polymorphonuclear cell infiltration, fibrinous vascular thrombosis with necrosis, and microorganisms within the destroyed fascia and dermis. Gram staining may also reveal Gram-positive clostridial bacilli. Histopathology can also identify fungal infection and invasive fungal infection with vascular thrombosis. Fine-needle or large-bore needle aspiration is another method to establish the diagnosis [30].

17.5 Scoring Systems for Prediction of NF

The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) scoring system has been useful in the diagnosis of NF when severe soft tissue infection was already suspected. It has 13 variables (including age, sex, serum potassium, and platelet

count); the most reliable indicators of underlying NF were found to be CRP, creatinine, hemoglobin, leukocyte count, sodium, and serum glucose. A score of 6 using the LRINEC system "raises the suspicion," with a score ≥8 being "strongly predictive" of NF. For patients scoring >6, the positive predictive value for NF was 92 % and the negative predictive value was 96 %. The LRINEC score may also indicate outcome: mortality of those patients with LRINEC score of <6 was 11 %, compared with 21 % for those scoring >6 [26, 31].

17.6 Treatment of NF

It is a dire emergency, and urgent surgical referral improves survival and needs a team approach with expertise from critical care, surgery, reconstructive surgery, and rehabilitation specialists [32]. The principles of treatment are fluid resuscitation and correction of electrolyte and acid–base imbalance, early initiation of antibiotics, surgical debridement of the affected area, and supportive measures for organ failure. In addition to antimicrobial therapy, complete debridement of infected tissue is key to successful treatment. Resuscitation with intravenous fluids and colloids, and inotropic agents, is usually necessary. Blood cultures, baseline full blood count, urea and electrolytes, liver function tests, clotting studies, and CRP and CK levels should be performed. Serum lactate and CRP are markers of severity of the infection and help guide therapy [33].

17.6.1 Antibiotic Therapy

As the condition is sporadic, it is not possible to have randomized double-blind controlled trials. Whereas antibiotic therapy may be guided by the Gram stain of aspirates or biopsies, the poor sensitivity and the fulminant nature of the infection make broad-spectrum empirical therapy covering most types of NF seem sensible. Subsequent antibiotic prescribing may be based on culture data [34]. Intravenous benzyl penicillin and clindamycin, imipenem, vancomycin, linezolid, and daptomycin are the drugs of choice in NF. Early initiation of antimicrobial therapy is essential and adjunctive to debridement. The current empirical antimicrobial regimes are piperacillin–tazobactam at 3.375 g every six hours with clindamycin 400–600 mg every 4–6 h with ciprofloxacin 400 mg every 12 h in type I infections. For type II infections, penicillin (2–4 million units very 4–6 h) with clindamycin is recommended. Injection linezolid (600 mg every 12 h) or vancomycin (30 mg/kg/day in two divided doses) may be considered in those allergic to penicillin. For type III clostridial infections, combination of penicillin with clindamycin is effective. In case of *Vibrio* or *Aeromonas* infection, doxycycline in a dose of 1 g every 12 h is effective. Clindamycin suppresses the toxin production by *S. aureus*, hemolytic *streptococci*, and clostridia and should be included when these organisms are present or suspected [35]. For suspected *Vibrio* spp. NF, therapy with doxycycline 100 mg twice daily plus intravenous ceftazidime 2 g eight hourly is recommended

[36]. Drotrecogin α (activated protein C) has not been used effectively in NF, and its use is limited to those patients not actively bleeding or within 24 h of surgery. After resuscitation, potent antibiotics, and surgical debridement, some patients still do not respond, and in these cases intravenous immunoglobulins may be tried.

17.7 Surgical Treatment of NF (Figs. 17.4, 17.5, and 17.6)

Surgery is vital in reducing the mortality of NF. In cases of doubt about the viability of tissues, the tissue oxygen tension can be measured with a probe using transcutaneous soft tissue oximetry. The oxygen tension is significantly lower in NF than cellulitis (52 % in NF, cf. 84 % in patients with simple cellulitis) with a sensitivity of 100 % and a specificity of 97 % [12]. Aggressive surgery removes the source of infection and toxins, and removal of infarcted tissue improves the penetration of antibiotics. The area of necrosis often extends beyond what is anticipated based on external appearance of the skin due to thrombosis of the dermal capillary beds that precedes skin necrosis. All obviously necrotic skin, subcutaneous tissue, fascia, and muscle must be excised. When there is crepitance present over an area of normal-appearing skin, an exploratory incision should be made through the involved area to determine whether the underlying tissues are viable. The presence of soft tissue gas does not mandate excision as long as the underlying tissues are viable. This crepitance often resolves after the necrotic tissue is removed. Amputation is done in 25–50 % of the cases where the affected extremity is either nonviable or would not be functional following debridement [37]. Early thorough and repeated

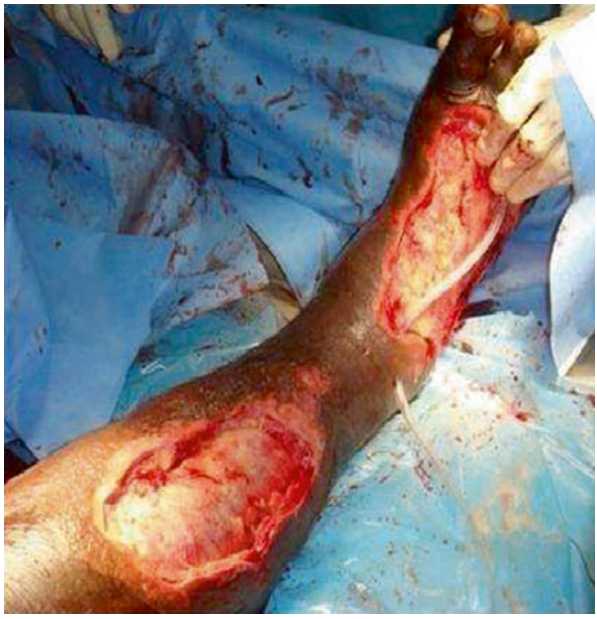

Fig. 17.4 Debridement of wound

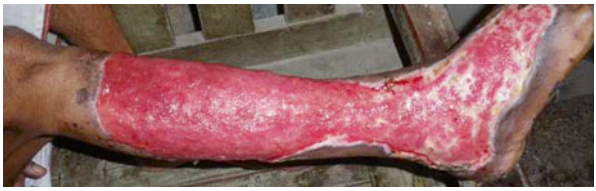

Fig. 17.5 Healthy granulation tissue after debridement

Fig. 17.6 Skin grafting after proper bed preparation

debridement is essential. Inadequate or delayed surgery is associated with a mortality of 38 % (8/21), compared with a mortality of only 4.2 % (2/48) in those who underwent aggressive surgery at recognition. Delaying surgery by 24 h increased the mortality associated with *Vibrio* spp. NF from 35 to 53 %, with 100 % mortality if surgery was not performed within 3 days [38–40].

Anesthesia for patients with NF is often difficult. The incision is often larger than expected, and the patient is cardiovascularly unstable with multiorgan failure, coagulopathy, and blood loss. Massive third-space fluid loss necessitates aggressive fluid replacement which may have a dilutional effect on the doses of antimicrobials administered. The rate of spread of NF may be very fast. Most patients need intensive care initially. Some surgeons believe that all infected material should be removed in one operation, but usually a "second-look" procedure is usually advisable. Repeat debridements are often necessary with a mean of 3–4 such procedures during admission. Extensive debridement produces large areas that need covering. Negative-pressure therapy [vacuum-assisted closure or (VAC) dressing] with a continuous pressure of 40–100 mmHg is useful for wound coverage and encourages granulation before and after skin grafting [41].

17.8 Hyperbaric Oxygen

Hyperbaric oxygen switches off α-toxin production, so it is believed to increase the bactericidal action of neutrophils since at low oxygen tensions peroxide-dependent killing mechanisms are less efficient. However, the overall evidence of benefit in non-clostridial NF is weak. Despite reports of rapid amelioration of clinical and mental status after only one hyperbaric oxygen session, there are few published data to support the use of hyperbaric oxygen in NF. Hyperbaric oxygen chambers are usually not available, but if facilities exist, it may be used [42].

Table 17.2 Clinical score predictive of death for patients with necrotizing soft tissue infections

Parameters	Score
Heart rate more than 110 beats per minute	1
Temperature less than 36 °C	1
Serum creatinine more than 1.5 mg/dL	1
Hematocrit more than 50 %	3
Age more than 50 years	3
White blood cell count more than 40,000/mcL	3
Points 0–2, 6 % mortality; 3–5, 24 % mortality; 6 or more, 88 % mortality	

Anaya et al. [37]

17.9 Outcome

Generally, synergistic NF has a better immediate prognosis, although underlying malignancy or other comorbidities account for later demise. The absence of myonecrosis or myositis in beta-streptococcal infection is associated with a better prognosis as myositis and organ failure increase mortality from 9 to 63 %. In the past, the mortality rate in NSTI was as high as 46 %. A decade ago, pooled analysis determined it to be nearly 34 %. Anaya et al. looked into clinical predictive markers for mortality looking into heart rate, temperature, serum creatinine, hematocrit, age, and WBC count and calculated the mortality [37] (Table 17.2). Kalaivani et al. analyzed their patients and found increasing age, raised creatinine, and delay in the first debridement were mainly associated with increasing mortality [43].

Conclusion

NF is an aggressive disease and delay in recognition and effective treatment increases the mortality of NF; thus, early diagnosis and management of NF is essential. In cases where the diagnosis is uncertain, repeated clinical assessment and a multiparametric approach integrating a range of diagnostic modalities and multidisciplinary involvement will optimize the diagnosis. Antimicrobial management should be tailored to the nature of the infecting organism and infection control aspects considered as soon as the diagnosis is entertained. Early surgical referral is essential, both for diagnostic confirmation and therapeutic removal of as much infected tissue as possible, although a "second look" is advisable.

References

1. Jones J,. Surgical Memoirs of the War of the Rebellion: Investigation Upon the Nature, Causes and Treatment of Hospital Gangrene as Prevailed in the Confederate Armies 1861–1865. New York: US Sanitary Commission; 1871.
2. Martin A. Necrotising fasciitis – early recognition and treatment can minimise risk of fatalities. N Z Publ Health Rep. 1994;1:9–10.

3. Cunningham JD, Silver L, Rudikoff D. Necrotizing fasciitis: a plea for early diagnosis and treatment. Mt Sinai J Med. 2001;68:253–61.
4. Regev A, Weinberger M, Fishman M, et al. Necrotizing fasciitis caused by Staphylococcus aureus. Eur J Clin Microbiol Infect Dis. 1998;17:101–3.
5. Lacy MD, Horn K. Nosocomial transmission of group A streptococcal infections from patient to health care worker. Clin Infect Dis. 2009;49:354–7.
6. Jain D, Kumar Y, Vasishta RK, et al. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. Mod Pathol. 2006;19:1221–6.
7. Giuliano A, Lewis Jr F, Hadley K, et al. Bacteriology of necrotizing fasciitis. Am J Surg. 1977;134:52–7.
8. Gozal D, Ziser A, Shupak A, et al. Necrotizing fasciitis. Arch Surg. 1986;121:233–5.
9. Murphy JJ, Granger R, Blair GK, Miller GG, Fraser GC, Magee JF. Necrotizing fasciitis in childhood. J Pediatr Surg. 1995;8:1131–4.
10. Bross MH, Soch K, Morales R, Mitchell RB. Vibrio vulnificus infection: diagnosis and treatment. Am Fam Physician. 2007;76:539–44.
11. Cook DA, Heiner JP, Rao VK. Necrotizing candidal fasciitis following hip surgery. Orthopedics. 1990;13:768–70.
12. Wang TL, Hung CR. Role of tissue oxygen saturation monitoring in diagnosis in necrotizing fasciitis of the lower limbs. Ann Emerg Med. 2004;44:222–8.
13. Heitmann C, Czermak C, Germann G. Rapidly fatal necrotising fasciitis after aesthetic liposuction. Aesthetic Plast Surg. 2000;24:344–7.
14. Smeets L, Bous A, Heymans O. Necrotising fasciitis: case report and review of literature. Acta Chir Belg. 2007;107:29–36.
15. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the management of skin and soft tissue infections. Clin Infect Dis. 2005;41:1373–406.
16. Ben-Abraham R, Keller N, Vered R, Harel R, Barzilay Z, Paret G. Invasive group A streptococcal infections in a large tertiary center: epidemiology, characteristics and outcome. Infection. 2002;30:81–5.
17. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. Br J Surg. 2014;101:e119–25.
18. Freischlag AJ, Ajalat G, Busuttil RW. Treatment of necrotising fasciitis, the need for a new approach. Am J Surg. 1985;149:741–55.
19. Frazee BW, Fee C, Lynn J, 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;34:139–46.
20. Khanna AK, Tiwary SK, Kumar P, Khanna R, Khanna A. A case series describing 118 patients with lower limb necrotizing fasciitis. Int J Low Extrem Wounds. 2009;8:112–6.
21. Buchanan CS, Haserlick JR. Necrotizing fasciitis due to group A beta-haemolytic streptococci. Arch Dermatol. 1970;101:664–8.
22. Barnham MR, Weightman NC, Anderson AW, et al. Streptococcal toxic shock syndrome: a description of 14 cases from North Yorkshire, UK. Clin Microbiol Infect. 2002;8:174–81.
23. Simonart T, Simonart JM, Derdelinckx I, et al. Value of standard laboratory tests for the early recognition of group A streptococcal necrotizing fasciitis. Clin Infect Dis. 2001;32:E9–12.
24. Simonart T. Group A, beta-haemolytic streptococcal necrotising fasciitis: early diagnosis and clinical features. Dermatology. 2004;208:5–9.
25. Wall DB, de Virgilio C, Black S, et al. Objective criteria may assist in distinguishing necrotizing fasciitis from non-necrotizing soft tissue infection. Am J Surg. 2000;179:17–21.
26. Wong CH, Khin LW, Heng KS. The laboratory risk indicator for necrotising fasciitis score: a tool for distinguishing necrotising fasciitis form other soft tissue infection. Crit Care Med. 2004;32:135–41.
27. Stamkenovicz I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen section biopsy. N Engl J Med. 1984;310:1689–93.
28. Zacharias N, Velmahos GC, Salama A, et al. Diagnosis of necrotizing soft tissue infections by computed tomography. Arch Surg. 2010;145:452–5.

29. Parenti GC, Marr CI, Calandra G, et al. Necrotizing fasciitis of the soft tissues: role of diagnostic imaging and review of the literature. Radiol Med. 2000;99:334–9.
30. Lee PC, Turnidge J, McDonald PJ. Fine-needle aspiration biopsy in diagnosis of soft tissue infections. J Clin Microbiol. 1985;22:80–3.
31. Su Y-C, Chen H-W, Hong Y-C, et al. Laboratory risk indicator for necrotizing fasciitis and the outcomes. Aust N Z J Surg. 2008;78:968–72.
32. Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. Crit Care Med. 2010;38:S460–8.
33. Sudarsky LA, Laschinger JC, Coppa GF, Spencer FC. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg. 1987;206:661–5.
34. Janecicius RV, Hann SE, Batt MD. Necrotising fasciitis. Surg Gynecol Obstet. 1982;154:97–102.
35. May AK. Skin and soft tissue infections. Surg Clin North Am. 2009;89:403–20.
36. Tang HJ, Chang MC, Ko WC, et al. In vitro and in vivo activities of newer fluoroquinolones against Vibrio vulnificus. Antimicrob Agents Chemother. 2002;46:3580–4.
37. Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg. 2005;140:151–7.
38. Klontz KC, Lieb S, Schreibver M, et al. Syndromes of Vibrio vulnificus infections. Clinical and epidemiological features in Florida cases, 1981–1987. Ann Intern Med. 1988;109:318–23.
39. Lille ST, Saito TT, Engrav LH. Necrotizing soft tissue infections: obstacles in diagnosis. J Am Coll Surg. 1996;182:7–11.
40. Bilton BB, Zibarui GB, McMillan RW, et al. Aggressive surgical management of necrotising fasciitis serves to decrease mortality: a retrospective study. Am Surg. 1998;64:397–401.
41. Mulla ZD. Streptococcal myositis. Br J Plast Surg. 2003;56:424.
42. Escobar SJ, Slade HJB, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen (HBO_2) for necrotising fasciitis reduces mortality and amputation rate. Undersea Hyperb Med Soc. 2005;32:437–43.
43. Kalaivani V, Hiremath BV, Indumathi VA. Necrotising soft tissue infection – risk factors for mortality. J Clin Diagn Res. 2013;7:1662–5.

Pyoderma Gangrenosum

18

Jyoti Yadav and Sanjay Singh

18.1 Introduction

Pyoderma gangrenosum (PG) is a rare, non-infectious, inflammatory disease of unknown etiology, characterized by sterile neutrophilic infiltration of the skin. It is commonly associated with underlying systemic disease [1–4].

18.2 History and Nomenclature

Pyoderma gangrenosum was first described by Brocq in 1916 [5] and later in 1930 by Brunsting et al. [1]. Brunsting, Goeckerman, and O'Leary coined the term "pyoderma gangrenosum" in 1930. The prevalence of PG in inflammatory bowel disease was discussed by Greenstein et al. in 1976 [6]. Several clinical variants of PG have been described, and PG at unusual sites or with specific triggers, such as pathergy, has been reviewed [7]. There is some evidence that the pustular type of PG may be mainly associated with inflammatory bowel disease (IBD) and the bullous type with hematological malignancies (Table 18.1). Peristomal pattern is mainly, but not exclusively, associated with IBD, and the vegetative type of PG is not associated with underlying disease [2, 8]. Although the above-mentioned associations have been described, none of the morphologies is consistently or exclusively associated with any specific cause. Although the vegetative pattern of PG is not accompanied by other lesions. Different morphologies may coexist with each other or with other neutrophilic dermatosis or pustular vasculitis or may evolve from one form to another [9]. 50–70 % of patients with PG will have an underlying disease, equally

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Table 18.1 Different associated diseases reported with pyoderma gangrenosum

Category of disorders	Examples
Gastrointestinal	Ulcerative colitis, Crohn's disease, collagenous colitis, gastritis, gastroduodenal ulcers, intestinal polyps
Hematological	Leukemia (myelogenous, hairy cell), myelofibrosis, myelodysplastic syndromes, paraproteinemia, Waldenstrom macroglobulinemia, paroxysmal nocturnal hemoglobinuria
Hepatic	Chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis
Collagen vascular disorders	Wegener's granulomatosis, Takayasu's arteritis, Behcet's disease, systemic lupus erythematosus, systemic sclerosis
Acne and related disorders	Acne conglobata, acne fulminans, hidradenitis suppurativa, PAPA
Autoimmune	Thyroid disease, diabetes mellitus
Drugs	Colony-stimulating factors, gefitinib, interferon, propylthiouracil, isotretinoin
Solid organ tumors	Colon, pancreas, breast, bronchus, carcinoid
Miscellaneous	Sarcoidosis, HIV infection

divided between inflammatory bowel disease, arthritides and hematological disorders (IgA monoclonal gammopathy, acute myelogenous leukemia, myelodysplasia); but clinical course of PG is usually unrelated to their severity or activity [10].

18.3 Epidemiology

Pyoderma gangrenosum occurs worldwide. Accurate epidemiological data on PG are missing. The peak of incidence occurs between the ages of 20 and 50 years with women being more often affected than men [11]. Cases in infants and adolescents account for only 4 % of PG. PG in elderly people has occasionally been reported [12]. The general incidence has been estimated to be between 3 and 10 per million per year [10].

18.4 Etiology and Pathogenesis

The etiology of PG is unknown and its pathogenesis is poorly understood. Currently an immune-mediated process is thought to play an important role. Both humoral and cell-mediated abnormalities have been reported with PG, but none of these findings have been demonstrated consistently and it is not clear whether they are of primary importance or represent an epiphenomenon [2].

Pathergy phenomenon is reported to occur in 20–30 % of patients with PG. This refers to heavy neutrophilic infiltrates or pustular reaction that develops at the site of nonspecific trauma [13]. Pathergy phenomenon is elicited by injecting 0.1 ml of normal saline obliquely to the depth of 5 mm with a 20–22-gauge needle [13]. An erythematous papule of more than 2 mm at the prick site develops within 48 h.

Humoral defects described in PG include autoantibodies against skin and bowel, a dermo-necrotic factor and a serum factor [14, 15]. Some studies have suggested the mechanism to be consistent with Arthus and Shwartzman reaction [14–17], in which circulating immune complexes are deposited in blood vessels leading to activation of complement pathways.

Cross-reactivity between cutaneous and bacterial antigens, especially *Escherichia coli*, has been suspected. A recent support for this possibility was documented in a study [18]. Appearance of PG-like lesions in these patients represents an abnormal reaction to bacteria rather than a form of pathergy and suggests a local failure to terminate IL8 production resulting in marked neutrophilic infiltration. However, the role of bacterial antigens warrants further study. Cell-mediated defects described in PG include cutaneous anergy to candida, streptokinase and purified protein derivative, as well as altered production of macrophage inhibition factor by lymphocytes [19]. Oligoclonal T-cell response due to antigenic stimulus and trafficking between the skin and other organs occurs in PG [20]. Decreased neutrophil chemotaxis and impaired monocyte phagocytosis have been reported in association with PG [21]. The leukocyte abnormalities may contribute to the pathergy phenomenon [11, 22, 23]. Elevated levels of IL8 in the blood have been documented in PG [24], and high IL8 levels have been demonstrated in fibroblasts from PG lesions [25]. Cytokines like IL1 or TNF-α stimulate production of IL8.

Although ulcerative colitis is more commonly associated with PG than Crohn's disease, the latter became increasingly recognized as having association with PG; both classic and peristomal PG have been reported with ulcerative colitis, Crohn's disease, and collagenous colitis. Smoking is a significant factor favoring the development of extraintestinal manifestations of ulcerative colitis including PG and erythema nodosum [26].

PG is not associated with vasculitis, but cases with positive tests for c-ANCA or p-ANCA have been reported specially drug-induced PG (thiouracil). Recently a patient with PG and c-ANCA specific for h-lamp-2 has been reported [27]. Several families with inherited PG have been described [28, 29]. There is predisposition to PG in patients with mutation in caspase recruitment domain 15 leading to autosomal dominant autoinflammatory syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne; the mutations affect CD2-binding protein 1 [30, 31].

18.5 Clinical Features (Figs. 18.1 and 18.2)

Pyoderma gangrenosum can have a variety of clinical presentations. The lesions can be classified morphologically as (a) classic ulcerative, (b) bullous, (c) pustular, (d) vegetative (superficial granulomatous), and (e) pyostomatitis vegetans. These clinical variants of PG differ in their clinical presentation, location, and associated diseases.

Patients with PG complain of severe pain that is out of proportion to the clinical appearance of lesions. Pathergy occurs in 20–30 % of patients; it is defined as the development of lesions at sites of cutaneous trauma (needle stick, venesection,

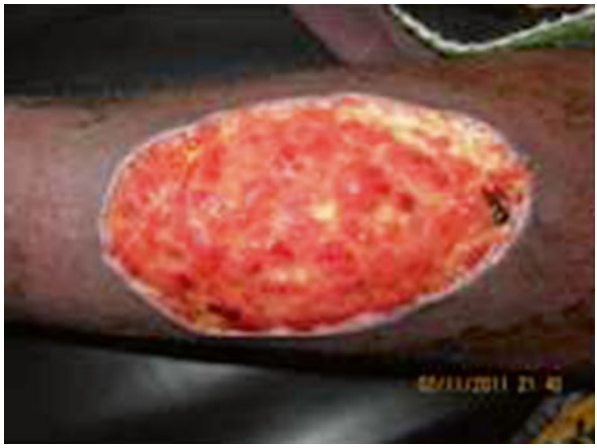

Fig. 18.1 An ulcer of pyoderma gangrenosum on the leg

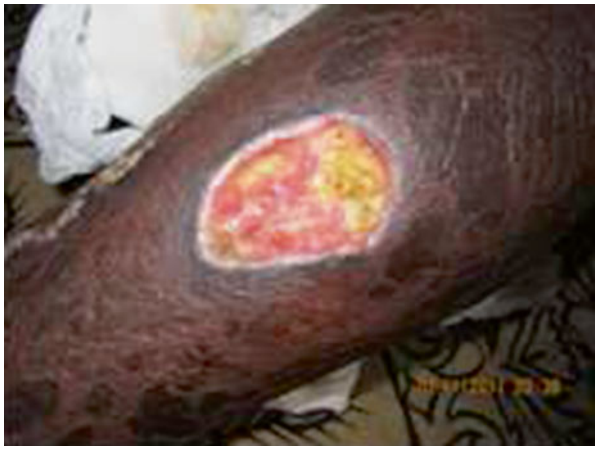

Fig. 18.2 Close-up view of a lesion of pyoderma gangrenosum on the leg showing a well-defined ulcer with violaceous undermined edges, granulation tissue, and purulent exudate at the base

insect bite, scalds, varicella, or surgical procedures, especially breast surgery, may act as trigger).

Cutaneous lesions most frequently develop on lower extremities especially on pretibial areas but can occur anywhere including mucous membranes. Sterile neutrophilic abscesses of internal organs (lungs, bones, joints, central nervous system, cardiovascular system, eye, intra-abdominal viscera) can occur with or precede cutaneous PG.

Skin lesions begin as tender papulopustule with surrounding erythematous or violaceous induration, or erythematous nodule or bulla on violaceous base. Necrosis occurs forming a central ulcer; a fully developed ulcer has purulent base with irregular undermined and overhanging, gunmetal color border which extends centrifugally. Re-epithelialization from margins occurs and lesions heal with atrophic cribriform pigmented scarring. Ulcers may be single or multiple and are rapidly progressive, but some may be less inflammatory and expand slowly.

PG-associated hematological disorders or drug-induced PG presents with acute onset hemorrhagic or purulent bullous lesions with widespread distribution and

rapid progression. Fever and signs of toxicity are present. PG associated with inflammatory disorders is usually a chronic slowly enlarging ulcer with increased granulation tissue at base, and it sometimes regresses spontaneously. PG in children is clinically similar to adults, but the lesions occur more frequently on head and anogenital areas.

18.6 Clinical Variants

18.6.1 Classic or Ulcerative PG

It is the commonest clinical variant. It presents with small tender red-blue papule, pustule, or plaque that erodes into painful ulcers with violaceous undermined edges, and the base shows granulation tissue, necrosis, or purulent exudate (Figs. 18.1 and 18.2). Most common site is lower extremities (70 %) but it may occur at other sites. Healing occurs with atrophic cribriform scar. Constitutional symptoms are present. Genital and mucosal involvement can occur. Seventy percent of the patients have associated disorders. Peristomal and postoperative PG present as ulcerative PG.

18.6.2 Pustular PG

It usually occurs during acute exacerbation of inflammatory bowel disease and presents as discrete painful sterile pustules with surrounding erythema on normal skin usually on extensor aspects of limbs. Lesions often resolve with control of inflammatory bowel disease (in some cases using treatment appropriate for both PG and IBD), but some may evolve into ulcerated classic PG [31].

18.6.3 Bullous PG

Superficial hemorrhagic bullae are present on the face, dorsum of hands, and upper extremities. Clinical and histopathological findings may be similar to superficial bullous variant of Sweet's syndrome, but bullous PG typically ulcerates and heals with scarring [31]. It is commonly associated with myeloproliferative disorders and can also occur with acute flare of inflammatory bowel disease.

18.6.4 Superficial Vegetative PG or Superficial Granulomatous Pyoderma

It presents as furunculoid nodule, abscess, plaque, or superficial ulcer most commonly on the trunk. It has non-purulent base and lacks the violaceous, undermined border [2, 32, 33]. Lesion is usually solitary, slowly progressing, and relatively painless. It is not associated with any systemic disease and resolves with less aggressive treatment [34, 35].

18.6.5 Peristomal PG

It is an ulcerative PG, accounting for about 15 % of cases. It may coexist with pustular vasculitis or PG at other sites. It is almost always associated with inflammatory bowel disease. Other associations include diverticular disease, bowel carcinoma, perforated bowel, neurogenic bladder, collagenous colitis, and systemic sclerosis.

18.6.6 Pyostomatitis Vegetans

It is characterized by oral mucosal thickening with multiple pustules and snail track ulcers on an erythematous base. It is strongly linked with inflammatory bowel disease (active ulcerative colitis). Skin lesions (pyodermatitis vegetans) have flexural distribution and are clinically similar to pemphigus vegetans. Based on evidence it is best to view it as inflammatory bowel disease-associated eruption and not a form of PG [31].

18.7 Histopathology

The histopathological findings of PG are variable and nonspecific but are useful in excluding other possible etiologies. The findings depend on clinical variant, type of lesion, site of lesion, site within the lesion, stage of evolution of lesion, and the treatment taken by the patient [2]. Site of biopsy is important because biopsy taken from the center of established ulcerative, bullous, or pustular PG lesions usually shows marked neutrophilic infiltration with abscess formation in mid and deep dermis extending to the panniculus, whereas those taken from peripheral areas (ulcer edge or inflammatory zone of erythema) show mixed or predominantly lymphocytic inflammatory infiltrate.

Typical findings are central necrosis and ulceration of the epidermis and dermis, surrounded by acute inflammatory cell infiltrate with peripheral mixed or chronic inflammatory cells.

Each clinical variant has additional more specific features which are as follows:

(a) Ulcerative: dermal-epidermal neutrophilic infiltrate extending to panniculitis with abscess formation.
(b) Pustular: perifollicular neutrophilic dense dermal infiltrate with intraepidermal vesicle.
(c) Vegetative: granulomatous reaction with palisading histiocytes and giant cells in the setting of focal dermal neutrophilic abscess and pseudoepitheliomatous hyperplasia is seen.
(d) Bullous: subepidermal or intraepidermal necrosis and marked upper dermal edema with prominence of neutrophils.

In most patients with typical PG, chronic ulcers have inflammation at the edge of ulcer bed. Presence of vasculitis in PG is debatable. True vasculitides and infective causes should be excluded if vasculitis is evident. Lymphocytes may be seen to infiltrate vessel wall with intramural or intravascular fibrin deposition (lymphocytic vasculitis). Culture and staining of biopsy tissue for bacteria, fungi, and

mycobacteria should be done if granuloma is present in absence of inflammatory bowel disease.

18.8 Evaluation of a Patient with PG

Clinical presentation of PG may be diverse, and there is neither a diagnostic laboratory test nor pathognomic histopathological findings; therefore, it is a diagnosis of exclusion. Most important considerations are exclusion of infection, vascular disease (stasis, occlusion, and vasculitis), and malignancy. Thorough history should be taken to rule out systemic involvement due to associated disorders, malignancy-related symptoms, and exposure to drugs (iodides, bromides, hydroxyurea), and physical examination should be done.

Skin biopsy and tissue culture should be done to rule out other causes. The best site for skin biopsy (incisional) is from the edge of the lesion (reducing potentially misleading features that may occur in any chronic ulcer) [2]. The patient should be investigated to rule out associated disorders (arthritis, inflammatory bowel disease, and hematological malignancies). Serological evaluation may also be performed (antinuclear antibodies, antiphospholipid antibodies, serum protein electrophoresis, ANCA).

18.9 Diagnosis

There is no confirmatory diagnostic test for pyoderma gangrenosum. The following diagnostic criteria have been proposed for cutaneous lesions of classic ulcerative PG [36]. Diagnosis requires both of the major criteria and at least two minor criteria (Table 18.2).

Table 18.2 Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum [36]

Major criteria
1. Rapid[a] progression of a painful[b], necrolytic cutaneous ulcer[c] with an irregular, violaceous and undermined border
2. Other causes of cutaneous ulceration have been excluded[d]
Minor criteria
1. History suggestive of pathergy[e] or clinical finding of cribriform scarring
2. Systemic diseases associated with pyoderma gangrenosum[f]
3. Histopathologic findings (sterile dermal neutrophilia,+/−mixed inflammation,+/− lymphocytic vasculitis)
4. Treatment response (rapid response to systemic corticosteroids)[g]

[a]Characteristic margin expansion of 1–2 cm per day or a 50 % increase in ulcer size within 1 month
[b]Pain is usually out of proportion to the size of ulceration
[c]Typically preceded by a papule, pustule or bulla
[d]Usually necessitates skin biopsy and additional evaluation to exclude other causes
[e]Ulcer development at sites of minor cutaneous trauma
[f]Inflammatory bowel disease, arthritis, IgA gammopathy, or underlying malignancy
[g]Generally responds to prednisone (1–2 mg/kg/day) or another corticosteroid at an equivalent dosage, with 50 % decrease in size within 1 month

18.10 Differential Diagnosis

18.10.1 Early Inflammatory Non-ulcerative Stage (Papules, Pustules, Plaques, or Nodules)

- Follicular infections (folliculitis, furuncle, carbuncle of bacterial, fungal, or viral origin)
- Cellulitis or cellulitis-like lesion (bacterial, mycobacterial, or fungal origin)
- Insect bite reaction
- Cutaneous T- and B-cell lymphomas
- Halogenoderma (iododerma or bromoderma)
- Panniculitides (inflammatory, infectious, metabolic, neoplastic)
- Cutaneous polyarteritis nodosa
- Sweet's syndrome
- Behçet's disease
- Bowel-associated dermatosis–arthritis syndrome

18.10.2 Later Ulcerative or Vegetative Stage

- Infections – streptococcal synergistic gangrene, botryomycosis, ecthyma gangrenosum, gummatous treponemal ulcers, cutaneous lesions of the deep mycoses (e.g. blastomycosis, coccidioidomycosis, paracoccidioidomycosis, chromomycosis), and atypical and typical mycobacterial infections
- Parasitic infections – leishmaniasis, amebiasis, and schistosomiasis
- Vascular diseases – ulcerations due to venous hypertension, arterial insufficiency, non-septic emboli, hemoglobinopathies, and thrombosis (secondary to hypercoagulability)
- Vasculitis – cutaneous polyarteritis nodosa, microscopic polyangiitis, granulomatous vasculitides (Wegener's granulomatosis, Churg–Strauss syndrome, temporal arteritis), autoimmune connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis), and Behçet's disease
- Malignancy – squamous cell carcinoma, basal cell carcinoma, and cutaneous T- and B-cell lymphomas
- Miscellaneous – brown recluse spider bite, ulcerative necrobiosis lipoidica, pemphigus vegetans of the Hallopeau or Neumann type, blastomycosis-like pyoderma, nonhealing surgical wound, factitious ulcers, ulcers in patients with Chédiak–Higashi syndrome, and leukocyte adhesion deficiency

18.11 Treatment

There is neither specific nor uniformly effective therapy for PG. The nature and intensity of the therapeutic approach depend on the number, size and depth of the lesions, the rate of expansion and appearance of new lesions, the associated

disorder, the medical status of the patient, and the risk and patient tolerance of prolonged therapy. The therapeutic thrust is to reduce the inflammatory process of the wound in order to promote healing and reduce pain and to control the contributing underlying disease (especially leukemias and inflammatory bowel disease) with least adverse effects. The treatment of PG consists of (a) general measures, (b) wound care, and (c) specific therapy (topical, intralesional, systemic). The specific treatment of PG is local or combined local and systemic corticosteroid therapy with or without adjunctive systemic therapy.

18.11.1 General Measures

Adequate bed rest, efficient pain relief, correction of anemia, and appropriate therapy of associated disease should be started. If surgery is anticipated, appropriate measures (use of subcuticular sutures and systemic steroid cover) should be adopted to avoid precipitating new postoperative PG lesions. Patient should be given realistic expectations of the speed of recovery in the disease.

18.11.2 Wound Care

The cutaneous lesions of PG are usually extremely tender so cleansing should be carried out with tepid sterile saline or a mild antiseptic solution. Potassium permanganate solution diluted 1:2,000 is helpful if there is marked exudation; it also inhibits bacterial growth. Nonadhesive dressing should be applied over lesion with a crepe elasticized bandage. Hydrocolloid dressings can be used for superficial lesions. Patient should be instructed to avoid use of irritants such as chemical desloughing agents, caustics, gauze impregnated with soft paraffin or antibacterial agents, or pressure dressings.

A variety of bacteria may be cultured from the wound, but they usually represent contaminants and antibiotics are not required unless there are signs of incipient cellulitis around the wound.

18.11.3 Specific Therapy (Table 18.3)

Key to evidence-based support: (1) prospective controlled trial, (2) retrospective study or large case series and (3) small case series or individual case reports.

Systemic corticosteroids have generally been the most predictable and effective medication when delivered in adequate dosage. Unfortunately, more resistant lesions require more protracted therapy (>3 months) at a higher than desirable dosage, thus inviting adverse side effects. Such patients should be closely monitored and should receive supplemental calcium (1500 mg/day) and vitamin D (800 IU/day). Bisphosphonates may be used when required. Cyclosporine is an alternative first-line therapy of PG [38, 39] or may be used in combination with systemic

Table 18.3 Therapeutic ladder for the treatment of pyoderma gangrenosum [37]

Drugs	Dosage	Level of evidence
Inflammatory disease		
(a) Mild disease		
Intralesional corticosteroids		2
Topical tacrolimus		2
Clofazimine	100–400 mg PO daily	2
Superpotent topical corticosteroids		3
Oral antibiotics (sulfonamides, minocycline)		3
Colchicine	0.6 mg PO thrice daily	3
Dapsone	50–150 mg PO daily	3
Combination colchicine/dapsone		3
Others (oral potassium iodide, intralesional cyclosporine, topical cromolyn sodium, nicotine patch or cream)		3
(b) More severe disease		
TNF-α inhibitors[a]: infliximab	5 mg/kg IV at weeks 0, 2, 6	1
Adalimumab	80 mg sc as initial dose then 40 mg sc weekly or every other week	3
Etanercept	50–100 mg sc weekly	3
Prednisone	60–120 mg PO daily	2
Cyclosporine	2.5–5 mg/kg PO daily	2
Thalidomide[b]	50–150 mg PO nightly	2
Methotrexate[c]	2.5–25 mg PO or IM weekly	
Azathioprine[c]	50–100 mg PO twice daily	3
Mycophenolate mofetil[c]	1–1.5 g PO twice daily	3
Methylprednisolone[d]	1 g daily for 3–5 days (IV pulse)	3
Tacrolimus	0.1–0.2 mg/kg PO daily	3
Cyclophosphamide	50–100 g daily	3
Chlorambucil	4–6 mg PO daily	3
IV Ig	2–3 g/kg IV monthly (given over 2–5 consecutive days)	3
Granulocyte apheresis, plasmapheresis		3
Total colectomy (severe chronic ulcerative colitis)		3
Non-inflammatory disease		
Bio-occlusive dressings compression, limb elevation		

[a]Especially in patients with inflammatory bowel disease
[b]Especially in patients with Behcet's disease
[c]Often used in combination with other agents or maintenance therapy
[d]Followed by daily oral prednisone

corticosteroids to achieve rapid control of disease. Tacrolimus [39–42] and mycophenolate mofetil have been used successfully in the treatment of PG either as monotherapies or in combination with systemic corticosteroids or cyclosporine [43]. Pulsed intravenous corticosteroid therapy has been reported to be effective in some cases refractory to oral corticosteroids, and it has been recommended in PG refractory to other forms of treatment. Methotrexate and TNF-α inhibitors like infliximab, adalimumab, and etanercept are being used especially where there is associated inflammatory bowel disease or inflammatory arthritis. Thalidomide has been effective as well, especially in those who have Behçet's disease. For treating PG of PAPA syndrome, anakinra (IL1 receptor antagonist) and infliximab have found to be effective [44–51].

Other treatment modalities found to be effective in small studies include plasmapheresis, leukocytapheresis or granulocytapheresis IVIG, and low-dose colchicines [52–57]. Evidence for benefit from minocycline, dapsone, and clofazimine is anecdotal. Surgical procedures, if required, should be carefully performed in patients with PG because pathergy phenomenon can take place [56–58]. Aggressive surgical debridement is contraindicated, but split-skin grafts and cultured keratinocyte autografting have been successfully performed while using prolonged courses of immunosuppressants to minimize the pathergy phenomenon [59–61].

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References

1. Brunsting LA, Goeckerman WH, O'Leary PA. Pyoderma gangrenosum: clinical and experimental observations in five cases occurring in adults. Arch Dermatol. 1930;22:655–80.
2. Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. J Am Acad Dermatol. 1996;34:395–409.
3. Callen JP. Pyoderma gangrenosum. Lancet. 1998;351:581–5.
4. Bennett ML, Jackson JM, Jorizzo JL, et al. Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. Medicine. 2000;79:37–46.
5. Broq L. Nouvelle contribution a' l'e'tude du phagedenisme geometrique. ANN Dermatol Syphiligr (Paris). 1916;6:1–39.
6. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine (Baltimore). 1976;55:401–12.
7. Callen JP. Neutrophilic dermatoses. Dermatol Clin. 2002;20:409–19.
8. Powell FC, Collins C. Pyoderma gangrenosum. Clin Dermatol. 2000;18:283–93.
9. Marzano AV, Tourlaki A, Alessi E, Caputo R. Widespread idiopathic pyoderma gangrenosum evolved from ulcerative to vegetative type: a 10-year history with a recent response to infliximab. Clin Exp Dermatol. 2007;33:156–9.
10. Powell FC, Schroeter AL, Su WP, et al. Pyoderma gangrenosum: a review of 86 patients. Q J Med. 1985;55:173–86.
11. Van den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. Br J Dermatol. 1997;137:1000–5.

12. Dick DC, Mackie RM, Patrick WJA, et al. Pyoderma gangrenosum in infancy. Acta Derm Venereol. 1982;62:348–50.
13. Madke B, Pande S, Khopkar U. Phenomena in dermatology. Indian J Dermatol Venereol Leprol. 2011;77:264–75.
14. Samitz MH. Cutaneous vasculitis in association with ulcerative colitis. Cutis. 1966;2:383–7.
15. Ebringer A, Doyles AE, Harris GS. Dermonecrotic factor I: nature and properties of a dermonecrotic factor to guinea pig skin found in human serum. Br J Exp Pathol. 1969;50:559–65.
16. Samitz MH, Dana AS, Rosemberg P. Cutaneous vasculitis in association with Crohn's disease: review of statistics of skin complications. Cutis. 1970;6:51–6.
17. Lotti T, Ghersetich I, Comacchi C, et al. Cutaneous small-vessel vasculitis. J Am Acad Dermatol. 1998;39:667–87.
18. Marks DJB, Rahman FZ, Novelli M, et al. An exuberant inflammatory response to E. coli: implications for the pathogenesis of ulcerative colitis and pyoderma gangrenosum. Gut. 2006;55:1662–3.
19. Lazarus GS, Goldsmith LA, Rocklin RE, et al. Pyoderma gangrenosum, altered delayed hypersensitivity, and polyarthritis. Arch Dermatol. 1972;105:46–51.
20. Brooklyn TN, Williams AN, Dunnill MGS, Probert CS. T-cell receptor repertoire in pyoderma gangrenosum: evidence for clonal expansions and trafficking. Br J Dermatol. 2007;157:960–6.
21. Nerella P, Daniela A, Guido M, et al. Leukocyte chemotaxis and pyoderma gangrenosum. Int J Dermatol. 1985;24:45–7.
22. Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. Expert Rev Dermatol. 2006;1:391–400.
23. Wollina U. Pyoderma gangrenosum—a review. Orphanet J Rare Dis. 2007;2:19.
24. Oka M, Berking C, Nesbit M, et al. Interleukin-8 overexpression is present in pyoderma gangrenosum ulcers and leads to ulcer formation in human skin xenografts. Lab Invest. 2000;80:595–604.
25. Oka M. Pyoderma gangrenosum and interleukin-8. Br J Dermatol. 2007;157:1279–81.
26. Manguso F, Sanges M, Staiano T, et al. Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis. Am J Gastroenterol. 2004;99:327–34.
27. Hoffman MD. Pyoderma gangrenosum associated with c-ANCA (h-lamp-2). Int J Dermatol. 2001;40:135–7.
28. Alberts JH, Sams HH, Miller JL. Familial ulcerative pyoderma gangrenosum: a report of two kindreds. Cutis. 2002;69:427–30.
29. Khandpur S, Mehta S, Reddy BS. Pyoderma gangrenosum in two siblings: a familial predisposition. Pediatr Dermatol. 2001;18:308–12.
30. Shoham NG, Centola M, Mansfield E, et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. Proc Natl Acad Sci U S A. 2003;100:13501–6.
31. Cox NH, Jorizzo JL, Bourke JF, Savage COS. Vasculitis, neutrophilic dermatosis and related disorders. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's textbook of dermatology. 8th ed. Chichester: Wiley Blackwell; 2010. p. 50.64–73.
32. Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. Clin Dermatol. 2005;23:612–20.
33. Wilson-Jones E, Winkelmann RK. Superficial granulomatous pyoderma: a localized vegetative form of pyoderma gangrenosum. J Am Acad Dermatol. 1988;18:511–21.
34. Quimby SR, Gibson LE, Winkelmann RK. Superficial granulomatous pyoderma: clinicopathologic spectrum. Mayo Clin Proc. 1989;64:37–43.
35. Lichter MD, Welykyj SE, Gradini R, et al. Superficial granulomatous pyoderma. Int J Dermatol. 1991;30:418–21.
36. Su WPD, Davis MD, Weenig RH, et al. Pyoderma gangrenosum: clinicopathological correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43:790–800.
37. Moschella SL, Davis Mark DP. Neutrophilic dermatoses. In: Bolognia JL, Jorizzo JL, Schaffer JV, editors. Bolognia's textbook of dermatology. 3rd ed. USA: Elsevier Saunders; 2012. p. 427–31.

38. Vidal DG, Puig L, Gilaberte M, Alomar A, et al. Review of 26 cases of classical pyoderma gangrenosum: clinical and therapeutic features. J Dermatol Treat. 2004;15:146–52.
39. Ackerman D, Abu-Elmagd K, Venkataramanan K, et al. Recalcitrant psoriasis and pyoderma gangrenosum treated with FK506. J Invest Dermatol. 1991;96:536.
40. Lee MR, Cooper MJ. Mycophenolate mofetil in pyoderma gangrenosum. J Dermatol Treat. 2004;15:303–7.
41. Cox NH, Palmer JG. Bowel-associated dermatitis-arthritis syndrome associated with ileo-anal pouch anastomosis, and treatment with mycophenolate mofetil. Br J Dermatol. 2003;149:1296–7.
42. Daniels LH, Callen JP. Mycophenolate mofetil is an effective treatment for peristomal pyoderma gangrenosum. Arch Dermatol. 2004;140:1427–9.
43. Gettler S, Rothe M, Grin C, Grant-Kels J, et al. Optimal treatment of pyoderma gangrenosum. Am J Clin Dermatol. 2003;4:597–608.
44. Stichweh DS, Punaro M, Pascual V. Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. Pediatr Dermatol. 2005;22:262–5.
44. Johnson RB, Lazarus GS. Pulse therapy: therapeutic efficacy in the treatment of pyoderma gangrenosum. Arch Dermatol. 1982;118:76–84.
45. Pomerantz RG, Husni ME, Mody E, Qureshi AA. Adalimumab for treatment of pyoderma gangrenosum. Br J Dermatol. 2007;157:1274–5.
46. Pastor N, Betlloch I, Pascua JC, et al. Pyoderma gangrenosum treated with anti-TNF alpha therapy (etanercept). Clin Exp Dermatol. 2005;31:152–3.
47. Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. Br J Dermatol. 2005;152:1059–61.
48. Reguiaï Z, Grange F. The role of anti-tumor necrosis factor-alpha therapy in pyoderma gangrenosum associated with inflammatory bowel disease. Am J Clin Dermatol. 2007;8:67–77.
49. Munro CS, Cox NH. Pyoderma gangrenosum associated with Behçet's syndrome: response to thalidomide. Clin Exp Dermatol. 1988;13:408–10.
50. Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. Mayo Clin Proc. 2000;75:842–4.
51. Brenner M, Ruzicka T, Plewig G, Thomas P, Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol. 2009;161:1199–201.
52. Kaminska R, Ikaheimo R, Hollmen A. Plasmapheresis and cyclophosphamide successful treatments for pyoderma gangrenosum. Clin Exp Dermatol. 1999;24:81–5.
53. Fujimoto E, Fujimoto N, Kuroda K, Tajima S. Leukocytapheresis treatment for pyoderma gangrenosum. Br J Dermatol. 2004;151:1090–2.
54. Okuma K, Mitsuishi K, Hasegawa T, et al. A case report of steroid and immunosuppressant-resistant pyoderma gangrenosum successfully treated by granulocytapheresis. Therap Apher Dial. 2007;11:387–90.
55. Dirschka T, Kastner U, Behrens S, et al. Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. J Am Acad Dermatol. 1998;39:789–90.
56. Cummins DL, Anhalt GJ, Monahan T, Meyerle JH. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. Br J Dermatol. 2007;157:1235–9.
57. Kreuter A, Reich-Schupke S, Stücker M, et al. Intravenous immunoglobulin for pyoderma gangrenosum. Br J Dermatol. 2008;158:856–7.
58. Kontochristopoulos GJ, Stavropoulos PG, Gregoriou S, et al. Treatment of pyoderma gangrenosum with low-dose colchicine. Dermatology. 2004;209:233–6.
59. Cliff S, Holden CA, Thomas PR, et al. Split skin grafts in the treatment of pyoderma gangrenosum. Ann Plast Surg. 2001;46:23–8.
60. Limova M, Mauro T. Treatment of pyoderma gangrenosum with cultured keratinocyte autografts. J Dermatol Surg Oncol. 1994;20:833–6.
61. de Imus G, Golomb C, Wilkel C, et al. Accelerated healing of pyoderma gangrenosum treated with bioengineered skin and concomitant immunosuppression. J Am Acad Dermatol. 2001;44:61–6.

Self-Inflicted Ulceration

19

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19.1 Introduction

The skin is an important organ of communication and plays an important role in socialization throughout life. The skin is the interface between the individual and the physical and social environment and an important medium for communication. The self-inflicted ulcerations are the type of ulcerations which are caused by repeated injuries by patients themselves knowingly or unknowingly. It may masquerade as numerous dermatological disorders and should be considered after exclusion of other skin diseases. The self-inflicted dermatoses are a chronic heterogeneous group of disorders, reported to be more common among females and are generally associated with different classes of psychopathology. Knowledge of these disorders is important in the evaluation of any psychiatric patient as these disorders are essentially a cutaneous sign of psychopathology. Psychocutaneous conditions are difficult to diagnose and a challenge to treat. A study conducted in community setup in Ireland showed that 4 % wounds were pressure ulcers, 2.9 % as leg ulcers, 2.2 % as self-inflicted ulcerations, and 1.7 % as surgical wounds [1].

There are three major self-inflicted dermatoses, namely, dermatitis artefacta, neurotic excoriations, and trichotillomania or traumatic alopecia. Psychiatric intervention is often the most crucial element in the treatment of these patients [2].

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19.2 Dermatitis Artefacta

Dermatitis artefacta is a factitious disorder and represents an obsessive compulsive spectrum disorder. Dermatitis artefacta has a much more wide ranging age of onset and is associated with a more heterogeneous group of psychiatric disorders, but it is most frequently encountered among individuals with immature personalities in the face of a stressful life situation. The patient creates skin lesions to satisfy an internal psychological need. There are cutaneous lesions that are wholly self-inflicted. The patients typically deny the self-inflicted nature of these lesions. It is more common among females, with a male-to-female ratio of at least 1–4 in the various studies. The age at onset of symptoms spans a broad range from 9 to 73 years. Typically, bizarre-looking necrotic lesions appear rather suddenly in areas that are easily accessible to the patient. In the right-handed person, the left side is usually involved. The lesions have wide-ranging morphologic features and are often bizarre looking with sharp geometric borders surrounded by normal-looking skin. They may occur at any site but are mainly confined to the patients hand, periocular skin, arms, legs, and breast. They may present as blisters, purpura, ulcers, erythema, edema, sinuses, or nodules, depending upon the means employed by the patient to create the lesions such as deep excoriation by fingernails or other sharp object and chemical and thermal burns. The lesions are usually asymmetric and may appear singly or in crops, with no history of a primary papule or vesicle. The patients are typically not able to describe how the lesions evolved. Self-inflicted dermatologic lesions have been associated with mental retardation, psychosis, Münchausen syndrome, and malingering. Loss or threatened loss, marital difficulties, and increased social isolation, especially among the elderly, may precede dermatitis artefacta [3, 4].

Early diagnosis is important as this may prevent unnecessary surgery and chronic morbidity. Diagnosis is usually confirmed by biopsy which indicates lack of a primary disease process. Treatment is a supportive and empathic approach. In some instances, recovery occurs after the initial psychiatric contact, whereas in other cases, the disorder may persist for decades. The prognosis is reported to be better in the younger age group where symptoms arise primarily in the context of a disturbed home situation.

19.3 Neurotic Excoriations

Neurotic excoriations are lesions produced by the patient as a result of repetitive self-excoriation which may be initiated by an itch, “a disturbing sensation” in the skin distinct from pruritus, or because of an urge to excoriate a benign irregularity on the skin. This initiates and perpetuates the “itch-scratch” cycle, which in some patients becomes a true compulsive ritual. Neurotic excoriation is the most common self-inflicted dermatosis and has been associated with suicide. Unlike dermatitis artefacta, the patients typically acknowledge the self-inflictive nature of their lesions. It is mainly among females, ranging from 52 to 92 % in the various studies with a mean age between 30 and 45 years. Unlike the frequently bizarre-looking

lesions of dermatitis artefacta, the lesions in neurotic excoriations do not stand out as being unusual and do not have the potential to mimic other dermatologic disorders. They are typically a few millimeters in diameter, weeping, crusted, or scarred, with postinflammatory hypopigmentation or hyperpigmentation. The lesions may range in number from a few to several hundred, and in chronic cases, scarring may be the only sign. The lesions are distributed in areas that the patient can reach, typically affected regions being the upper and lower extremities, face, and upper back. The repetitive self-excoriation can also exacerbate a preexisting dermatosis [5, 6].

The most consistent psychiatric disorders reported in association with neurotic excoriations are a personality with perfectionist and compulsive traits and depression. Unlike dermatitis artefacta, suicide has been reported to be more frequent in neurotic excoriations. Other psychopathologies include psychosis "conversion reactions," "hysteria", hypochondriasis, and anxiety states. Up to one third of these patients also have tension or migraine headaches and gynecologic symptoms related to menstruation.

Diagnosis must include investigations for other systemic and local causes of pruritus. The patients acknowledge that their scratching perpetuates the disorder. The histopathology of these lesions is consistent with repetitive localized trauma to the skin.

Although currently there are no controlled studies evaluating the efficacy of psychiatric intervention in these patients, the literature suggests that management of the underlying psychiatric disorder is the most important feature in the treatment of the dermatologic lesions and in preventing possible serious sequelae such as suicide and repeated major surgical procedures in some of these patients. Treatment improvement in the mental state has been associated with improvement in the cutaneous lesions. Benzodiazepines, amitriptyline 50–75 mg/day, and pimozide 4–6 mg/day have been used to treat neurotic excoriations. Prognosis is better when the lesions have been present for less than 1 year and worse when other physical complaints such as muscle tension headaches are also present.

Trichotillomania or traumatic alopecia mainly affects the scalp and so not described here.

19.4 Münchausen Syndrome

Münchausen syndrome is a psychiatric factitious disorder wherein those affected feign disease, illness, or psychological trauma to draw attention, sympathy, or reassurance to themselves. It is also sometimes known as hospital addiction syndrome, thick chart syndrome, or hospital hopper syndrome. True Münchausen syndrome fits within the subclass of factitious disorder with predominantly physical signs and symptoms, but they also have a history of recurrent hospitalization, travelling, and dramatic, untrue, and extremely improbable tales of their past experiences.

The syndrome name derives from Baron Munchhausen (Karl Friedrich Hieronymus Freiherr von Münchausen, 1720–1797), a German nobleman working in the Russian army, who purportedly told many fantastic and impossible stories

about himself, which Rudolf Raspe later published as *The Surprising Adventures of Baron Münchausen*. In 1951, Richard Asher was the first to describe a pattern of self-harm, wherein individuals fabricated histories, signs, and symptoms of illness. Remembering Baron Munchhausen, Asher named this condition Münchausen syndrome in his article in The Lancet in February 1951 [7].

Patients may have multiple scars on abdomen due to repeated "emergency" operations. There are several ways in which the patients fake their symptoms. Other than making up past medical histories and faking illnesses, patients might inflict harm on themselves such as taking laxatives or blood thinners, ingesting or injecting themselves with bacteria, cutting or burning themselves, and disrupting their healing process such as reopening wounds. Many of these conditions do not have clearly observable or diagnostic symptoms, and sometimes the syndrome will go undetected because patients will fabricate identities when visiting the hospital several times. Münchausen syndrome has several complications as these patients will go to great lengths to fake their illness. Severe health problems, serious injuries, loss of limbs or organs, and even death are possible complications.

Therapeutic and medical treatment should center on the underlying psychiatric disorder: a mood disorder in Münchausen syndrome, the affected person exaggerates or creates symptoms of illnesses in themselves to gain investigation, treatment, attention, sympathy, and comfort from the medical personnel. In some extreme cases, people suffering from Münchausen syndrome are highly knowledgeable about the practice of medicine and are able to produce symptoms that result in lengthy and costly medical analysis, prolonged hospital stay, and unnecessary operations. The role of "patient" is a familiar and comforting one, and it fills a psychological need in people with this syndrome. Risk factors for developing Münchausen syndrome include childhood traumas, growing up with parents/caretakers who were emotionally unavailable due to illness or emotional problems, a serious illness in childhood, failed aspirations to work in the medical field, personality disorders, and a low self-esteem. Münchausen syndrome is more common in men and seen in young or middle-aged adults. Those with a history of working in health care are also at greater risk of developing it.

A similar behavior called *Münchausen syndrome by proxy* (MSP) has been documented in the parent or guardian of a child. In 1977, Münchausen syndrome by proxy—also known as factitious disorder by proxy—was first described by Meadow [7–9]. One mother had poisoned her toddler with excessive quantities of salt, and another mother had introduced her own blood into her baby's urine sample. MSP refers to a parent or other adult caretaker who repeatedly seeks medical attention for their children, whose symptoms they have faked or induced, sometimes causing real harm to the child and/or subjecting them to unnecessary investigations and interventions. Many hypotheses have been proposed to explain MSP. Some have noted that patients with the condition often present traumatic events—particularly abuse and deprivation and numerous hospitalizations in childhood—and as adults may have lacked support from family and friends. The adult ensures that his or her child will experience some medical affliction, therefore compelling the child to suffer treatment for a significant portion of their youth in hospitals. Furthermore, a disease may

actually be initiated in the child by the parent or guardian. This condition is considered distinct from Münchausen syndrome. In fact, there is a growing consensus in the pediatric community that this disorder should be renamed "medical abuse" to highlight the real harm caused by the deception and to make it less likely that a perpetrator can use a psychiatric defense when real harm is done.

The patient's prognosis depends upon the category under which the underlying disorder falls; depression and anxiety, for example, generally respond well to medication and/or cognitive behavioral therapy, whereas borderline personality disorder, like all personality disorders, is presumed to be pervasive and more stable over time.

Malingering is defined as a deliberate behavior for a known external purpose. There are three types of malingering: (1) *pure malingering* in which the individual falsifies all symptoms, (2) *partial malingering* in which an individual has symptoms but exaggerates the impact they have on daily life, and (3) *false imputation* in which the individual has valid symptoms but is dishonest as to the source of the problems. Other forms of malingering are *simulation* in which a person emulates symptoms of a specific disability and *dissimulation* in which the patient denies the existence of problems that would account for the symptoms (e.g., drug abuse). Patients were identified as (1) needing medical care, (2) thinking they needed medical care, (3) faking, or (4) making direct pleas for medical dispensation [10, 11].

Conclusion

Neurotic excoriation is the most common self-inflicted dermatosis and has been associated with suicide. Dermatitis artefacta has a much more wide ranging age of onset and is associated with a more heterogeneous group of psychiatric disorders, but it is most frequently encountered among individuals with immature personalities in the face of a stressful life situation. Although currently there are no controlled studies evaluating the efficacy of psychiatric intervention in these patients, the literature suggests that management of the underlying psychiatric disorder is the most important feature in the treatment of the dermatologic lesions and in preventing possible serious sequelae such as suicide, self-inflicted ulcerations, and repeated major surgical procedures in some of these patients and self-inflicted ulcerations.

References

1. McDermott Scales L, Cowman S, Gethin G. Prevalence of wounds in a community care setting in Ireland. J Wound Care. 2009;18:405–17.
2. Ehsani AH, Toosi S, Shahshahani TM, Arbabi M, Noormohammadpour P. Psycho-cutaneous disorders: an epidemiologic study. JEADV. 2009;23:945–7.
3. Boyd AS. Cutaneous Munchausen syndrome: clinical and histopathologic features. J Cutan Pathol. 2014;4:333–6.
4. Barańska-Rybak W, Cubała WJ, Kozicka D, Sokołowska-Wojdyło M, Nowicki R, Roszkiewicz J. Dermatitis artefacta – a long way from the first clinical symptoms to diagnosis. Psychiatr Danub. 2011;23:73–5.

5. Gupta MA, Gupta AK, Haberman HF. The self-inflicted dermatoses: a critical review. Gen Hosp Psychiatry. 1987;9:45–52.
6. Filaković P, Petek A, Koić O, Radanović-Grgurić L, Degmecić D. Comorbidity of depressive and dermatologic disorders – therapeutic aspects. Psychiatr Danub. 2009;31:401–10.
7. Kinns H, Housley D, Freedman DB. Munchausen syndrome and factitious disorder: the role of the laboratory in its detection and diagnosis. Ann Clin Biochem. 2013;50:194–203.
8. Meadow R. Munchausen syndrome by proxy. The hinterland of child abuse. Lancet. 1977;13:343–5.
9. Pulman A, Taylor J. Munchausen by internet: current research and future directions. J Med Internet Res. 2012;14:e115.
10. Usatine RP, Saldaña-Arregui MA. Excoriations and ulcers on the arms and legs. J Fam Pract. 2004;53:713–6.
11. Gupta MA, Gupta AK, Ellis CN, et al. Psychiatric evaluation of the dermatology patient. Dermatol Clin. 2005;23:591–9.

Pressure Ulcers of the Lower Limb

20

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20.1 Introduction

Pressure ulcers are a type of injury that breaks down the skin and underlying tissue when an area of skin is placed under constant pressure for certain period of time causing tissue ischemia, cessation of nutrition and oxygen supply to the tissues, and eventually tissue necrosis. Constant pressure resulting in "distortion or deformation damage" is probably the most accurate description of a pressure ulcer [1]. Pressure ulcers can range in severity from patches of discolored skin to open wounds that expose the underlying muscles, bones, and joints.

A pressure ulcer can be described as localized, acute ischemic damage to any tissue caused by the application of external force (either shear, compression, or a combination of the two). Pressure ulcers are also known as "bedsores," "decubitus ulcers," and "decubiti" although these names are now rarely used as it is recognized that the ulcers are not caused by lying or being in bed. The areas that are particularly prone to pressure sores are those that cover the bony areas such as trochanters, sacrum, malleoli, and heel. In the leg the pressure ulcers in a bedridden patient are usually on the posterior aspect of the heel and at times over the lateral malleoli, but in an ambulatory patient can occur over other pressure points like prominent heads and bases of metatarsals, weightbearing areas of deformed limb, and pressure points of ill-fitting prosthesis (Fig. 20.1a–g).

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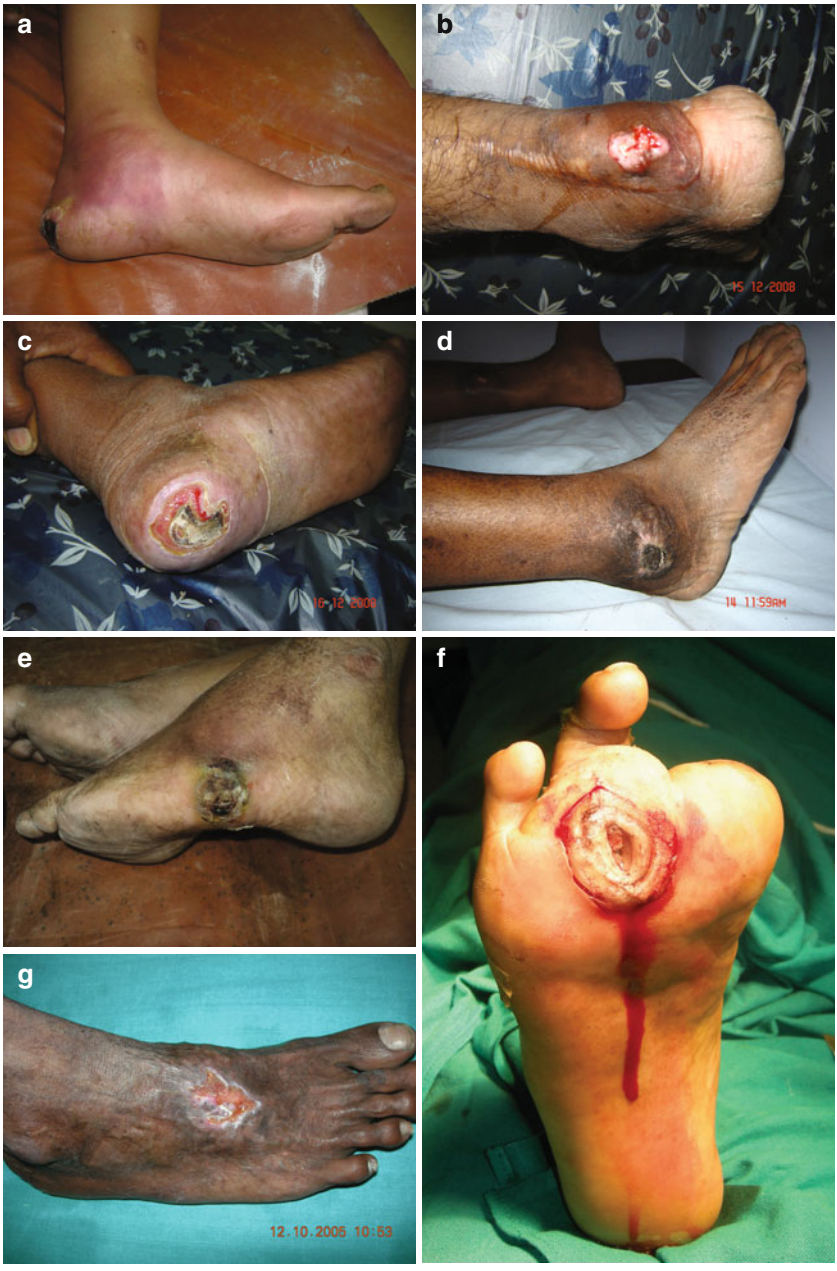

Fig. 20.1 Common locations of pressure or trophic ulcers of lower limb. Heel is the most common site of pressure or trophic ulcer (**a**–**c**), as this portion is the most pressure bearing area of limb. It can be acute or chronic. The acute variety of heel ulcer is most commonly found in ICUs and any acute illness need to be bedridden, and commonly located in the posterior portion of heel (**a**) along with lower portion of tendo-achilis (**b**). If not protected well & early, they can turn very deep and leads to damage of deeper structures including tendo-achilis. The chronic variety is found in unprotected insensate heel (**c**). The other area may be any pressure points like lateral and medial malleoli (**d**) (especially by ill fitting shoes & prosthesis), base of 5th metatarsal (**e**), head of metatarsal (**f**), and dorsum of foot (**g**)

"Pressure sores" is the term used commonly in the United Kingdom, but again pressure injuries that are not open wounds (such as blisters and non-blanching erythema) are not true sores, but only "pressure damage," and still belong to this family of pressure ulcers. "Pressure ulcers" is a term used widely in the United States and other countries and has been accepted as the Europe-wide term by the European Pressure Ulcer Advisory Panel (EPUAP).

20.2 Etiology (Mechanism of Ulcer Formation)

There are many factors that can contribute to the development of pressure ulcers, but the final common pathway to ulceration is tissue ischemia. The tissues are capable of sustaining pressure on the arterial side of around 30–32 mm Hg for only a small duration of time. But when pressure increases even slightly above capillary filling pressure, it causes microcirculatory occlusion, and this in turn initiates a downward spiral toward tissue ischemia and ulceration [2, 3].

Pressure ulcers can develop when a large amount of pressure is applied to an area of skin over a short period of time. They can also occur when less pressure is applied over a longer period of time. The extra pressure disrupts the flow of blood through the skin. Without a blood supply, the affected skin becomes starved of oxygen and nutrients and begins to break down, leading to ulcer formation.

The majority of people affected with pressure sores are those having health conditions (mental or physical) that encourage immobility, especially those who are confined to bed or chair for prolonged periods of time. Several other health conditions that influence blood supply and capillary perfusion, such as type 2 diabetes, can make a person more vulnerable to pressure ulcers. Age is also a factor that majority (approx two thirds) of pressure ulcers occur in old age people (60–80 years) [4]. To put it more simply, any individual, with or without a medical condition, who is incapable of avoiding prolonged periods of uninterrupted compression, is at a risk of pressure ulcers. Majority of patients affected with pressure ulcers frequently develop it over a bony prominence. Approximately 67 % of cases reported are affected over the area where skin covers the bones such as sacral, ischial, and trochanteric pressure ulcers [5], and in the lower extremities, these are seen in the malleolar, heel, patellar, and pretibial locations – account for approximately 25 % of all pressure sores [6]. Leg and foot ulcers have many causes that may further define their character (Fig. 20.2a–g). Table 20.1 describes the various direct and indirect causes of pressure ulcers of the lower extremity.

20.2.1 Direct Causes

Pressure ulcers develop when the soft tissues of the body are distorted and contorted in a fixed manner by the prolonged external force or pressure. This distortion occurs

either because the soft tissues are compressed and/or sheared between the skeleton and a support, such as a bed or chair when the person is sitting or lying, or because something is pressing into the body, such as a shoe, a prosthesis, a surgical appliance, or clothing elastic. Blood vessels within the distorted tissue are compressed, angulated, or stretched out of their usual shape, and blood is unable to pass through them [7]. The tissues supplied by these blood vessels become ischemic. Besides occluding the blood flow, tissue distortion also obstructs lymphatic flow, which in turn leads to accumulation of metabolic waste products, proteins, and enzymes in the affected tissue. This too can compound the tissue damage.

As the living tissues are not static, the way they are distorted changes over time. When constant pressure is maintained, soft tissues mold themselves to accommodate

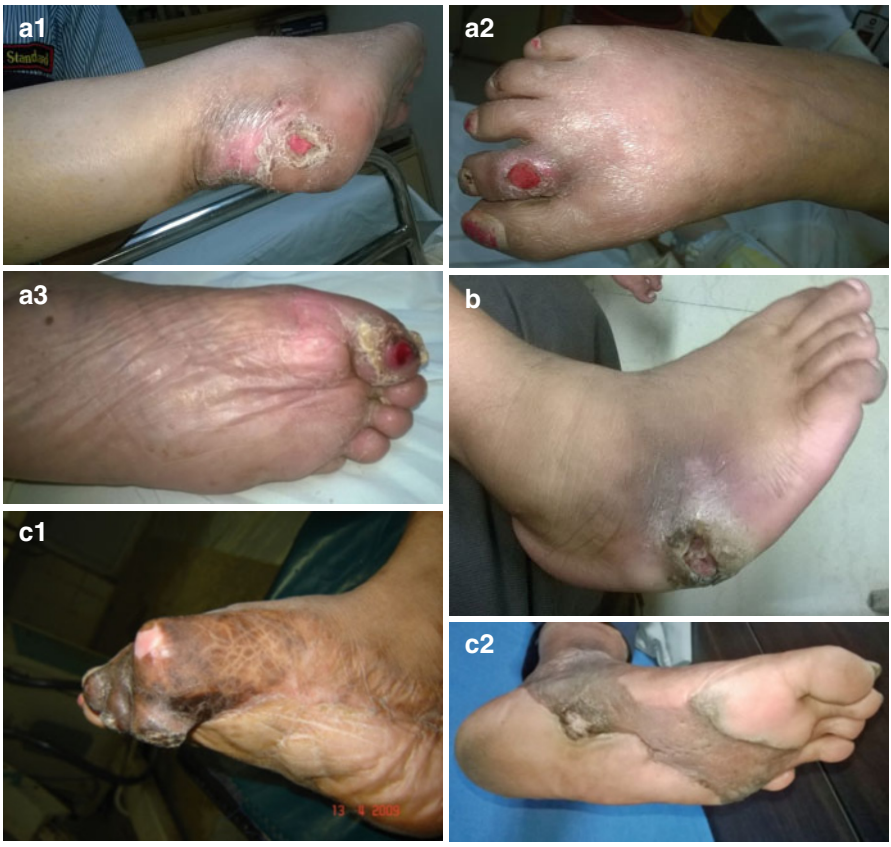

Fig. 20.2 Various etiologic factors of pressure ulcer specific to lower extremity. Deformity of limb or foot that can change the pressure distribution (location or surface area) of limb may lead to pressure ulcer of limb/foot. The common causes are: Neurologically deformed limb (**a1**–**a3**), Charcot's foot (**b**), Post burn contracture and deformities (**c**), walking over the grafted or reconstructed heel or sole (**d**), pressure due to ill-fitting prosthesis (**e**), Diabetic foot associated trophic ulcer (**f**), and ulcers due to continuous pressure and friction by footwear over prominent metatarsal head (**g**)

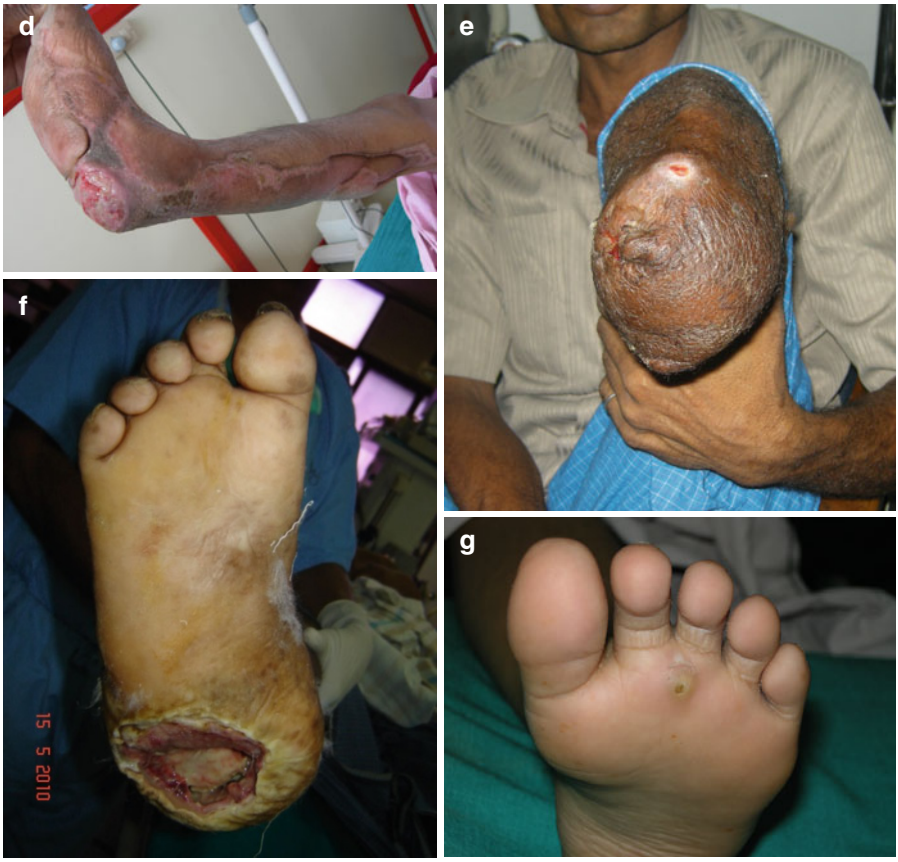

Fig. 20.2 (continued)

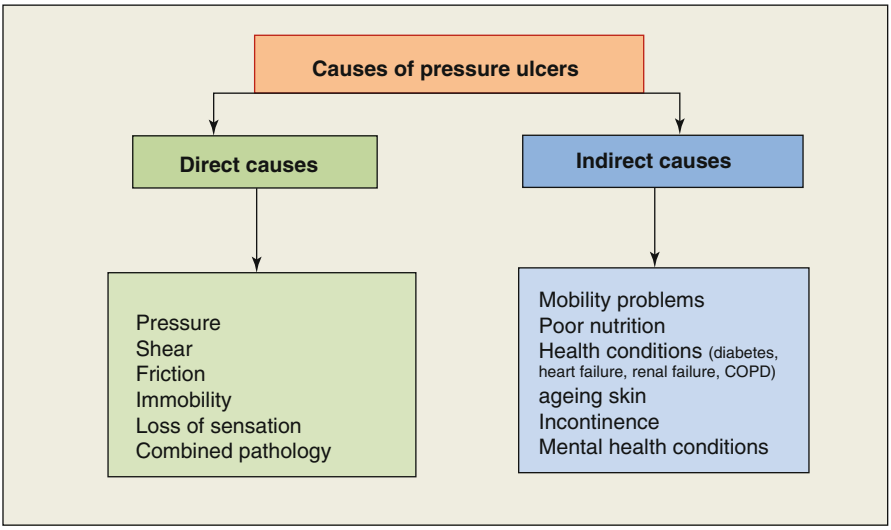

Table 20.1 Causes of pressure ulcers of the lower extremities

the external shape. This is known as tissue creep [8]. This may reduce the external pressures but may also exaggerate internal distortions. The chances of atrophy of the skin with thinning of this protective barrier, making the skin more susceptible to minor compression, and internal conjugation of soft tissues are significantly high in paraplegic patients [9], and particularly in these susceptible patients, pressure ulcers can occur within 1 to 2 hours [10]. If ischemia persists for a sufficient length of time, necrosis takes place. This is usually the beginning of a pressure ulcer.

20.2.1.1 Pressure

Although pressure is the main cause of promoting ulcers, it is important to understand that the application of pressure in itself does not cause damage. Divers and soft-bodied sea organisms can operate at great depths of water with no risk of pressure damage. Although the external pressures can be extremely high, they do not cause tissue distortion because the pressure is uniformly spread. It is only when pressure becomes nonuniform and pressure gradients occur between adjacent areas of tissue that distortion occurs and the potential for pressure damage arises. The damage only occurs when the pressure becomes nonidentically scaled and evokes the pressure distortion.

Areas particularly susceptible to pressure damage include bony prominences [5] which have a thin covering of soft tissue, such as the posterior heel, malleoli, trochanters, and elbows. When the body is supported on these pressure points, large compressive force is accumulated on to a small surface area, and there is little padding to disperse this pressure. The height of the available tissue cover over the bony prominence is not the only determining factor for developing pressure sores. Although the soles of the feet have a thin covering of soft tissue, they have a vasculature that is particularly well adapted to withstand considerable distorting forces. On the sacrum and ischial tuberosity on the other hand, although there is a relatively thick covering of soft tissue and a wide supporting surface, the blood vessels are not adapted for weight bearing, which means that even with fairly light compression, pressure ischemia can develop rapidly. Hence, soles of feet do not develop pressure sores even after prolong weight bearing in ambulatory patients unless there are underlying causes, making them insensate and more prone to pressure damage.

When compression occurs, pressure is applied from at least two sides – the boney prominence inside and the unyielding support outside (Fig. 20.3a). This is the reason why pressure damage can present in two distinct clinical patterns. Tissue distortion and superficial damage occur with pressure on the skin surface, particularly if the supporting surface is uneven. If this is maintained for a prolonged period, it may still result in extensive damage as successive layers of tissues are destroyed. Superficial pressure ulcers caused by compression with minimal shearing tend to have a characteristic regular outline and can often be matched easily to the shape of the underlying bony prominence (Fig. 20.3b) or the object that caused the ulcer.

The most serious pressure damage usually occurs as a result of the deformation in the deep tissues much closer to the underlying bony prominences. Because the pressures can be much higher than at the skin/support interface and because larger blood vessels are more likely to be affected, necrosis of a large volume of tissue often takes place. When the supporting structures of the skin have been destroyed, more extensive parts

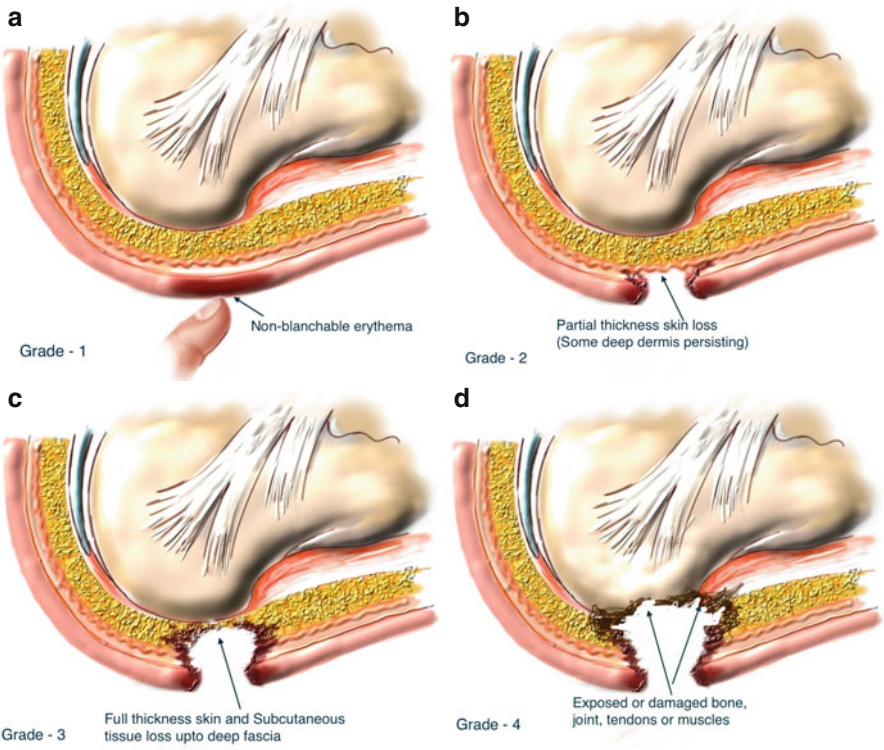

Fig. 20.3 (**a**–**d**) Severity or grading of pressure ulcers

of the skin become nonviable and die subsequent to the primary deep tissue destruction. As the nonviable skin breaks down, a cavity filled with necrotic tissue is revealed or large areas of undermining under viable skin are encountered (Fig 20.3c, d).

20.2.1.2 Shear

When external forces that move in different directions are applied to the same tissue mass, shearing occurs. The bony structure of the body tends to move toward the feet if someone is sitting up in bed, because the gravitational force drags the upper part of the body downward. However, at the skin/support interface, frictional forces resist the movement of the body. The tissues between the skin and the skeleton are therefore distorted, and any blood vessels running through the area become sheared along with the rest of the tissue. Shearing occludes flow more easily than compression (e.g., it is easier to cut off flow in a water hose by bending than by pinching it), so shear can be considered to be even more significant than pressure in the causation of pressure ulcers [11]. Areas of the body particularly susceptible to shearing include ischial tuberosities, heels, shoulder blades, and elbows. These are areas on which the body is frequently supported when in a position (such as sitting or lying semi-recumbent) which allows forward slide. Superficial pressure ulcers caused by shearing tend to have uneven appearance.

20.2.1.3 Friction

Friction, along with pressure and shear, is also frequently cited as a cause of pressure ulcers [12]. Friction can cause pressure ulcers both indirectly and directly. In the indirect sense friction is necessary to generate the shearing forces. However, it is often directly responsible for tissue damage, as when blisters are caused by a patient being dragged up a bed with a rough sheet, or ill-fitting footwear causing blister formation. However, this type of injury is an acute mechanical and heat trauma, and the etiology is quite different to that of pressure ulcers. Friction is not, therefore, a direct cause of pressure ulcers, although it is clearly possible that skin weakened by pressure ischemia may be more susceptible to friction, and the two will act together to hasten skin breakdown.

20.2.1.4 Immobility

Immobility is not a primary cause of pressure ulcers, but in the presence of additional factors, it can initiate them. Even small bodily movements such as leaning forward or readjusting are usually sufficient to give adequate pressure relief. Patients with ill-fitting plaster casts do not have this choice as they cannot move away from the pressure which is causing distortion of their tissues. Patients with profound immobility but intact sensation rarely develop pressure ulcers when they can still communicate. The pain of tissue ischemia ensures that these patients frequently ask for their position to be changed. Patients with orthopedic casts should be encouraged to report any discomfort and pain in order to prevent iatrogenic pressure ulcers.

20.2.1.5 Loss of Sensation

This is probably the most common cause of pressure ulceration. The person affected cannot feel the discomfort and pain normally caused by prolonged tissue distortion, does not have reflex protective responses to this type of stimulation, and is not stimulated to make protective movements by discomfort or pain.

The problem may arise in one of two ways:

1. Damage or severance of the nervous system. This damage may be:
   (i) Congenital (e.g., spina bifida)
   (ii) Traumatic (e.g., spinal injury)
   (iii) A disease process (e.g., ischemic damage to the spine following rupture of an aortic aneurysm, metastatic disease, peripheral neuropathy secondary to diabetes or leprosy, and neurological diseases)
   (iv) Iatrogenic causes (e.g., spinal anesthesia and local nerve block)
2. Causes in central nervous system: This may be due to unconsciousness or brain damage as in head injuries or brain diseases such as Alzheimer's disease or long-term treatment for psychiatric conditions such as depression or schizophrenia. Although there is apparently adequate sensation, circulation, and mobility to prevent pressure ulcers, the brain seems to suppress protective reflexes and disregards sensory warnings of tissue ischemia. These patients may or may not feel ischemic pain, but even if they do, they do not make appropriate movements to relieve pressure.

With neuropathy being the underlying cause of ulceration (neurotrophic ulcers), many patients complain of burning, tingling, or numbness of the feet on presentation. The ulcer is usually on the plantar aspect of the foot, most commonly heel, under the great toe, or first metatarsal head (Fig. 20.1c, f). Because of pressure, it is often surrounded by a rim of hyperkeratotic tissue, which may even cover the ulcer and give the illusion that the ulcer has healed, when it in fact has not. Infected ulcers may be associated with cellulitis, lymphangitis, adenopathy, calor, edema, foul odor, and purulent drainage. Systemic signs such as fever and chills may be related, but are often absent, even in the presence of severe infection. There may be foot deformity or prominent areas of pressure associated with the ulcer (Fig. 20.2a–c). Neuropathy is the gateway to the development of foot ulceration in diabetic patients.

20.2.1.6 Combined Pathology

When the reactive hyperemia cycle ceases to function adequately, a pressure ulcer will almost certainly develop unless preventive action is taken. There are three potential causes of pressure ulcers:

- Loss of movement
- Failure of reactive hyperemia
- Loss of sensation

The creation of a pressure ulcer can involve one or a combination of these factors. The diabetic patient with neuropathy of the feet is likely to have abnormal circulatory function in the involved area. On the other hand, the paralyzed patient with a spinal injury looses sensation and the ability to move the affected areas, and the ventilated patient doesn't feel able or move due to anesthesia while the peripheral circulation may be compromised by the administration of inotropes (Fig. 20.1a).

20.2.1.7 Failure of Reactive Hyperemia Cycle

It is a known fact that tissue distortion causes ischemia that in turn stimulates protective movements to relieve pressure and circulatory activity to restore normal blood flow in the affected areas. These protective movements are often reflexes as the person is unaware of making them. However, if these prompt actions prove insufficient to relieve ischemia, the central nervous system is stimulated by constant signals of discomfort and pain to make sure that pressure is relieved before any permanent damage occurs. Once the pressure is relieved and the circulation restored, local capillaries begin to dilate and increased blood flow takes place, referred to as reactive hyperemia. As a result, a bright pink transitory patch appears on the skin, often called blanching erythema because it blanches on pressure unlike the dull red non-blanching erythema that indicates tissue damage (Fig. 20.1a) [13]. Reactive hyperemia ensures a rapid restoration of oxygen and carbon dioxide balance; it also flushes out waste products. Erythema subsides as soon as tissues are restored to their resting state.

Patients who fail to produce reactive hyperemia cannot recover from the pressure-induced ischemic episodes resulting in permanent damage to the tissues. Failure of reactive hyperemia can occur in very sick and dying patients in whom there is insufficient peripheral blood pressure to refill capillary beds emptied by compression. Clinically, this presents as white patches in pressure areas which do not change color rapidly to the red of reactive hyperemia, as they would in a healthy person. Rather, the white patches remain for many minutes before slowly returning directly to a more normal skin color with little or no reactive hyperemia being observable. Similar effects can be seen in critical care patients who are on high doses of inotropes, such as adrenaline.

20.2.2 Indirect Causes (Associated Factors)

1. Age-related physiological alterations can lower the threshold for pressure-induced injury in elderly patients. For example, an increase in the fragility of blood vessels and connective tissue and a loss of fat and muscle leading to a reduced capacity to dissipate pressure.
2. Any condition that is associated with prolonged, impaired wound healing such as diabetes mellitus, which affects 11 % of adults over the age of 70 years.
3. Oxygen is required for all stages of wound healing; thus, any condition that is associated with a low tissue oxygen tension is a major cause of pressure ulcers. These include heart failure, atrial fibrillation, myocardial infarction, and chronic obstructive pulmonary disease.
4. Peripheral vascular disease, which affects 20 % of older adults, has a negative impact on wound healing.
5. Contractures and spasticity can contribute by repeatedly exposing tissues to pressure through flexion of a joint.
6. Loss of sensations – the pain signal that would normally cause an immobile individual to change position – is lost.
7. Paralysis and insensibility may produce atrophy of the skin leading to a thinning. This renders the skin more susceptible to the friction and shear forces a patient experiences when being moved.
8. Nutritional insufficiency conditions such as malnutrition [14], hypoproteinemia [15], and anemia [16] can cause significant delays in wound healing and hasten the formation of pressure ulcers [17].
9. Moisture causes maceration which predisposes the skin to injury. De-epithelialization caused by trauma leads to transdermal water loss that creates maceration and adherence of the skin to clothing and any other supports in contact, resulting into further injury [8].

These associated factors that (independently or combined) can cause pressure ulceration such as being elderly and unable to move the body or specific parts without help or any condition that is associated with weakened wound healing (such as

chronic diseases as diabetes mellitus or vascular disease), incontinence, and/or mental disability (often after brain or spinal injury) [18, 19] are explained below in some details:

20.2.2.1 Mobility Problems

Person with mobility problem is unable take preventive actions to pain signal; possible reasons for having a mobility problem are the following:

1. Spinal cord injury that causes some or all limbs to be paralyzed
2. Brain damage caused by an event such as a stroke or severe head injury, which results in paralysis
3. Progressive damage to the nerves used to move parts of the body, such as Alzheimer's disease, multiple sclerosis, or Parkinson's disease
4. Severe pain that makes it difficult to move some or all body parts as seen in skeletal secondaries of malignant diseases
5. Fractures in limbs causing immobility and abnormal limb posture
6. In postoperative phase – particularly if left on a ventilator or with an epidural catheter
7. Coma
8. Extremely painful joint movements such as rheumatoid arthritis

20.2.2.2 Poor Nutrition

Reasons that the patient's diet may lack nutrition include the following:

1. Anorexia nervosa – a mental health condition where a person has an unhealthy obsession with maintaining a low body weight
2. Dehydration
3. Dysphagia – esophageal cancer, oropharyngeal cancer, and severe stomatitis
4. Loss of appetite – stomach cancer

20.2.2.3 Health Conditions

1. *Type 1 diabetes and type 2 diabetes* – the high levels of blood sugar associated with diabetes can cause accelerated atherosclerosis and progressive ischemia.
2. *Peripheral arterial disease* – the blood supply in the legs becomes restricted due to the gradual narrowing of the lumen of the arteries of the legs – by spasm, angiitis, thrombus deposition, and luminal obliteration.
3. *Heart failure* – previous damage to the heart means it is no longer able to pump enough blood around the body.
4. *Kidney failure* – which can lead to a buildup of dangerous toxins and products of metabolism in the blood that can cause tissue damage.
5. *Chronic obstructive pulmonary disease* (*COPD*) – the low levels of oxygen in the blood associated with COPD can make the skin more vulnerable to anoxia and ischemic damage.

20.2.2.4 Aging Skin

With age, the skin loses some of its elasticity (stretchiness), which makes it more vulnerable to damage by minimal shearing force. Aging also results in reduced blood flow to the skin and a reduction in the height of the subcutaneous fat.

20.2.2.5 Incontinence

Both urinary incontinence (inability to control your bladder) and bowel incontinence (inability to control your bowels) can cause certain areas of the skin to become moist and prone to infection. This can trigger pressure ulcers to develop.

20.2.2.6 Mental Health Conditions

People with severe mental health conditions such as schizophrenia or severe depression have an increased risk of pressure ulcers for a number of reasons:

- Their diet tends to be poor, resulting in hypoproteinemia.
- They often have other physical health conditions, such as diabetes or incontinence.
- They may neglect their personal hygiene, making their skin more vulnerable to injury and infection that help an ulcer to form.

20.3 Diagnosis

The foundation of proper ulcer care is accurate diagnosis because treatment of any disease depends upon the diagnosis as misdiagnosis may result in mismanagement of the wound with a failure to heal leading to devastating consequences. The primary means of obtaining the correct diagnosis include history and physical examination. The early signs and symptoms of the ulcers allow clinicians to make the correct diagnosis for the most common types of leg and foot ulcers. Patients with an atypical appearance may require further pathological investigation or referral to a specialist, while longstanding ulcers may require biopsy to rule out malignancy.

Neurological examination: Diabetic patients should be tested for neuropathy because its presence completes the causal pathway to foot ulceration [20]. Vibratory testing may be performed with a 128-Hz tuning fork on the dorsum of the great toe. Achilles tendon reflex, patellar tendon reflexes and sense of vibration should also be examined [21]. The most effective means of detecting neuropathy is examination with a 10-g monofilament for sensory deficit under metatarsal heads. A patient with a history of neuropathy who complains of new-onset pain in the extremity should raise concern for a pathological process, such as infection or Charcot's neuropathic arthropathy [22].

Examination of vascular system: A proper vascular assessment is critical to the evaluation of the pressure ulcer. Vascular examination, including palpation of the dorsalis pedis and posterior tibial pulses, as well as general inspection of the

extremities, should be performed. Patients with evidence of ischemia should be further investigated with Doppler and angiography and DSA. An excellent tool is the ankle-brachial index (ABI), which is determined by dividing the highest systolic pressure of the anterior tibial or posterior tibial vessels by the highest systolic brachial pressure [23]. Ankle pressure is determined with the assistance of a Doppler probe; a result of 1.0–1.1 is normal. Values less than 1.0 are abnormal and reflect decreased perfusion to the lower extremity. Other vascular studies that may assess perfusion are segmental pressure determination, pulse volume recordings, duplex scanning, transcutaneous oxygen diffusion, contrast angiography, and magnetic resonance angiography.

Any *infection* must be ruled out as infected ulcers may lead to limb amputation and even be life threatening. The base of ulcers should be inspected carefully. Foot ulcers should be probed, because they often reveal a tract under the skin that may harbor an abscess. In addition, probing may assess the depth of the ulcer [24]. Deep culture of tissue or purulence is helpful in establishing the microbiology of the infection. Superficial swabbing of the ulcer is unreliable. Bone culture is the definitive method to diagnose osteomyelitis. It is best to go for biopsy when it becomes difficult to differentiate between a bacterial infection and simple contamination. The radiographs should be obtained if the bone infection is suspected. Films should be inspected for gas in the tissues. Signs of osteomyelitis include periosteal reaction, osteopenia, and cortical erosion, but appearance of these signs is quite delayed. Bone scanning and magnetic resonance imaging (MRI) are other useful means for establishing the early diagnosis of bone infection.

20.3.1 Severity of Pressure Ulcers

Healthcare professionals use several grading systems to describe the severity of pressure ulcers; most common is the European Pressure Ulcer Advisory Panel (EPUAP) grading system. Pressure sores are categorized into four stages (Table 20.2) corresponding to the depth of damage [25–27]. It must however be emphasized that when an eschar is present, accurate staging is not possible.

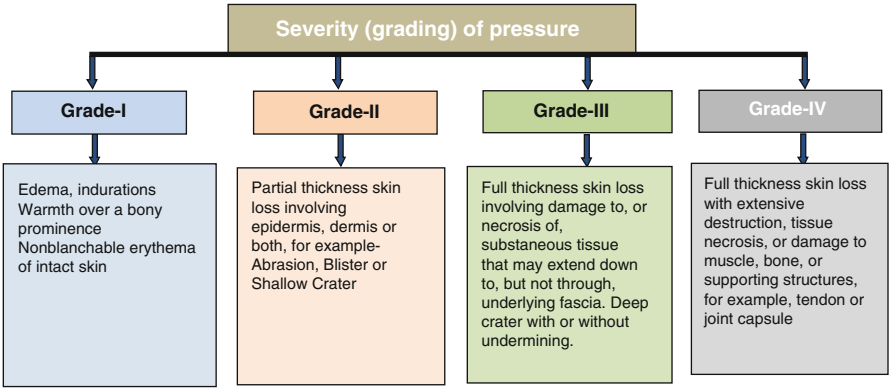

Table 20.2 Grades of pressure ulcers (also see Fig. 20.3)

20.3.1.1 Grade 1

A grade one pressure ulcer is the most superficial type of ulcer. The skin of the affected area appears discolored and is red in white people and purple or blue in darker colored people (Fig. 20.3a). One important thing to remember is that grade one pressure ulcers do not turn white when pressure is placed on them. The skin remains intact but it may hurt or itch. It may also feel either warm and spongy or hard.

The characteristics are as follows:

- Non-blanchable erythema of intact skin can be difficult to assess in patients with darkly pigmented skin.
- Edema and induration.
- Warmth over a bony prominence.
- When an eschar is present, accurate staging is not possible.

20.3.1.2 Grade 2

In grade two pressure ulcers, some of the outer surface of the skin (the epidermis) or the deeper layer of skin (the dermis) is damaged, leading to skin loss (Fig. 20.3b). The ulcer looks like an open wound or a blister. The characteristics are as follows:

- Partial-thickness skin loss involving epidermis, dermis, or both, for example, abrasion, blister, or shallow crater

20.3.1.3 Grade 3

In grade three pressure ulcers, skin loss occurs throughout the entire thickness of the skin. The underlying tissue is also damaged, but the underlying muscle and bone are not damaged. The ulcer appears as a deep cavity-like wound (Fig. 20.3c). The characteristics are as follows:

- Full-thickness skin involving damage to, or necrosis of, subcutaneous tissue that may extend down to, but not through, the underlying fascia
- Presents clinically as a deep crater with or without undermining

20.3.1.4 Grade 4

A grade four pressure ulcer is the most severe type of pressure ulcer. The skin is severely damaged, and the surrounding tissue begins to die (tissue necrosis). The underlying muscles or bone may also be damaged (Fig. 20.3d). People with grade four pressure ulcers have a high risk of developing a life-threatening infection. The characteristics are as follows:

- Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures, for example, tendon or joint capsule. Undermining and sinus tracts may be associated with this stage of wound progression.
- Similar to grading a burn with the addition of a stage 4 that is deeper than a stage 3 ulcer or 3rd-degree burn.

20.4 Treatment

Where possible, treatment of ulcers is planned with an aim to reverse the factors that have originally caused the ulcer. Ulcers are often the result of combined pathology (like diabetes, pressure, loss of sensation). Careful assessment is needed before planning for treatment. In general the possible causative factor should be removed (pressure, shear, friction), and the associated general condition should be controled (like treatment of associated comorbid illness and improvement in the nutrition). The affected area requires thorough cleaning and dressing. The limb must be elevated to improve the venous and lymphatic drainage, and the part must be given some rest from the weight bearing, pressure, and friction. However, as full range of motion and active physiotherapy of joints improve circulation, non-weightbearing physiotherapy is desirable.

The rest of the management of ulcer depends on many factors, and Table 20.3 illustrates an algorithm to help formulate a treatment plan.

Wound healing requires adequate protein, iron, vitamin C, and zinc. Supplements may be prescribed if they are deficient in the diet. Various treatment options are available to treat pressure ulcers; they include the following:

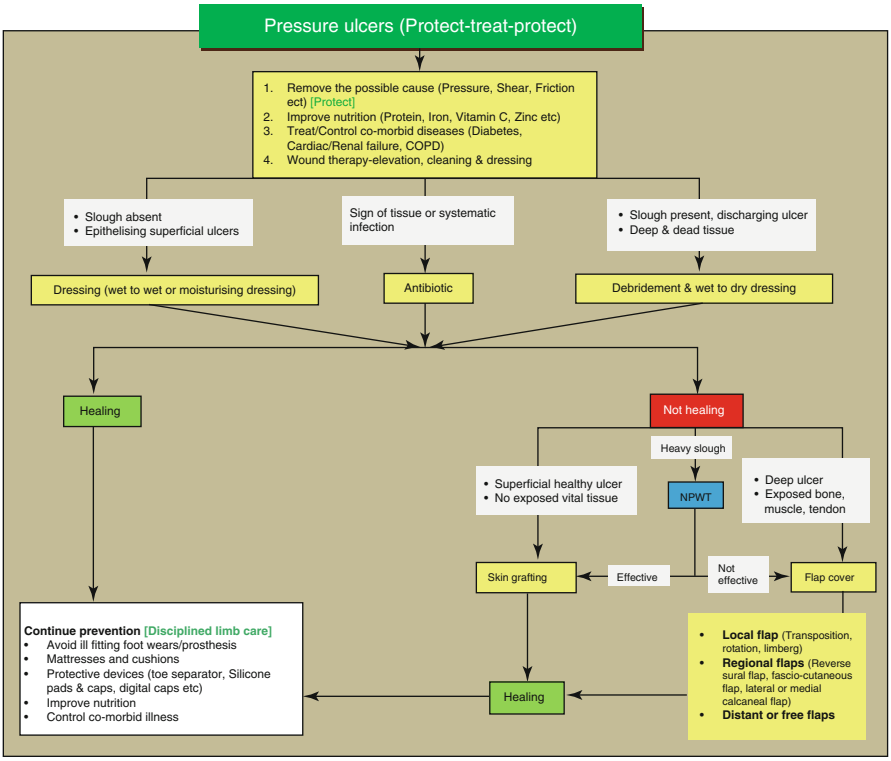

Table 20.3 Algorithm for treating pressure ulcers

20.4.1 Cleaning and Debridement

Cleaning of the wound and meticulous skin care are the most essential parts of the treatment. The process involves removal of surface contamination and meticulous excision of all dead tissue. This is debridement. Besides the conventional surgical debridement, other types of debridement include mechanical debridement or medical debridement using repeated wet and dry dressings, enzymatic debridement using enzymes to liquefy dead tissue in the wound and remove them with the dressings, and biological debridement or maggots and larval therapy [28, 29] in which the larvae eat all the dead tissue and make the wound clean without harming the living tissues. They also help to fight infection by releasing substances that kill bacteria and stimulate the healing process. Sharp surgical debridement using blade or scissors is the most commonly used and most effective method of debridement in able surgical hands. Dead tissue may be removed using mechanical means. Some mechanical debridement techniques include the following:

Cleansing and pressure irrigation – where dead tissue is removed using high-pressure water jets. There is no evidence available to support any specific and effective cleansing techniques or solution, in particular [30].
Ultrasound – dead tissue is removed using low-frequency energy waves.
Laser – dead tissue is removed using focused beams of light.

Basically, debridement is done for converting the chronic wound into an acute wound so that it can progress through the normal stages of healing.

20.4.2 Wound Dressings

The dressing used for various stages of wound healing is specialized for every stage; in fact there is a whole range of dressings available to assist with the different stages of wound healing. These are classified as nonabsorbent, absorbent, debriding, self-adhering, and many others. It is vital to determine the most appropriate dressing as it ultimately depends on the site/type of ulcer, for hospital care or domiciliary management, personal preference, and cost to the patient.

Dressings are usually occlusive so the ulcers heal better in a moist environment. If the ulcer is clean and dry, occlusive dressings are usually changed weekly, and more frequent changes are avoided as dressing changes remove healthy cells along with debris. Contaminated or weeping wounds may require more frequent dressing changes, sometimes every few hours. Heavily contaminated ulcers are treated with negative pressure wound therapy (NPWT).

Specialized dressings and bandages are used to protect and speed up the healing process of the pressure ulcers. These dressings include the following:

Hydrocolloid dressings – these contain a special gel that encourages the growth of new skin cells in the ulcer and keeps the nearby healthy area of the skin dry.

Alginate dressings – these are made from seaweed that contains sodium and calcium known to speed up the healing process. Honey-impregnated alginate dressings are known to accomplish total wound healing to pressure ulcers [31].

Nano silver dressings – these use the antibacterial property of silver to clean the ulcer.

Creams and ointments – To prevent further tissue damage and help speed up the healing process, topical preparations, such as cream and ointments, are frequently used.

20.4.3 Antibiotics

All pressure sores do not require antibiotics [7]. Antibiotics are usually only prescribed to treat an infected pressure ulcer and prevent the infection from spreading. If tissue infection exists, antibiotics are necessary to treat the infection, but effort must be made to debride the ulcer thoroughly and leave all viable tissues only; otherwise, antibiotics alone will not clean up the ulcer. Antibiotics are adjunct to surgical debridement and not an alternative to it.

The symptoms of infected pressure ulcer are pain, cellulitis in adjoining areas, and exudates. Pyrexia and toxemia may quickly appear in old, infirm, and immune-compromised patients. Infection should be treated with surgical debridement and antibiotics chosen according to wound culture studies. Topical antibiotics should be avoided because their use may increase antibiotic resistance and allergy. Antiseptic cream may also be applied topically to pressure ulcers to clear out any bacteria that may be present.

It has been noticed that the longstanding leg ulcers are frequently colonized by microorganisms in a biofilm. The biofilm may be composed of bacteria, fungi, or other organisms, which are embedded in and adherent to the underlying wound. Such conditions often contribute to the failure of the ulcer to heal, but at this time the best way to diagnose and control biofilm is unknown. The organisms are protected from the effect of conventional antibiotics; unnecessary prescription of antibiotics may in fact select more resistant organisms. We address the problem of biofilm by changing the pH of the wound – dressing with dilute ascetic acid if it is alkaline, which usually is and curetting out all the undermining, cracks, and crevices of the ulcer.

Negative pressure wound therapy (NPWT): This is an invaluable tool in the management of pressure sores and involves the application of subatmospheric pressure to a wound using a computerized unit to intermittently or continuously convey negative pressure to promote wound healing. Negative pressure treatment, called negative pressure wound therapy (NPWT), is effective for deep, cavitating, infected, and copiously discharging pressure ulcers, particularly with exposed bone [32]. With growing clinical experience, it can be said with certainty that it assists wound healing and its benefits can be summarized thus:

- Assists granulation
- Applies controlled, localized negative pressure to help uniformly draw wounds closed
- Helps remove interstitial fluid allowing tissue decompression
- Helps remove infectious materials and quantifies exudates loss
- Provides a closed, moist wound healing environment
- Promotes flap and graft survival
- Both hospital and domiciliary use
- Reduces hospital/dressings/nursing cost

20.4.4 Newer Research

There are many supportive therapies to promote healing of pressure ulcers. While some are in clinical use, others are in the realm of research. Many products are available to aid wound but should be prescribed only under strict medical advice, as they still require further research to determine their effectiveness. These include the following:

1. Growth factors and cytokines [33].
2. Hyperbaric oxygen to increase tissue oxygen tension [34]
3. Skin graft substitutes (bioengineered skin) [35]
   (a) Connective tissue matrix
   (b) Expanded epidermis
   (c) Epidermal stem cells [36]
4. Bone marrow or adipose-derived stem cell therapy [37]

1. *Cytokines and growth factors*: Chronic pressure ulcers displayed high levels of inflammation and disruption of the collagen matrix, along with increased indications of apoptosis and decreased levels of growth factors and their receptors. These characteristics can be used to comprehensively evaluate the etiology and treatment of these ulcers [38]. Robson et al. compared the healing response of sequential topically applied cytokines to that of each cytokine alone and to a placebo in pressure ulcers and to evaluate the molecular and cellular responses [39]. Ulcers treated with cytokines had greater closure than those in placebo-treated patients. Patients treated with bFGF alone did the best, followed by the GM-CSF/bFGF group. Patients treated with GM-CSF or bFGF had higher levels of their respective cytokine after treatment. Patients with the greatest amount of healing showed higher levels of platelet-derived growth factor (PDGF) on day 10 and transforming growth factor beta ($TGF_{\beta 1}$) on day 36. Message for the bFGF gene was upregulated after treatment with exogenous bFGF, suggesting auto-induction of the cytokine. Both cytokines and growth factors will have a big role to play in the treatment of pressure ulcers in future.

2. *Hyperbaric oxygen therapy*: Hyperbaric oxygen (HBO) therapy is being used for the treatment of pressure sores. Specially constructed devices equipped with controlled pressure sealing and automatic relief valves are fitted in HBO chambers. A constant pressure of 22 mm Hg (1.03 atm absolute) is maintained inside the chamber using pure oxygen at a flow rate of 2–8 l per minute with direct discharge to atmosphere [38]. It has proven to be very successful and safe as adjunctive treatment to daily wound dressing, administration of antibiotics, and surgical debridement because of the following:
   (a) It increases oxygen transport to wound area stopping further tissue damage.
   (b) It facilitates growth of new capillaries (angiogenesis) improving the microcirculation.
   (c) It speeds up wound healing by reducing inflammation and swelling.
   (d) It relieves pain.
   (e) It reduces infection by eliminating bacteria directly and increasing capacity of white blood cell to fight infection.
   (f) It improves microcirculation and elimination of toxins in the blood.
   (g) It enhances the effect of some antibiotics.
   (h) It stimulates release of stem cells from the bone marrow.
   (i) It decreases blood viscosity and risk of thrombosis and stroke.
   (j) It improves lymphatic circulation.
   (k) It improves bone density and mineralization and speeds up bone healing.
   (l) It enhances peripheral nerve regeneration for improved sensitivity.
   (m) It prepares tissue and bone for grafting before surgery.
   (n) It speeds up healing after surgery and improves chances of graft survival.
3. *Skin substitutes* (*bioengineered skin*): Cultured keratinocytes have been used for the treatment of various types of wounds for more than a decade [40]. Researches explain that in patients with partial-/full-thickness skin defects, the most effective therapy is cultured dermal substitute (CDS), while cultured epidermal substitute (CES) and cultured skin substitute (CSS) have also been used as biological wound dressings [41]. The artificial dermis induces angiogenesis and fibroplasia in deep, poorly vascularized tissue defects with fewer vascular invasions. However, it is difficult to apply collagen matrix to pressure ulcers, because they are usually accompanied by infection with discharge of excessive amounts of exudate or pus and generally exposed to external forces that prevent graft fixation [42]. The allogeneic cultured dermal substitute effectively treats intractable ulcers while bone marrow cell implantation combined with allogeneic cultured dermal substitute in treating severely ischemic ulcers [43].
4. *Bone marrow/adipogenic stem cells*: "Cell therapy" can be defined as a set of strategies which use live cells for therapeutic purposes. The aim of such therapy is to repair, replace, or restore the biological function of a damaged tissue or organ. Bone marrow mononuclear cells (BM-MNCs) can be easily obtained in large numbers by aspiration without extensive manipulation or cultivation before transplant, and cells can be transplanted directly without *in vitro* expansion. Using the entire mononuclear fraction, no potentially beneficial cell type is

omitted and MNCs from a patient's own bone marrow promote angiogenesis [37], and this seems to be a key factor for optimal healing of skin wounds. Marrow stem cells (MSCs) which make up a small proportion of BM-MNCs secrete paracrine factors that could recruit macrophages and endothelial cells to enhance wound healing [44]. The repair functions of MSC are thought to involve the secretion of factors such as VEGF [45] or FGF [46], which could help prevent apoptosis, promote angiogenesis, assist in matrix reorganization, and increase the recruitment of circulating MSCs [47]. Bone marrow harvesting is rather invasive and painful. In 2001, Zuk et al. [48] identified and characterized adipose tissue-derived MSCs (ASCs) from lipo-aspirates and even a section of whole fat (biopsy). A very small percentage of the nucleated cells which compose the BM are actually MSCs, whereas the amount of ASCs is approximately 500-fold greater when isolated from an equivalent amount of adipose tissue [49]. Even though cell therapy is a relatively new tool, several studies prove these types of cells may be used safely, and they have demonstrated their efficacy in healing wounds.

20.4.5 Surgical Management of the Pressure Ulcer

Surgery may be considered for very large and painful ulcers, particularly if the ulcer fails to heal with conservative management and for longstanding ulcers. First, the state of the venous and arterial systems should be assessed, infection eliminated, and underlying associated diseases such as diabetes, thrombophilia (tendency to blood clots) or malnutrition controlled. Surgery involves debriding the ulcer and then reconstructing the defect.

20.4.5.1 Reconstructive Surgery

Sometimes the deeper pressure ulcer (grade III or IV) fails to heal; in such cases, surgery is required to fill the wound and prevent any further tissue damage. This is usually done by cleaning the wound and closing it by bringing together the edges of the wound (direct closure), by applying various types of skin grafts, or by using local and regional flaps and free tissue transfer. It is prudent to remember and use reconstructive ladder during planning of reconstructive surgery for pressure ulcers of the lower limb (Table 20.3).

There are many risks and complications that can occur after surgery, including infection, necrosis of flap, muscle weakness, blisters, recurrence of the pressure ulcers, septicemia, infection of the bone (osteomyelitis), bleeding, abscesses, and deep vein thrombosis. Despite the risks, surgery is often a necessity and the only option to prevent limb and life-threatening complications.

The available reconstructive options are the following:

1. *Split-thickness skin grafting*: When the ulcer is superficial and vital tissues like bone, vessels, nerves, or tendons are not exposed, and the ulcer is not copiously discharging, skin grafting is the first option for surgical treatment. The slimy layer over the surface of ulcer is sharply debrided to get a healthy vascular bed

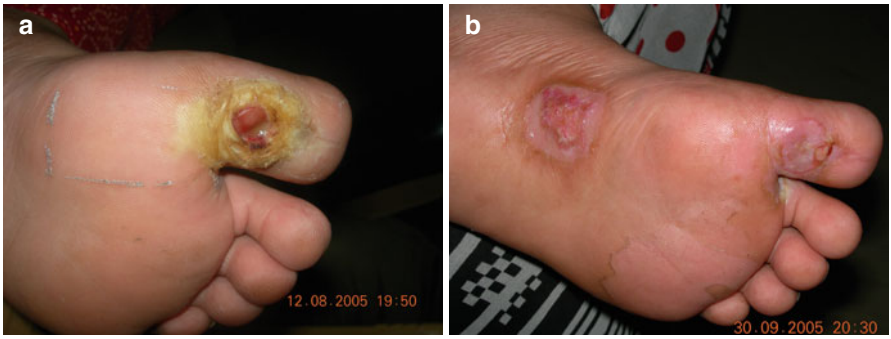

Fig. 20.4 (**a**, **b**) Split skin grafting

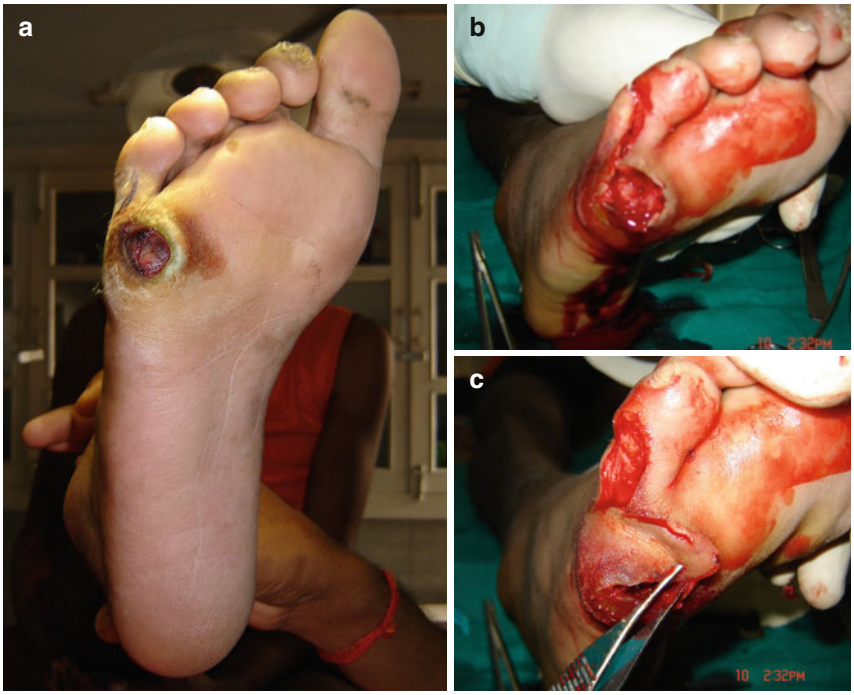

Fig. 20.5 (**a**–**c**) Transposition flap from adjacent toe

for skin grafting. The graft may be harvested from any part of the body, but to replace any weightbearing area of the skin, the glabrous thick skin of non-weightbearing medial planter skin can be a good option for reconstruction of small and superficial sole defects (Fig. 20.4).

2. *Local flaps*: Varity of local flaps can be used to reconstruct the defect created by the excision of lower extremity pressure ulcer. Local transposition (Figs. 20.5 and 20.6), rotation, and Limberg flap (Fig. 20.7) are the available options. Limberg flap is a very versatile flap and can be used at many places safely and effectively.

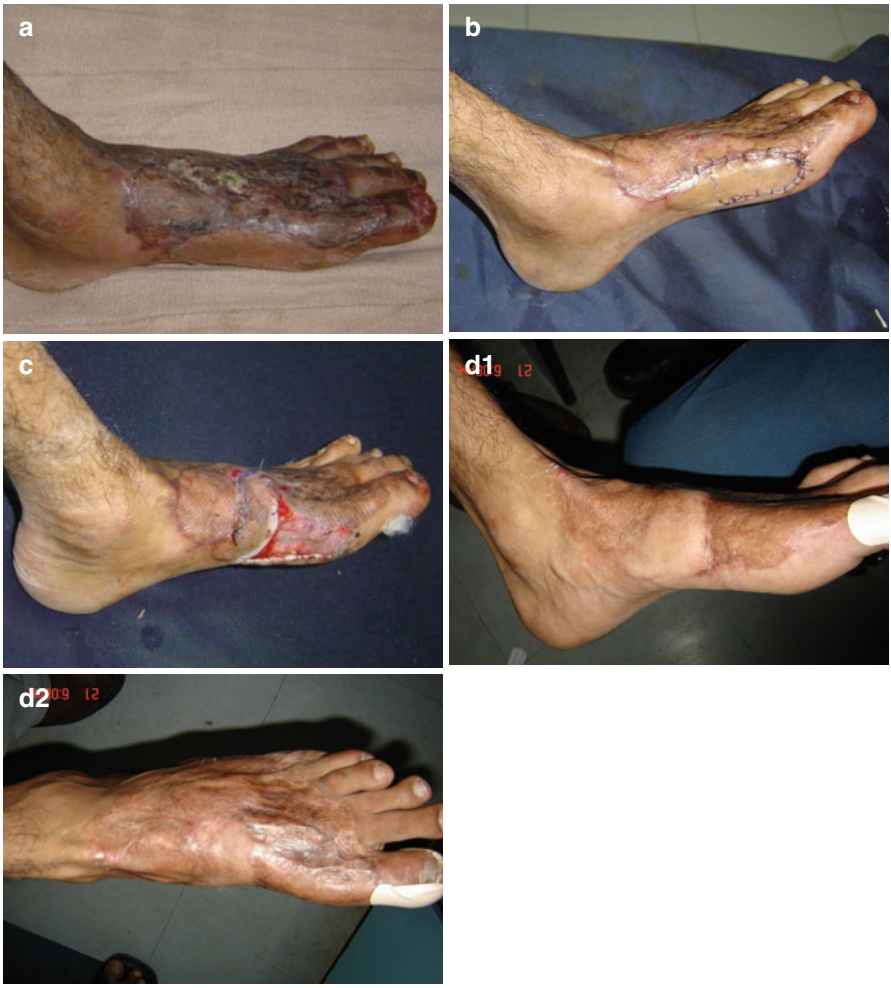

Fig. 20.6 (**a**–**d**) Transposition flap. A friction and pressure ulcer over the previously grafted dorsum of foot (**a**). A proximally based random pattern flap is delayed on the medial surface of foot (**b**). After a delay of 5 days the flap is elevated and used to cover the excised ulcer (**c**). The donor site is covered by split thickness skin graft. The delayed result shows excellent and stable coverage of ulcer area and nicely healed donor site (**d1** and **d2**)

3. *Regional flaps*: Sometimes the local or Limberg flap cannot close the larger defects due to their size or location resulting in need for regional flaps. Islanded medial planter flap (Fig. 20.8), reverse sural flap (Fig. 20.9), varieties of fasciocutaneous flaps from the same leg or cross-leg flaps (Fig. 20.10), and lateral or medial calcaneal flaps (Fig. 20.11) may provides a huge reconstructive option for lower extremity pressure ulcer reconstruction. Perforator-based V-Y advancement (Fig. 20.12) or rotational flap is another good option if the anatomy permits.

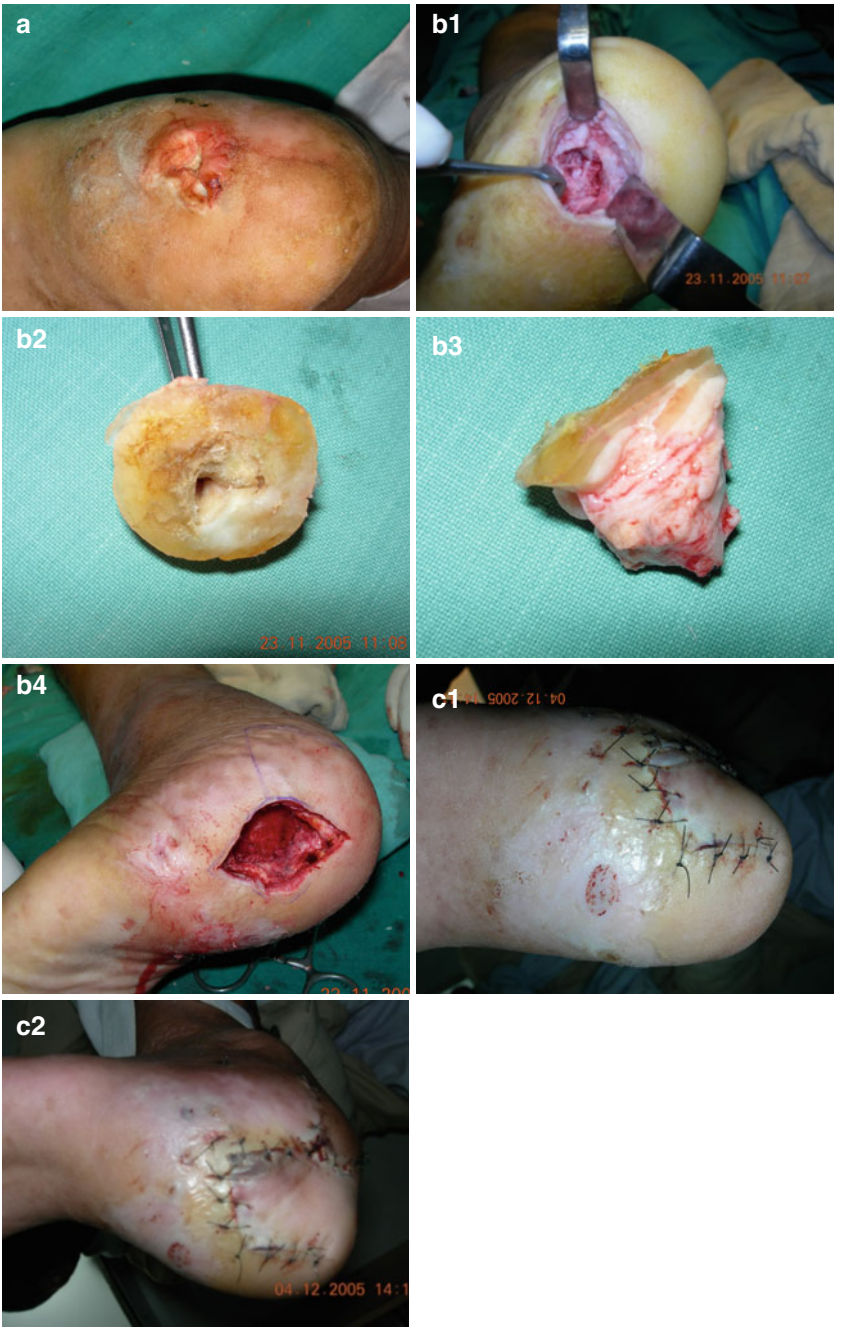

Fig. 20.7 (**a**–**c**) Limberg flap for heel ulcer – trophic ulcer of heel in a paraplegic patient with deep invasion and underlying destruction upto bone (**a**). The ulcer was sharply excised till healthy margin (**b1**). The excised specimen (**b2** and **b3**). A posteriorly based lateral Limberg flap was selected to close the resultant defect (**b4**). At three-week follow upprior to suture removal showing a viable and well settled flap (**c1** and **c2**).

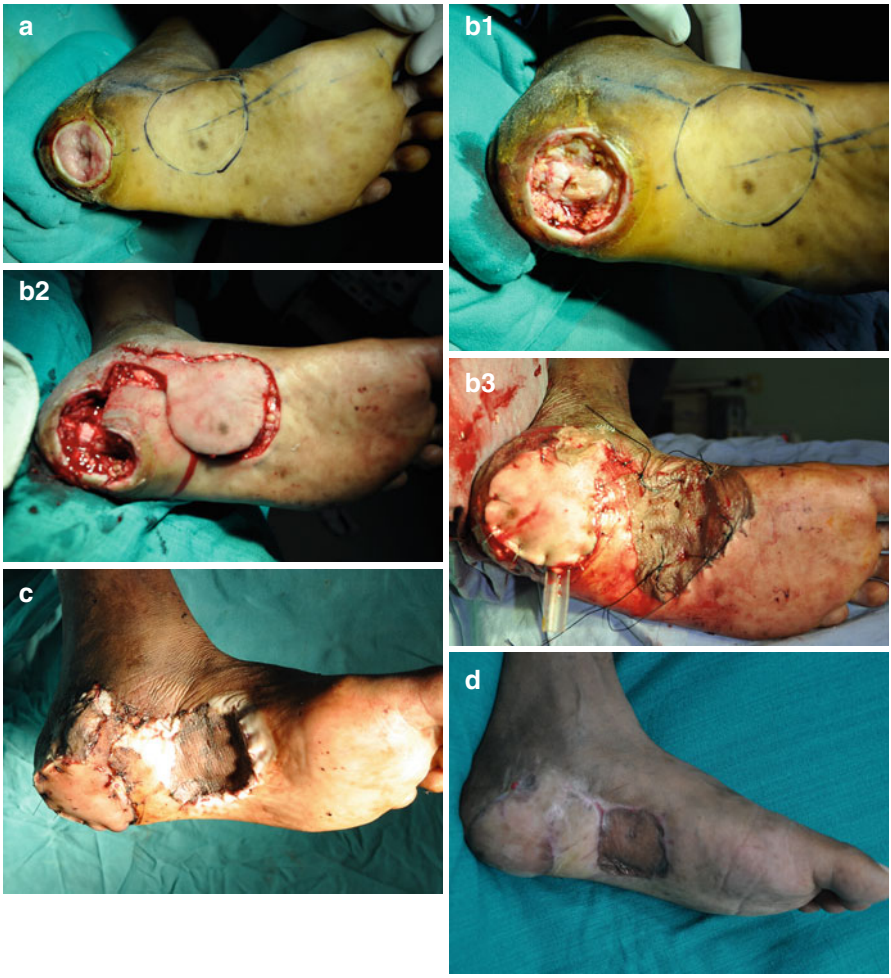

Fig. 20.8 (**a**–**d**) Medial planter flap for heel ulcer. A long-standing deep trophic ulcer of heel (**a**). The ulcer was sharply excised with healthy margin all around. Almost all the heel pad was removed by this debridement (**b1**). The islanded medial planter flap was planned to cover this defect (**b2**). The flap is elevated on branches of medial planter vessels, islanded and transposed to the defect and the resultant donor site was covered by split thickness skin graft (**b3**). The 1-week (**c**) and three months (**d**) post op pictures showing stable coverage. Patient allowed full weight bearing from 6th week along with silicone footpad protection

4. *Microvascular free flaps*: Microvascular free flaps are usually reserved for some selected cases where the local and regional flap options are either not available or have failed and the depth of the pressure ulcer demands adequate volume restoration for proper weight bearing. In fact the latter reason is so vital that many large pressure ulcers on weightbearing soles or on tip of amputation stumps are today being primarily treated with microvascular free tissue transfer (Fig. 20.13).

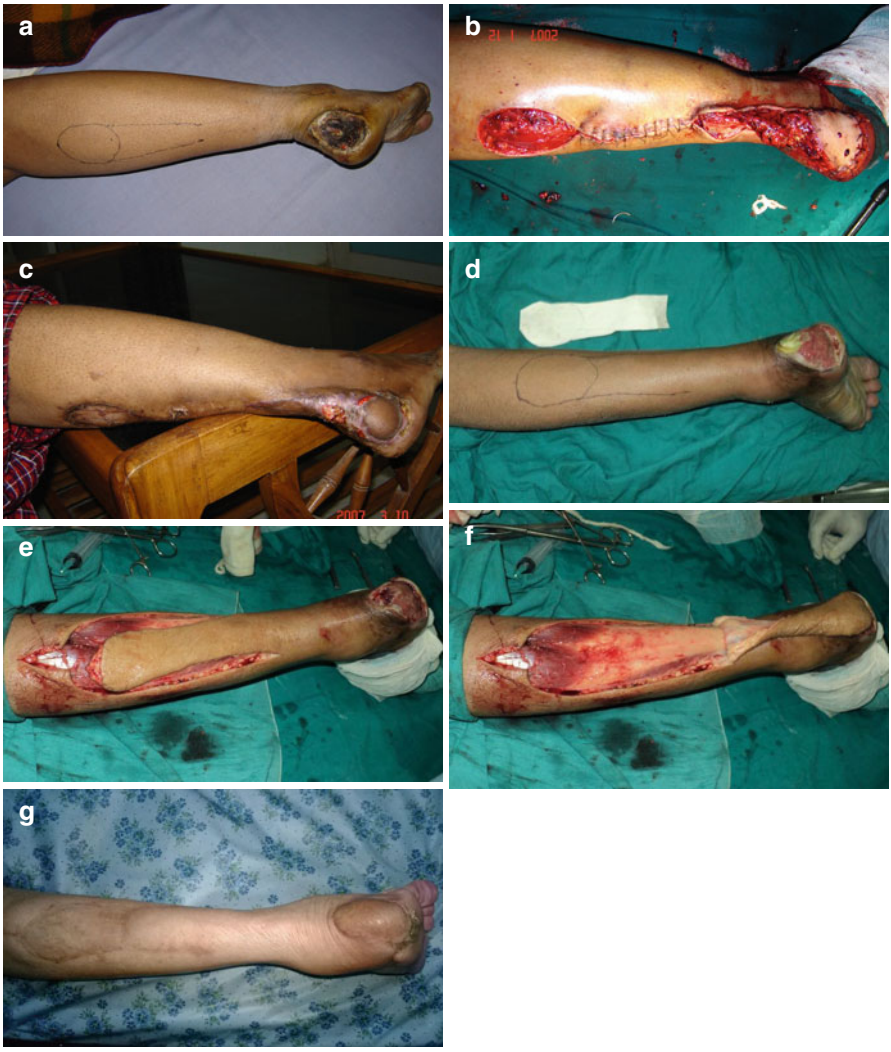

Fig. 20.9 (**a**–**g**) Reverse sural flap for posterior heel ulcer. A full thickness (grade-4) acute pressure ulcer of posterior heel (**a**). Under lying ligaments and tendons were involved and exposed. The ulcer was sharply excised and covered with the reverse sural flap (**b**). The donor site and distal half of the island pedicle was covered with split skin graft in this one stage repair. The 3-weeks follow up shows settled graft and flap (**c**). Yet another example of the same flap – flap planning (**d**), flap elevation (**e**), flap cover (**f**) and a 36-months post operative follow up (**g**)

20.4.6 Prevention: Mattresses and Cushions

Protection is the best way to prevent ulcers. This can be done by frequent change of posture, and with the help of special mattresses, cushions and by many protective devices for lower limbs are available that can relieve the external pressure on

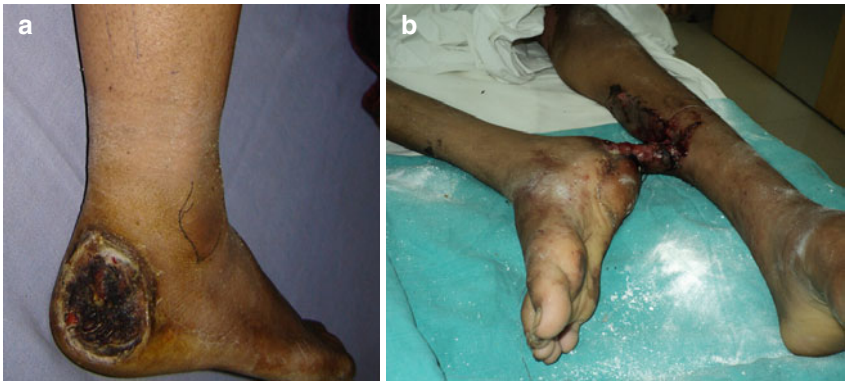

Fig. 20.10 (**a**, **b**) Cross leg flap for posterior heel ulcer

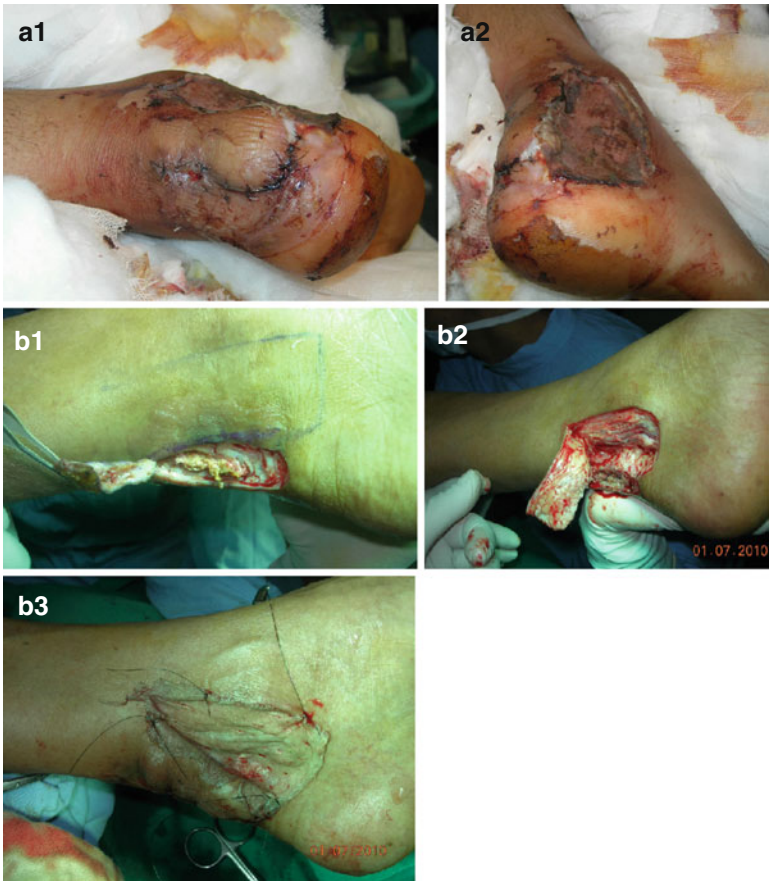

Fig. 20.11 Lateral calcaneal flap (**a1** and **a2**) and Medial calcaneal flap (**b1**–**b3**) to cover posterior heel pressure ulcer

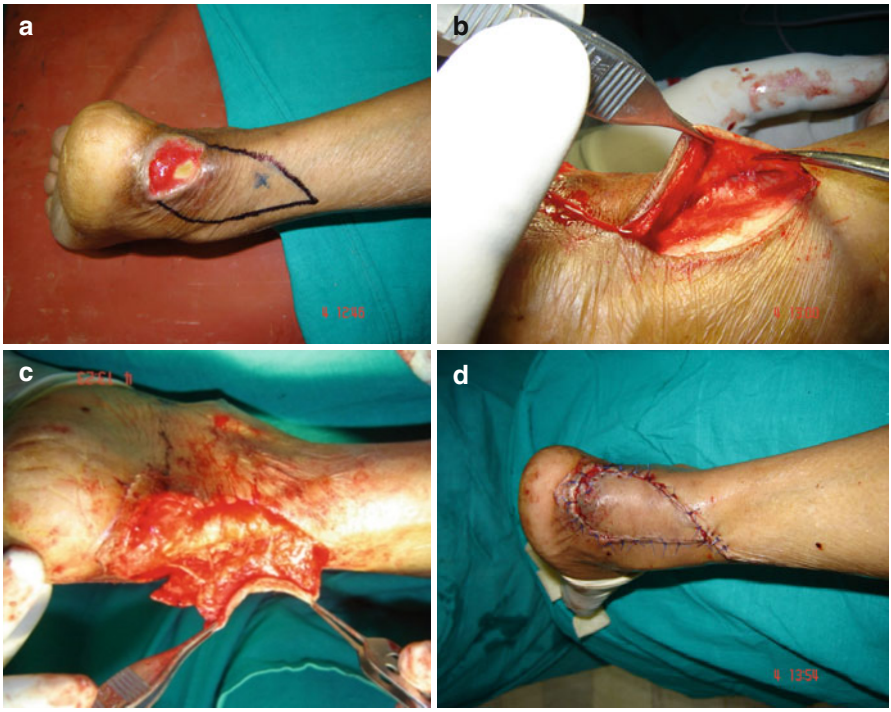

Fig. 20.12 (**a**–**d**) Perforator-based V-Y advancement flap for posterior heel ulcer. The tentative flap marked and perforator was identified by Doppler and marked with X (**a**). The flap was elevated from lateral side and perforator was identified and preserved (**b**). Now the whole flap was elevated and the flap mobility was checked (**c**). The V-Y closure was done (**d**)

vulnerable areas of body or lower limb. These specially designed protective devices can be very helpful in patients who thought to be at risk of developing pressure ulcers or who have preexisting grade one or two pressure ulcers. We are using water-filled tied surgical hand gloves (Fig. 20.14a) as pressure-relieving devices at hospital setups as well as advise the patients to use these at their home as a very easy to make, very low cost pressure-relieving device.

Many soft silicone elastomer-based commercially available devices may be effectively used to avoid the pressure from the affected or at-risk area of the limb. The commonly used are partial or full silicone sole, silicone pads and digital caps, toes separators, etc. (Fig. 20.14).

20.5 Summary

Pressure ulcers are breakdown of the skin and underlying tissue when an area of the skin is placed under constant pressure between the weightbearing skeleton and a hard surface for certain period of time causing tissue ischemia, cessation of

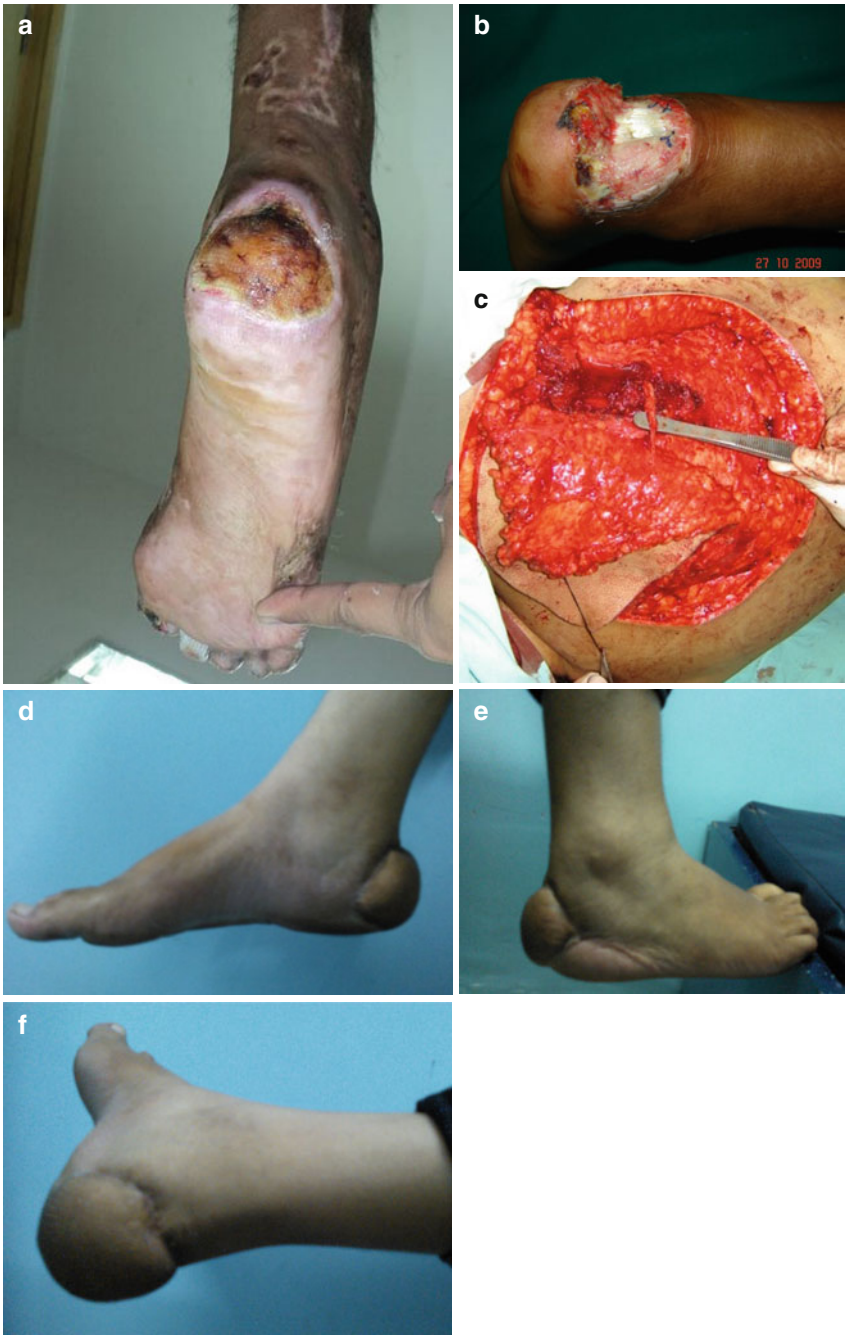

Fig. 20.13 (**a**–**f**) Microvascular free flap for posterior heel ulcer. Pressure Ulcer on the heel of Lt. foot (**a**), after debridement (**b**), Parascapular flap being harvested (**c**), 3 years post operative photographs (**d**–**f**)

nutrition and oxygen supply to the tissues, and eventually necrosis of the tissues caught in between two hard and unyielding surfaces. Pressure and loss of sensation are two major causes in the development of pressure ulcers, though their etiology is usually multifactorial. Pressure ulcers are progressive in nature and can be limb threatening or even life threatening if preventive actions are not taken timely. It is vital to trace the entire causative and contributing factors while making a diagnosis as reversal of these very factors is of vital importance to prevent recurrences. The treatment for each type and stage of pressure ulcer differs according to its severity, type, and location of these ulcers. Treatment should be planned according to treatment algorithm offered, but even more vital is to

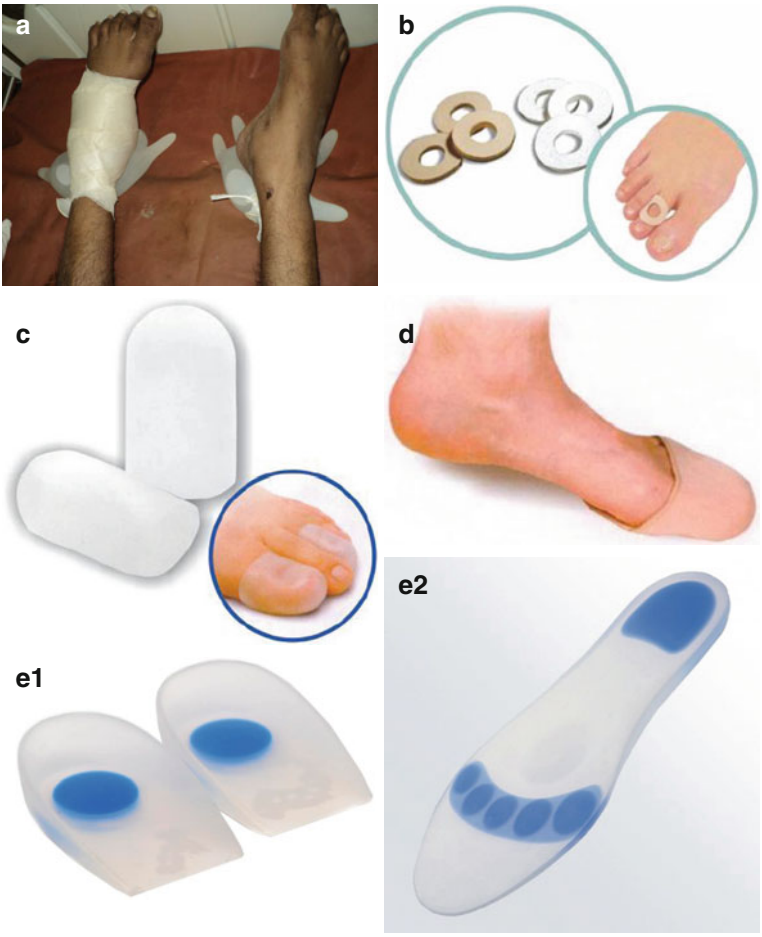

Fig. 20.14 (**a**–**g**) Variety of foot protective devices. Indigenous made (water filled and tied gloves) placed below the area needs pressure protection (**a**). Inexpensive, easy to fabricate, ideal for domiciliary care. Varieties of foot protective devices are commercially available, which are made up of soft silicone elastomer to protect respective areas to protect from pressure like – Adhesive pads (**b**), Digital caps (**c**), foot cover (**d**), silicone sole: partial or full (**e1** and **e2**), metatarsal pads (**f**), toe separator (**g1** and **g2**)

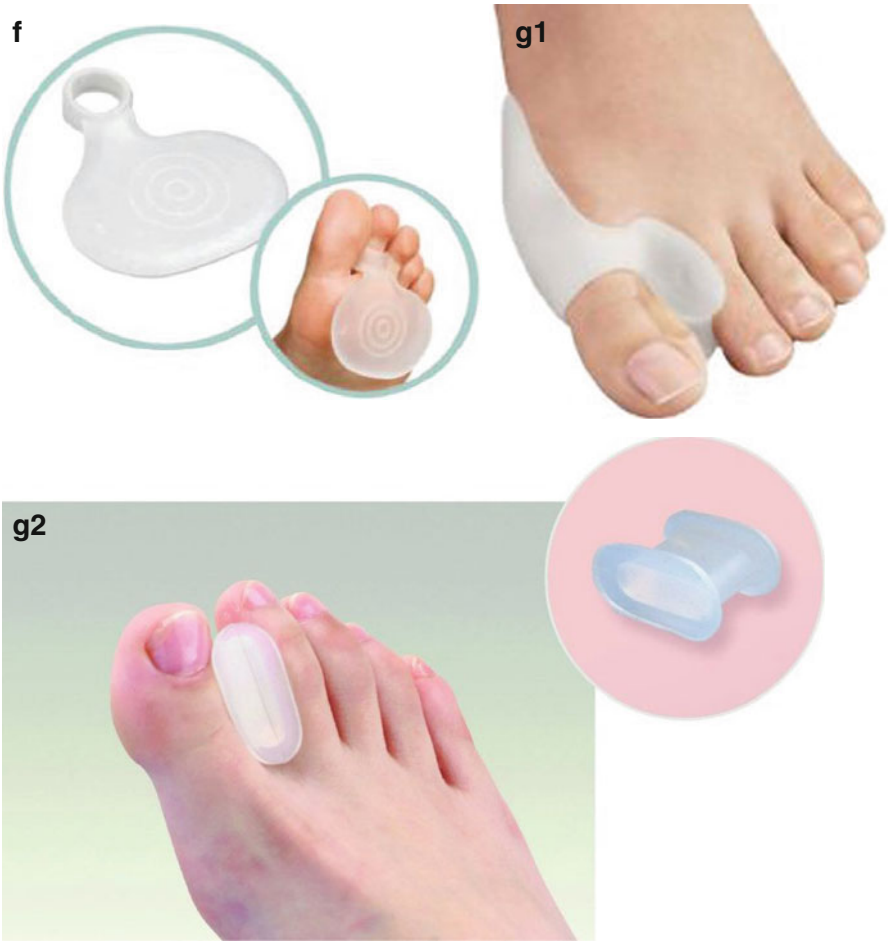

Fig. 20.14 (continued)

prevent these ulcers from occurring by addressing their causative factors and using special mattresses, cushions, and other ulcer-preventing protective devices. Ambulation and getting the pressure off the pressure points remain the most permanent prevention of these ulcers.

References

1. Krzysztof S. Gebhardt. Part 1. Causes of pressure ulcers. Nurs Times. 2002;98(11):4.
2. Gefen A. Reswick and Rogers pressure–time curve for pressure ulcer risk, Part-1. Nurs Stand. 2009;23(45):64, 66, 68 passim.
3. Gefen A. Reswick and Rogers Pressure–time curve for Pressure ulcer risk, Part-2. Nurs Stand. 2009;23(46):40–4.
4. Callam MJ, Ruckley CV, Dale JJ, et al. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J. 1985;290:1855–6.

5. Leblebici B, Turhan N, Adam M, Akman MN. Clinical and epidemiologic evaluation of pressure ulcers in patients at a university hospital in Turkey. J Wound Ostomy Continence Nurs. 2007;34(4):407–11.
6. Revis DR. Decubitus ulcers. In: Jacocks A, et al., editors. eMedicine. Medscape. 10 Sept 2004.
7. Cannon BC, Cannon JP. Management of pressure ulcers. Am J Health Syst Pharm. 2004;61:1895–905; quiz 1906–7.
8. Dodd KT, Gross DR. Three-dimensional tissue deformation in subcutaneous tissues overlying bony prominences may help to explain external load transfer to the interstitium. J Biomech. 1991;24(1):11–9.
9. Jay R. Pressure and shear: their effects on support surface choice. Ostomy Wound Manage. 1995;41:36–8, 40–2, 44–5.
10. Kuffler DP. Techniques for wound healing with a focus on pressure ulcers elimination. Open Circ Vasc J. 2010;3:72–84.
11. Goossens RH, Snijders CJ, Holscher TG, Heerens WC, Holman AE. Shear stress measured on beds and wheelchairs. Scand J Rehabil Med. 1997;29(3):131–6.
12. Allman RM. Pressure ulcer prevalence, incidence, risk factors, and impact. Clin Geriatr Med. 1997;13(3):421–36. Review.
13. Bliss MR. Hyperaemia. J Tissue Viability. 1998;8(4):4–13. Review.
14. Langemo D, Anderson J, Hanson D, Hunter S, Thompson P, Posthauer ME. Nutritional considerations in wound care. Adv Skin Wound Care. 2006;19:297–8, 300, 303.
15. Scivoletto G, Fuoco U, Morganti B, Cosentino E, Molinari M. Pressure sores and blood and serum dysmetabolism in spinal cord injury patients. Spinal Cord. 2004;42:473–6.
16. Keast DH, Fraser C. Treatment of chronic skin ulcers in individuals with anemia of chronic disease using recombinant human erythropoietin (EPO): a review of four cases. Ostomy Wound Manage. 2004;50:64–70.
17. Narsete TA, Orgel MG, Smith D. Pressure sores. Am Fam Physician. 1983;28:135–9.
18. Ferrell BA, Josephson K, Norvid P, Alcorn H. Pressure ulcers among patients admitted to home care. J Am Geriatr Soc. 2000;48:1042–7.
19. Berlowitz DR, Brandeis GH, Anderson J, Brand HK. Predictors of pressure ulcer healing among long-term care residents. J Am Geriatr Soc. 1997;45:30–4.
20. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. Preventive foot care in people with diabetes. Diabetes Care. 1998;21:2161–77.
21. Malgrange D, Richard JL, Leymarie F. Screening diabetic patients at risk for foot ulceration. A multi-centre hospital-based study in France. Diabetes Metab. 2003;13(3):261–8. doi:10.1016/S1262-3636(07)70035-6.
22. Aliasgharpour M, Nayeri ND. The care process of diabetic foot ulcer patients: a qualitative study in Iran. J Diabetes Metab Disord. 2012;11(1):27.
23. Yao ST, Hobbs JT, Irvine WT. Ankle systolic pressure measurements in arterial disease affecting the lower extremities. Br J Surg. 1969;56(9):676–9.
24. Grayson ML, Gibbons GW, Balogh K, et al. Probing to bone in infected pedal ulcers. JAMA. 1995;27:721–3.
25. Lowthian P. The classification and grading of pressure ulcers. 1987. J Tissue Viability. 2005;15:15–8.
26. Nixon J, Cranny G, Bond S. Pathology, diagnosis, and classification of pressure ulcers: comparing clinical and imaging techniques. Wound Repair Regen. 2005;13:365–72.
27. Bethell E. Controversies in classifying and assessing grade 1 pressure ulcers. Nurs Times. 2003;99:73–5.
28. Mumcuoglu KY, Lipo M, Ioffe-Uspensky I, Miller J, Galun R. Maggot therapy for gangrene and osteomyelitis. Harefuah. 1997;132:323–5, 382.
29. Sherman RA. Maggot versus conservative debridement therapy for the treatment of pressure ulcers. Wound Repair Regen. 2002;10:208–14.
30. Moore ZE, Cowman S. Wound cleansing for pressure ulcers. Cochrane Database Sys Rev. 2005;3:CD004983.
31. Molan PC. The evidence supporting the use of honey as a wound dressing. Int J Low Extrem Wounds. 2006;5:40–54.

32. Loree S, Dompmartin A, Penven K, Harel D, Leroy D. Is Vacuum Assisted Closure a valid technique for debriding chronic leg ulcers? J Wound Care. 2004;13:249–52.
33. Payne WG, Ochs DE, Meltzer DD, Hill DP, Mannari RJ, Robson LE, Robson MC. Long-term outcome study of growth factor-treated pressure ulcers. Am J Surg. 2001;181:81–6.
34. Marston WA. Dermagraft, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcer. Expert Rev Med Devices. 2004;1:21–31.
35. Sarasúa JG, López SP, MÁ V, Basterrechea MP, Rodríguez AF, Gutiérrez AF, Gala JG, Menéndez YM, Augusto DE, Arias AP, Hernández JO. Treatment of pressure ulcers with autologous bone marrow nuclear cells in patients with spinal cord injury. J Spinal Cord Med. 2011;34(3):301–7.
36. Kamata Y, Takahashi Y, Iwamoto M, Matsui K, Murakami Y, Muroi K, et al. Local implantation of autologous mononuclear cells from bone marrow and peripheral blood for treatment of ischaemic digits in patients with connective tissue diseases. Rheumatology (Oxford). 2007;46(5):882–4. [PubMed].
37. Robson MC, Hill DP, Smith PD, Wang X, Meyer-Siegler K, Ko F, VandeBerg JS, Payne WG, Ochs D, Robson LE. Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. Ann Surg. 2000;231(4):600–11.
38. Fischer BH. Topical hyperbaric oxygen treatment for pressure sores and skin ulcers. Lancet. 1969;294(7617):405–9.
39. Chen L, Tredget EE, Wu PY, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One. 2008;3(4), e1886.
40. Schönfeld M, Moll I, Maier K, Jung EG. Keratinocytes from cell culture for therapy of skin defects. Review and personal results. Hautarzt. 1993;44(5):281–9.
41. Kuroyanagi Y, Yamada N, Yamashita R, Uchinuma E. Tissue-engineered product: allogeneic cultured dermal substitute composed of spongy collagen with fibroblasts. Artif Organs. 2001;25(3):180–6.
42. Ichioka S, Ohura N, Sekiya N, Shibata M, Nakatsuka T. Regenerative surgery for sacral pressure ulcers using collagen matrix substitute dermis (artificial dermis). Ann Plast Surg. 2003;51(4):383–9.
43. Mizuno H, Miyamoto M, Shimamoto M, Koike S, Hyakusoku H, Kuroyanagi Y. Therapeutic angiogenesis by autologous bone marrow cell implantation together with allogeneic cultured dermal substitute for intractable ulcers in critical limb ischaemia. J Plast Reconstr Aesthet Surg. 2010;63(11):1875–82.
44. Tang YL, Zhao Q, Zhang YC, Cheng L, Liu M, Shi J, et al. Autologous mesenchymal stem cell transplantation induce VEGF and neovascularization in ischemic myocardium. Regul Pept. 2004;117(1):3–10.
45. Ono I, Yamashita T, Hida T, Jin HY, Ito Y, Hamada H, et al. Local administration of hepatocyte growth factor gene enhances the regeneration of dermis in acute incisional wounds. J Surg Res. 2004;120(1):47–55.
46. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem. 2006;98(5):1076–84.
47. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13:4279–95.
48. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived versus bone marrow derived mesenchymal stem and stromal cells. Stem Cells Dev. 2012;21:2724–52.
49. Jiang L, Dai Y, Cui F, Pan Y, Zhang H, Xiao J, Xiaobing FU. Expression of cytokines, growth factors and apoptosis-related signal molecules in chronic pressure ulcer wounds healing. Spinal Cord. 2014;52(2):145–51.

Atypical Leg Ulceration

21

Ajay K. Khanna and Divya Khanna

21.1 Introduction

Skin ulceration of the lower extremity poses a difficult clinical problem. Chronic ulceration of the lower legs is a relatively common condition among adults, one that causes pain and social distress and results in considerable healthcare and personal costs. Since numerous factors lead to lower leg ulceration, it is essential that health professionals adopt an interdisciplinary approach to the systematic assessment of the individual in order to ascertain the pathogenesis, a definitive diagnosis, and optimal treatment required. A correct diagnosis is essential to avoid inappropriate treatment that may delay wound healing, cause deterioration of the wound, or harm the patient [1]. Though a majority of the ulcers are venous, arterial, or diabetic ulceration, there are many unusual causes of the ulcers of the lower extremity. It has been reported that ulcers related to venous insufficiency constitute 70 %, arterial disease 10 %, and ulcers of mixed etiology 15 % of leg ulcer presentations. The remaining 5 % of leg ulcers result from less common pathophysiological causes, and this latter group comprise considerable challenges in diagnosis, assessment, and management.

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21.2 Unusual Causes of Leg Ulceration

21.2.1 Microcirculatory Disorders

Raynaud's phenomenon, scleroderma, hypertension: ulcus hypertensivum (Martorell ulcer), Increased blood viscosity (increased fibrinogen level, paraneoplastic, paraproteinemia, leukemia), Blood transfusion reactions.

21.2.2 Physical or Chemical Injury

Pressure (decubitus), pressure by shoes, plaster of Paris, orthopedic appliances, compression bandages, trauma, burn wounds, freezing, electricity, Roentgen damage, intra-articular injection of yttrium-90, chemical (corrosive agents), sclerotherapy, artificial (automutilation).

21.2.3 Infectious Diseases

Erysipelas (bullosa), ecthyma, fasciitis necroticans (*Streptococcus hemolyticus*), ulcerating pyoderma (*S. aureus*), gas gangrene (*Clostridium*), ecthyma gangrenosum (*Pseudomonas*), septic embolism (*Meningococcus* and others), bacterial endocarditis, anthrax (*Bacillus anthracis*), diphtheria (*Corynebacterium diphteriae*), osteomyelitis (several microorganisms), complications by secondary wound infections, toe web infection, herpes, cytomegalovirus, lues maligna (lues III, gummata), leprosy, frambesia (yaws), ulcerating cutaneous tuberculosis, lupus vulgaris, atypical mycobacteria, Buruli ulcer (*Mycobacterium ulcerans*), papulonecrotic tuberculid tularemia (*Francisella tularensis*), leishmaniasis, tropical ulcer (*Bacteroides*, *Borrelia vincenti,* and other bacteria) Madura foot, maduramycosis (eumycetoma⁄mycetoma), chromoblastomycosis, coccidioidomycosis, sporotrichosis, granuloma trichophyticum, amoebiasis, histoplasmosis, bacillary angiomatosis.

21.2.4 Neuropathic Diseases

Diabetes, leprosy, alcohol neuropathy, tabes dorsalis, syringomyelia, spina bifida, paraplegia, paresis, multiple sclerosis, poliomyelitis.

21.2.5 Vasculitis

Small vessel: small-vessel leukocytoclastic vasculitis, microscopic polyangiitis, Wegener granulomatosis, allergic granulomatosis (Churg–Strauss), Henoch–Schönlein purpura, essential cryoglobulinemic vasculitis, erythema induratum of Bazin, livedo reticularis, livedo vasculitis, and Sneddon syndrome.

Medium sized: polyarteritis nodosa, Kawasaki disease.

Large vessel: giant cell arteritis (polymyalgia rheumatica, Takayasu arteritis).

21.2.6 Hematological Disorders

Sickle cell anemia, other forms of anemia, thalassemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, essential thrombocythemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythemia, leukemia, monoclonal dysproteinemia (Waldenström disease, myeloma), polyclonal dysproteinemia (cryofibrinogenemia, purpura, hyperglobulinemia, cold agglutinins).

21.2.7 Clotting Disorders

Factor V Leiden, lupus anticoagulant, anticardiolipin (antiphospholipid syndrome), disturbed fibrinolysis, factor XIII deficiency (may be associated with colitis ulcerosa), antithrombin III deficiency, protein C or S deficiency, Marcoumar necrosis, large hematoma, purpura fulminans, diffuse intravasal coagulation.

21.2.8 Metabolic Diseases

Diabetes mellitus, necrobiosis lipoidica, porphyria cutanea tarda, gout, calciphylaxis, calcinosis cutis, homocystinuria, prolidase deficiency, hyperoxaluria.

21.2.9 Ulcerating Tumors

Basal cell carcinoma, squamous cell carcinoma, malignant melanoma, metastasis, pseudoepitheliomatous hyperplasia, epithelioma (Marjolin ulcer), lymphoma, leukemia, cutaneous T-cell and B-cell lymphoma, Hodgkin disease, sarcoma, lymphosarcoma, rhabdomyosarcoma, hemangiosarcoma, lymphangiosarcoma, Kaposi and pseudo-Kaposi sarcoma.

21.2.10 Ulcerating Skin Diseases

Pyoderma gangrenosum, pemphigoid and other bullous diseases, panniculitis, periarteritis nodosa, erythema induratum (Bazin), malignant atrophic papulosis (Degos), erythema exudativum multiforme, sarcoidosis, erythema elevatum diutinum, Behçet disease, cutaneous discoid and systemic lupus erythematosus, scleroderma, lichen planus, keratosis actinica, contact dermatitis, fat necrosis/pancreatic fat necrosis, trench foot, insect bites, lymphoedema, lipoedema, myxoedema, erythermalgia/erythromelalgia, perniosis (chilblains), hemangioma, Stewart–Bluefarb syndrome.

21.2.11 Drug Reactions

Steroid ulcus (intralesional injection), vaccination ulcer (BCG), halogens, ergotamine, methotrexate, hydroxyureum, paravasal injection of cytostatic and other drugs, granulocyte-colony-stimulating factor.

21.2.12 Miscellaneous

Corpus alienum, orthopedic fixation materials. Klinefelter syndrome, rheumatoid arthritis, Felty syndrome, ulcus phagedenicum, acro-osteopathia ulceromutilans (Bureau–Barrière), complement C3 deficiency. Langerhans cell histiocytosis, TAP 1 mutation.

21.3 Microcirculatory or Vascular Disorders

Microcirculatory and vascular disorders that can result in atypical leg ulceration include: Raynaud's phenomenon, Martorell ulcers, and cutaneous vasculitis.

21.3.1 Raynaud's Phenomenon

Raynaud's phenomenon is an episodic circulatory disorder where the peripheral microvasculature is overly sensitive to changes in external temperature. It typically causes color changes (white and/or blue and red) of the extremities on exposure to the cold (even mild temperature changes if they occur suddenly) or stress. These changes cause pain, numbness, or tingling sensations. The condition is commonly found in females and affects between 3 and 5 % of the general population. While the pathogenesis of Raynaud's phenomenon is unclear, recent research concludes that a combination of abnormalities of vascular, intravascular, and neural function may be contributory factors [2–4]. The patient may present with minor ulcerations of the tip of digits especially in the upper limb but may occur in the lower limb also. It may be primary without any cause or may be secondary to some cause. There is no current cure for Raynaud's phenomenon. Care is aimed at minimizing the incidence, extent, and severity of attacks. Specific medications that have been identified as triggers for Raynaud's phenomenon include: β-blockers, adrenergic receptor agonists, ergotamine drugs, oestrogens, immunosuppressants, interferons, cocaine, amphetamines, nicotine, etc.

21.3.2 Martorell Ulcer

Hypertension is a known risk factor for atherosclerotic occlusion. In addition, antihypertensive drugs (beta-blockers) may interfere with wound healing due to peripheral vasoconstriction. A rare condition exists called Martorell ulcer, seen in patients with prolonged, severe, or suboptimally controlled hypertension. The ulceration is secondary to tissue ischemia caused by increased vascular resistance. The ulcers are usually located at the lower limb and above the ankle region, contain black necrosis, and are extremely painful. By definition, the distal arterial pulsations are normal, and the diagnosis is made by histological examination, which shows concentric

intima thickening and marked hypertrophy of the media of small-sized and medium-sized arteries, and by exclusion of other conditions. Martorell ulcers are rare conditions that are occasionally seen in patients with prolonged, severe, or suboptimally controlled hypertension [5]. Ulcers tend to be necrotic and extremely painful, with the degree of pain disproportional to the size of the wound. Martorell ulcers are more common in females between 55 and 65 years. The diagnosis is generally made by eliminating other etiologies and histological examination, which demonstrate concentric intima thickening and hypertrophy of the media of small- and medium-sized arteries. Treatment consists of reducing hypertension, avoiding beta-blockers, adequate control of pain, and local wound care [6].

21.3.3 Cutaneous Vasculitis

Cutaneous vasculitis represents a heterogeneous group of disease types characterized by inflammatory vessel damage presenting with various clinical manifestations. Vasculitis of the skin usually results from the inflammation and ischemia of small- to medium-sized blood vessels. Although vasculitis is activated by many factors, current research suggests that the deposition of circulating immune complex is pivotal to the pathogenesis of most types of cutaneous vasculitis [7]. Several subdivisions can be made, based on vessel size (large vessel, medium sized, small vessel), infiltrate type (polymorphonuclear, mononuclear, granulomatous), or clinical presentation. Cutaneous vasculitis may present as purpura, erythema, urticaria, noduli, bullae, or skin infarction leading to ulceration. Cutaneous ulceration is usually caused by medium-sized to small-vessel leukocytoclastic vasculitis. Persistent or progressive ulceration due to histologically confirmed vasculitis is an indication for immunosuppressive therapy. Ulcerating vasculitis may be caused by antineutrophil cytoplasmic antibodies (ANCA), autoantibodies against antigens in neutrophils, such as myeloperoxidase and proteinase 3 (PR3). Using indirect immunofluorescence techniques, ANCA can be detected in a perinuclear pattern (often antimyeloperoxidase) or a cytoplasmic pattern (often anti-PR3). They were first identified in Wegener granulomatosis, later also in other types of small-vessel vasculitis, now classified as ANCA-associated vasculitides (Wegener disease, microscopic polyarteritis, idiopathic glomerulonephritis, and Churg–Strauss syndrome) [8].

21.4 Hematological Disorders

Various hematological disorders may be associated with ulcerations in lower leg as essential thrombocythemia, primary polycythemia, thalassemia, hemolytic anemia, clotting disorders, leukemia, hereditary spherocytosis, primary thrombocythemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythemia and polyclonal dysproteinemia, antiphospholipid syndrome, protein C and protein S deficiencies, factor V Leiden, lupus anticoagulant, factor XIII deficiency, and antithrombin III deficiency [9].

21.4.1 Sickle Cell Anemia

Sickle cell anemia, a genetic disorder, commonly results in the formation of small, painful leg ulcers that arise when sickle-shaped inflexible red blood cells obstruct capillaries and restrict blood flow to an organ or the skin. In sickle cell anemia, an increased number of activated endothelial cells has been found in the circulation, and it is hypothesized that an interaction between sickle cells and endothelial cells causes increased expression of endothelial cell adhesion molecules, which promotes thrombotic vasoocclusion. African and Caribbean populations have a higher disposition for sickle cell disease. Sickle cell anemia has a leg ulcer incidence rate between 25.7 and 75 % [10].

21.4.2 Antiphospholipid Syndrome

This rare syndrome is characterized by the presence of circulating autoantibodies against phospholipid compounds. It is associated with an increased risk for venous or arterial thrombosis, thrombocytopenia, and habitual abortus. The cutaneous symptoms (ulceration, livedo reticularis, acrocyanosis, Raynaud's phenomenon, capillaritis and thrombophlebitis) can all be explained by vascular thrombosis. The two most frequently found antibodies are lupus anticoagulant and anticardiolipin. In up to 40 % of patients with the antiphospholipid antibody syndrome (APAS), dermatologic abnormalities can be the primary or presenting manifestation. Painful ischemic leg ulcerations of varying sizes can occur. A devastating, widespread, full-thickness, cutaneous necrosis involving not only the legs but the arms, flanks, and breasts has also been described. Coexistent cutaneous findings may include purpura, ecchymosis, subcutaneous nodules, splinter hemorrhages, fixed digital cyanosis (with or without ulcerations and/or gangrene), Raynaud's phenomenon, acrocyanosis, and superficial thrombophlebitis. Therapy for antiphospholipid antibody syndrome-associated ischemic ulcerations is not well defined, although when widespread cutaneous necrosis and/or digital gangrene are present, full-dose anticoagulation appears prudent [11].

21.4.3 Symmetrical Peripheral Gangrene

Symmetrical peripheral gangrene (SPG) (Figs. 21.1 and 21.2) is a rare but devastating syndrome involving distal portions of two or more extremities simultaneously. Disseminated intravascular thrombosis and hemorrhagic infarction of skin with uninvolved proximal arteries are hallmark of this condition. Gangrene of the tip of the nose, ear lobules, lips, or genitalia may be accompanied in severe cases. Low-flow circulation and septicemia play a pivotal role in the development of symmetrical peripheral gangrene. Septicemia is rarely associated with peripheral

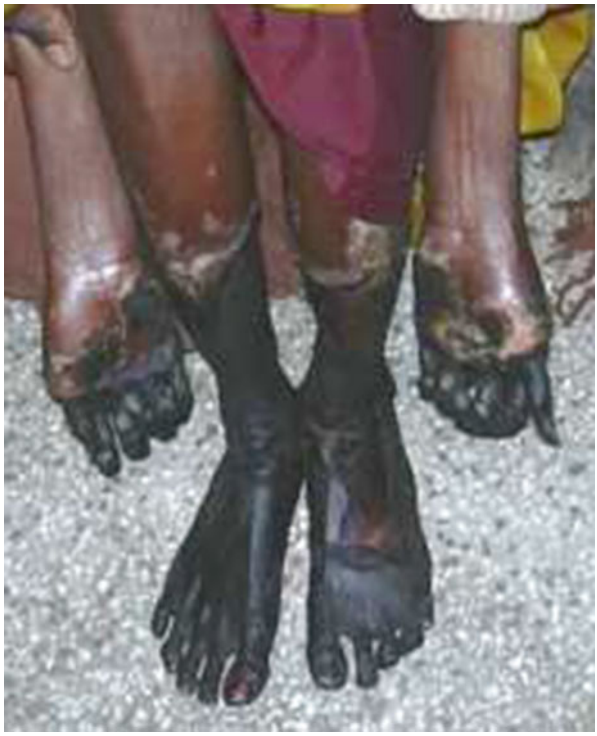

Fig. 21.1 Peripheral symmetrical gangrene involving all four limbs

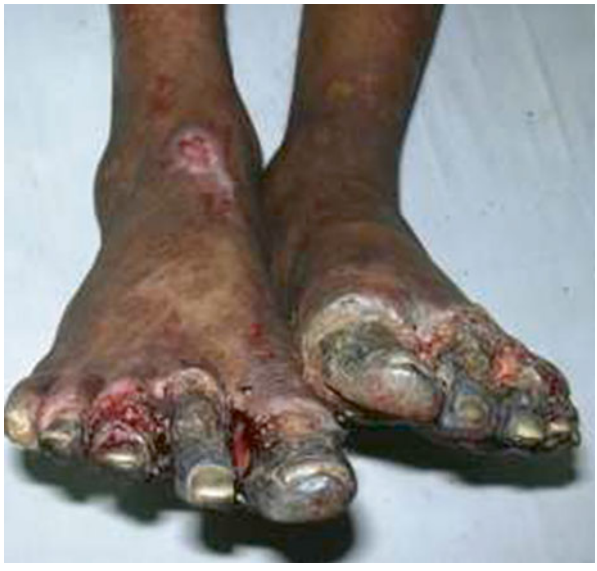

Fig. 21.2 Peripheral symmetrical gangrene involving both lower limbs

vascular disease, but a predominant role of infective etiology is present in symmetrical peripheral gangrene. Common organisms involved are pneumococcus, staphylococcus, and streptococcus, but gram-negative organisms have also been implicated. SPG can also occur as complication of measles, chickenpox, malignancy, ergotism, protein C or S, or antithrombin III deficiency. Aggravating factors are diabetes mellitus, increased sympathetic tone, asplenia, immunosuppression, cold injury to extremities, renal failure, and use of vasopressors. Cause of vascular occlusion is not exactly defined, but disseminated intravascular coagulation is present in up to 85 % patients with SPG. Low-flow state and septicemic conditions are almost invariably present. Fever followed by marked coldness, pallor, cyanosis, pain, and restricted mobility of extremity should always raise suspicion of SPG. If aggressive and prompt intervention is delayed, frank gangrene may develop. Ischemia starts and manifests from distal extremity, and proximal part is unaffected invariably. Vascular compromise in SPG results in erythematous cold extremities and dusky discoloration of the skin. Acral cynosis and hemorrhagic bulla are followed by development of dry gangrene within 24 h. Despite therapeutic interventions, different studies report mortality up to 40 % and amputation rate of 30–50 % [12].

21.5 Metabolic Disorders

21.5.1 Necrobiosis Lipoidica

Necrobiosis lipoidica is a rare chronic condition that primarily affects individuals with diabetes and results in collagen degeneration, reduced collagen synthesis, atrophy, and lipid deposits. Necrobiosis lipoidica occurs in about 0.7 % of diabetic patients with ulcers developing in 13–35 % of cases. Of ulcerated necrobiosis lipoidica, 70 % of the patients had diabetes mellitus of which 30 % had type I diabetes and 40 % had type II diabetes; 60 % of the patients suffered from arterial hypertension, obesity, and hypercholesterolemia; and 40 % of the patients suffered from psychiatric disorders such as depression and borderline disorder. Ulcerating necrobiosis lipoidica can be seen as part of a generalized inflammatory reaction similar to the inflammatory reaction already known in the pathophysiology of rheumatoid diseases or psoriasis. In patients with clinical atypical painful ulcerations, necrobiosis lipoidica should be considered as a possible differential diagnosis. Therapists should be aware of associated aspects in patients with ulcerated necrobiosis lipoidica who besides diabetes often suffer from other aspects of a metabolic syndrome with increased cardiovascular risk factors. Therefore, these related comorbidities should also be diagnosed and treated [13]. Lesions generally develop on the pretibial area as small red-brown erythematous markings that gradually enlarge. Lesions may present as single or multiple, clearly demarcated, waxy, yellow-brown plaques with depressed centers, which are associated with granulomatous inflammation and collagen degeneration [14].

21.5.2 Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) refers to a group of disorders that can be familial or acquired and which result in a deficiency in the function of the heme synthetic enzyme uroporphyrinogen decarboxylase (UROD) [15]. PCT is essentially an acquired disease, but some individuals have a genetic (autosomal dominant) deficiency of UROD that contributes to the development of PCT. These individuals are referred to as having "familial PCT." Most individuals with the inherited enzyme deficiency remain latent and never have symptoms. The symptoms of PCT are confined mostly to the skin. Blisters develop on sun-exposed areas of the skin, such as the hands, legs, and face. The skin in these areas may blister or peel after minor trauma. Increased hair growth, as well as darkening and thickening of the skin, may also occur. Liver function abnormalities are common but are usually mild, although they sometimes progress to cirrhosis and even liver cancer. PCT is often associated with hepatitis C infection, which can also cause these liver complications. However, liver tests are generally abnormal even in PCT patients without hepatitis C infection.

21.5.3 Gout

Gout is an inflammatory disorder of monosodium urate metabolism, which is characterized by the deposition of urate crystals in the joints and soft tissues. Gout usually presents as an acute attack of synovitis which clears completely in a week or so. As far as the tophaceous deposits are concerned, these are commonly present on the ears, in the tendons, and in the joints specially the knee and elbow. Regarding the local skin affections, gouty tophi mainly cause signs of local skin irritation in the form of pain, swelling, and skin erythema [16].

21.5.4 Calciphylaxis

Calciphylaxis is a rare and potentially grave vasculopathy of the skin and subcutaneous tissue that has a female-to-male ratio of 3:1. This condition occurs as a complication of chronic kidney disease, particularly in diabetics and in secondary hyperparathyroidism associated with abnormal calcium metabolism. Calciphylaxis occurs in 1 % of patients with chronic kidney disease and in 4 % of individuals on dialysis [17]. Calciphylaxis initially manifests as irregular livedo reticularis with subcutaneous nodules and plaques. Ultimately, markedly painful, large, necrotic ulcerations ensue. The lower extremities are most commonly involved, although the upper extremities, abdomen, and buttocks can also be affected. Unusual sites of calciphylaxis include the penis, breasts, and neck. The distal pulses may be palpable in the absence of severe peripheral artery disease. Elevated parathyroid hormone and hyperphosphatemia are the most common laboratory abnormalities. Therapy is

often ineffective yet controlling hypercalcemia, hyperphosphatemia, and hyperparathyroidism is recommended. Methods for controlling the calcium × phosphate product include eliminating vitamin D analogs, reducing calcium in the dialysis bath, decreasing dietary phosphate and calcium, and substituting sevelamer hydrochloride for calcium-based phosphate binders. Although parathyroidectomy is often recommended, its value remains controversial [18].

21.5.5 Calcinosis Cutis

Calcinosis cutis is a disorder whereby calcium and phosphorous salts are deposited in the dermis. Leg ulcers are generally asymptomatic but may be tender and present with numerous, dense, pale dermal papules, plaques, nodules, or subcutaneous nodules. The lesions may also be enclosed by a yellowish/whitish gritty substance that ulcerates. Lesions over joints can restrict mobility, while vascular calcification may cause diminished pulses and, in severe cases, cutaneous gangrene [19].

21.6 Neuropathic Disorders

21.6.1 Hansen's Disease (Leprosy)

Hansen's disease (leprosy) is caused by the *Mycobacterium leprae* organism that predominantly affects the skin and peripheral nerves. Approximately 30 % of people with Hansen's disease will develop nerve damage that results in peripheral nerve sensory loss, usually in the hands, feet, and eyes. Skin damage can present as thickened, cracked skin that becomes infected and ulcerates. Additional skin changes may include erythematous changes (papules and nodules) or hypopigmented plaques and alopecia [20]. Ulcers in patients with leprosy sequelae remain a major source of economic and social losses, even many years after they have been cured of M. leprae infection. Management of chronic ulcers in patients with leprosy includes different types of dressings, orthopedic and plastic surgeries, plaster casts, special footwear, splints, crutches, wheelchair use, and absolute rest. Despite this, clinical experience shows that patient compliance to the therapeutic procedures is a key consideration in treatment choice and that without patient collaboration the result of the treatment can be frustrating. Low patient adherence to rehabilitation and prevention of disabilities programs (e.g., usage of appropriate footwear) indicates that more research and educational measures are necessary to improve the adoption of such strategies. Ulcers in patients with leprosy can remain for several years after the initial infection is resolved and can result in large economic and social losses. Such losses were observed in this study, which was primarily composed of former patients that have lived with their ulcers for many years. The most important causal factor for neuropathic foot ulcers is the presence of a dynamic or static deformity leading to local areas of peak pressure on insensitive skin, which has been well illustrated by pressure studies. This repetitive overload on specific

areas of the sole could partially explain why plantar ulcers are deeper and smaller than leg and ankle ulcers. The free distribution of special footwear does not ensure its adequate utilization. Healthcare workers need to be constantly pushed to establish a patient continuum education process about self-care routines and to improve the techniques currently employed to encourage the use of preventive tools. Low adherence to such programs and self-care procedures is a concern of countries that still bear a significant leprosy burden [21]. The involvement of the peripheral nerves can lead to loss of sensation particularly affecting the hands and lower limbs. As in diabetes, the loss of sensation results in people not being aware of any cuts or burns that they may sustain. For this reason, people with leprosy are more prone to developing hand and lower limb injuries, which may develop into nonhealing ulcers. Leprosy always needs to be considered in the presentation of a nonhealing ulcer, especially in the indigenous population or those from countries where leprosy is noted by the World Health Organization to still occur at higher levels.

21.6.2 Pyoderma Gangrenosum (PG)

Pyoderma gangrenosum (PG) is a condition that causes tissue to become necrotic, causing deep ulcers that usually occur on the legs. When they occur, they can lead to chronic wounds. Ulcers usually initially look like small bug bites or papules, and they progress to larger ulcers. Though the wounds rarely lead to death, they can cause pain and scarring. There are two main types of pyoderma gangrenosum: the "typical" ulcerative form, which occurs in the legs, and "atypical" form that is more superficial and occurs in the hands and other parts of the body. Extracutaneous involvement of PG has been reported as cavitary lung lesions, pulmonary infiltrates, episcleritis, psoas abscess, splenic abscess, etc. The diagnosis of PG is by exclusion. Though the etiology is not well understood, the disease is thought to be due to immune system dysfunction and particularly improper functioning of neutrophils. At least half of all pyoderma gangrenosum patients also suffer from illnesses that affect their systemic function. The common conditions associated with pyoderma gangrenosum are: ulcerative colitis, Crohn's disease, rheumatoid arthritis, Behçet disease, seronegative arthritis, myelocytic leukemia, hairy cell leukemia, myelofibrosis, myeloid metaplasia, monoclonal gammopathy, etc. Systemic malignancy can occur in about 7 % of cases of PG and leukemia is the commonest neoplasm. First-line therapy for disseminated or localized instances of pyoderma gangrenosum is systemic treatment by corticosteroids and cyclosporine. Topical application of clobetasol, mupirocin, and gentamicin alternated with tacrolimus can be effective. Papules that begin as small "spouts" can be treated with Dakin's solution to prevent infection, and entire wounds that cluster also benefit from this disinfectant. Wet-to-dry applications of Dakin's solution can defeat spread of interior infection. Heavy drainage can be offset with Coban dressings. Grafting is not recommended due to tissue necrosis. If ineffective, alternative therapeutic procedures include systemic treatment with corticosteroids and mycophenolate mofetil, mycophenolate mofetil and cyclosporine, tacrolimus, thalidomide, infliximab, or plasmapheresis [22].

21.6.3 Kaposi's Sarcoma

Kaposi's sarcoma is an angio-proliferative, soft tissue disease that generally affects the skin. It may involve the lymphatic system, the lungs, and the gastrointestinal tract; bone, however, is rarely involved. Kaposi's sarcoma initially presents as pinkish, red, or brown-black, well-circumscribed, asymptomatic plaques on the skin. In individuals not infected with HIV, Kaposi's sarcoma is generally limited to the lower extremities. However, in the advanced stage of Kaposi's sarcoma, the lymphatic system is compromised, which causes edema with disseminated skin involvement [23].

21.7 Allergic Ulceration

Numerous local and systemic allergic responses are manifested on the skin. An allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms as a result of contact with or ingestion of an animal, vegetable, mineral, or chemical agent. Dermatitis is the term that encompasses local skin inflammation. The terms dermatitis and eczema are frequently used synonymously.

21.8 Factitious Ulceration

Factitious wounding refers to those wounds that are created by a deliberate act of force by an individual, aimed at causing damage to their own body.

21.9 Necrotizing Fasciitis

Necrotizing fasciitis (NF) (Figs. 21.3 and 21.4), now better called as necrotizing soft tissue infection (NSTI), also called as flesh-eating disease, flesh-eating bacteria, and flesh-eating bacteria syndrome, is a rare infection of the deeper layers of the skin and subcutaneous tissues, easily spreading across the fascial plane within the subcutaneous tissue. Many types of bacteria can cause necrotizing fasciitis (e.g., group A streptococcus (*Streptococcus pyogenes*), *Staphylococcus aureus*, *Clostridium perfringens*, *Bacteroides fragilis*, *Vibrio vulnificus*, *Aeromonas hydrophila*). The disease is classified as type I (polymicrobial, due to a number of different organisms) or type II (monomicrobial, due to a single infecting organism). The majority of cases of necrotizing fasciitis are polymicrobial, with 25–45 % of cases being type II. Such infections are more likely to occur in people with compromised immune systems secondary to chronic disease [24, 25].

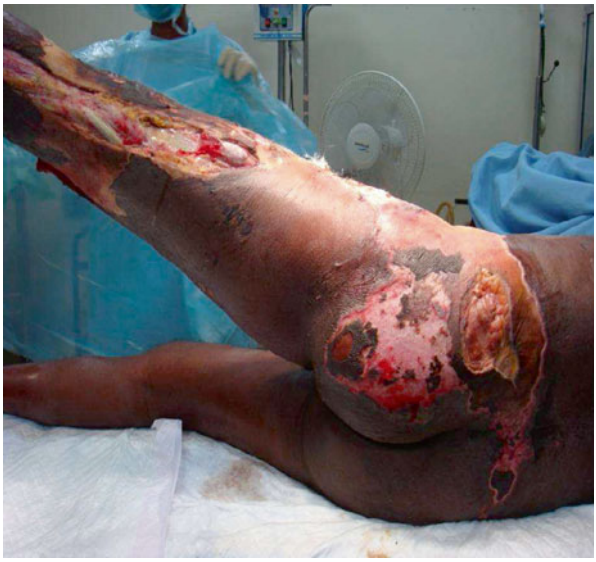

Fig. 21.3 Necrotizing fasciitis of leg and gluteal region

Fig. 21.4 Necrotizing fasciitis of thigh and gluteal region

21.10 Chemotherapy Extravasation Ulceration (Fig. 21.5)

Normally the chemotherapeutic drugs for malignancy are injected in the upper extremity, but in the absence of veins in the upper limb, the drug has been injected in the lower extremity veins. If there is extravasation of drugs like mitomycin, Adriamycin may lead to extravasation ulcers which are indolent and refuse to heal. If patient complains of pain at the site of injection, then drug administration should

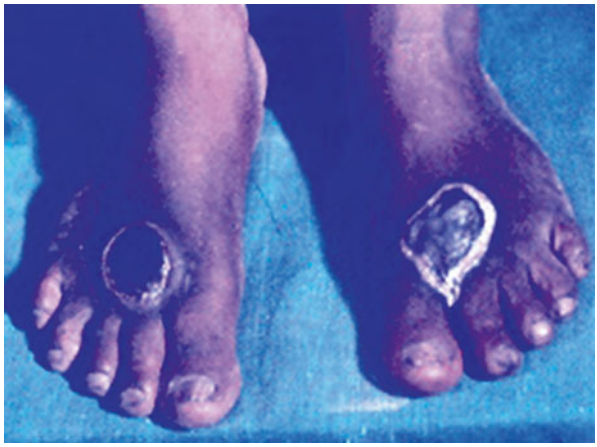

Fig. 21.5 Chemotherapy extravasation ulcer

be stopped immediately and the rest of the drug has to be given in the other limb to avoid cumulative action. The area may be injected with steroids and if possible drug should be extruded through the site to avoid ulceration [26].

Other atypical ulcers like necrotizing fasciitis, neoplastic ulceration, and pyoderma gangrenosum have been described in other chapters of this book.

Conclusion

A large variety of causes may lead to ulcerations in the lower extremity. Only after the common causes of ulceration like venous, arterial, and diabetic have been ruled out should one search for atypical causes of leg ulceration.

References

1. Rayner R, Carville K, Keaton J, Prentice J, Santamaria N. Leg ulcers: atypical presentations and associated comorbidities. Wound Pract Res. 2009;17(4):168–85.
2. Mekkes JR, Loots MAM, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148:388–401.
3. Reilly A, Snyder B. Raynaud phenomenon. Am J Nurs. 2005;105(8):56–65.
4. Wilson H, Vincent R. Autoimmune connective tissue disease: scleroderma. Br J Nurs. 2006;15(15):805–9.
5. 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.
6. Kluger N, Koijonen V, Senet P. Martorell ulcer. Duodecim. 2013;129(10):1031–6.
7. Grzeszkiewicz TM, Giorentino DF. Update on cutaneous vasculitis. Semin Cutan Med Surg. 2006;25(4):221–5.
8. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small vessel vasculitis. J Am Acad Dermatol. 1998;39:667–87.
9. King B. Is this leg ulcer venous? Unusual aetiologies of lower leg ulcers. J Wound Care. 2004;13:394–6.

10. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care. 2004;17(8):410–6.
11. Dean SM. Atypical ischemic lower extremity ulcerations: a differential diagnosis. Vasc Med. 2008;13:47–54.
12. Tiwary S, Shankar R, Khanna R, Khanna A. Symmetrical peripheral gangrene. Int J Surg. 2005;7:2.
13. Franklin C, Stoffels-Weindorf M, Hillen U, Dissemond J. Ulcerated necrobiosis lipoidica as a rare cause for chronic leg ulcers: case report series of ten patients. Int Wound J. 2013. doi:10.1111/iwj.12159.
14. Lacroix R, Kalisiak M, Rao J. Can you identify this condition? Can Fam Physician. 2008;54(6):857–67.
15. Harper P, Wahlin S. Treatment options in acute porphyria, porphyria cutanea tarda and erythropoietic protoporphyria. Curr Treat Options Gastroenterol. 2007;10(6):444–55.
16. Bassi JL, Mahindra P, Singh J. Bilateral upper and lower limb ulcers due to gout- *a case report*. Ind J Orthop. 2006;40:53–4.
17. Bliss DE. Calciphylaxis: what nurses need to know. Nephrol Nurs J. 2002;29(5):433–8.
18. Chertow GM, Raggi P, McCarthy JT, et al. The effects of sevelamer and calcium acetate on proxies of atherosclerotic and arteriosclerotic vascular disease in hemodialysis patients. Am J Nephrol. 2003;23:307–14.
19. Moss J, Syrengelas A, Antaya R, Lazova R. Calcinosis cutis: a complication of intravenous administration of calcium gluconate. J Cutan Pathol. 2006;33 Suppl 2:60–2.
20. Walker SL, Lockwood DNJ. Leprosy. Clin Dermatol. 2007;25:165–72.
21. Barreto JG, Salgado CG. Clinic-epidemiological evaluation of ulcers in patients with leprosy sequelae and the effect of low level laser therapy on wound healing: a randomized clinical trial. BMC Infect Dis. 2010;10:237.
22. Su WP, Davis MD, Weening RH, et al. Pyoderma gangrenosum. Clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43(11):790–800.
23. Potthoff A, Brockmeyer NH. HIV-associated Kaposi sarcoma: pathogenesis and therapy. J Dtsch Dermatol Ges. 2007;5(12):1091–4.
24. Jain A, Varma A, Mangalanandan Kumar PH, Bal A. Surgical outcome of necrotizing fasciitis in diabetic lower limbs. J Diab Foot Complications. 2009;1(4):80–4.
25. Tiwary SK, Khanna AK, Kumar P, Khanna R, Khanna A. A case series describing 118 patients with lower limb necrotizing fasciitis. Int J Low Extrem Wounds. 2009;8:112–6.
26. Khanna AK, Khanna A, Asthana AK, Misra MK. Mitomycin C extravasation ulcers. J Surg Oncol. 1985;28:108–10.

Squamous Cell Carcinoma

22

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22.1 Introduction

Cutaneous squamous cell carcinoma (SCC) is a common cancer arising from malignant proliferation of epidermal keratinocytes. SCC represents a broad range of disease, from superficially invasive to aggressive, highly lethal tumors.

The first reports of malignant SCC came from Percivall Pott in 1775, who described tumors secondary to occupational carcinogens in British chimney sweeps [1]. Jean-Nicholas Marjolin subsequently described SCC associated with burn scars in 1828, immortalizing the term Marjolin's ulcer [2]. Since then, arsenic [3], radiation [4–6], and multiple other etiologic causes have been identified. Accordingly, the clinical presentation of SCC is quite variable and is dependent on unique differences including exposures and patient-specific characteristics like age, ethnicity, and anatomic location. In the lower extremity, SCC has a spectrum or presentations with various degrees of morbidity and mortality [7]. It is therefore crucial for clinicians to be familiar with distinguishing features and risk factors and deliver appropriate care.

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This chapter will review the epidemiology, risk factors, pathogenesis, diagnosis, and treatment of cutaneous SCC, with a particular focus on disease in the lower extremity.

22.2 Epidemiology

The descriptive epidemiology of SCC must be interpreted in light of the fact that SCCs are not consistently reported in most cancer registries [8]. As a result, many epidemiologic studies combine data on SCC with basal cell carcinoma (BCC) and other nonmelanocytic skin tumors [9, 10] further concealing the true natural history of the disease. Despite these limitations, several key features of SCC can help to guide the clinician's evaluation and case-specific management.

SCC is one of the most common human malignancies. It is the second most common cutaneous neoplasm in Caucasians, Chinese, and Japanese, accounting for 20–30 % of skin cancers (Table 22.1) [4, 9, 11–15]. Conversely, SCC accounts for 30–65 % of skin cancers in Blacks and Asian-Indians, making it the most common cutaneous malignancy in both races, respectively [16, 7, 17]. These statistics should be interpreted cautiously as rates of SCC vary by race, sex, environmental exposures, and region [18–21].

Several studies suggest that the incidence of SCC has been steadily rising worldwide over the past several decades [20, 22]. This increase may be related to higher levels of sun exposure, tanning bed use, aging population, and/or improved skin cancer detection [23, 24]. Accordingly, mortality from SCC has also decreased by 20–30 % over this time period [8]. Certain subgroups including Blacks and Hispanics have seen relative stability in SCC incidence; however mortality in these subgroups remains disproportionally larger [7, 21].

In absolute terms, the risk of developing SCC in the setting of lower extremity ulcers is low, approaching 0.4 %. However, as described in one of the largest epidemiological studies of leg ulcers and SCC performed by Baldurrson et al., this represents a greater than 5-fold increase over the general population (RR = 5.69, 95 % CI 1.6–15.08) [25].

Table 22.1 Cancer incidence rates

Race	Incidence
Caucasian [20]	30–360 per 100,000
Hispanic [21]	~20 per 100,000
Black [7]	~3 per 100,000
Japanese [18]	~20 per 100,000
Chinese [14]	6–9 per 100,000
Asian, Indian [17]	Unknown

22.2.1 Risk Factors

Lower extremity (LE) SCCs arise in the context of multiple etiologies. While there is no single pathologic event that leads to SCC, particularly in the setting of LE ulcers, de novo disease is likely the cumulative effect of multiple risk factors. The incidence of SCC increases with age [26, 27]. Rates of disease are at least 5–10 times higher in patients over 75 and some studies estimate a 50–300 times higher prevalence compared to those under the age of 45 [20, 28, 29]. Gender differences are fairly consistent worldwide, with higher SCC rates in men than in women. LE SCCs occur much more commonly in women [30–32], a finding which may be partially explained by clothing and lifestyle [33].

Although less common in darker-skinned ethnic groups, SCC in these populations is associated with greater morbidity and mortality. In Africans, East Asians, and South Asians, SCC frequently occurs in areas of chronic injury or inflammation, including chronic leg ulcers, burn scars, skin infections, or sites of irritation from tight clothing [34–37]. There is a propensity for SCC to occur on the lower extremities in these populations, a site that also tends to be the most common location of repeated cutaneous injury. In particular, the anterior surface of the LE is more prone to trauma, and SCCs tend to occur on the front of the leg [38].

Because of the stark difference of SCC presentation in darker-pigmented persons, ultraviolet radiation is not believed to play an equally important etiologic role [7]. Darker-skinned groups are believed to receive photoprotection from increased melanocyte activity and larger, more dispersed melanosomes [39, 40]. Compared to light-skinned individuals, it is estimated that a 30-fold higher dose of ultraviolet radiation (UVR) is required to produce even minimally perceptible erythema and skin damage [41].

However it remains evident that LE SCCs, like SCCs in general, are in part related to sunlight exposure [41, 33]. UVR from the sun is thought to be the most important environmental exposure responsible for SCC [8, 31]. Both lifetime and occupational sun exposure have been linked to SCC [30, 42]. Additionally, the anterior surface of the leg may receive more sun exposure than the rest of the leg, resulting in 10–17 % higher rates in this area [43]. This causal etiology of UVR is further substantiated by evidence supporting the efficacy of daily sunscreen use in reducing the incidence of SCC [44].

Other forms of radiation have also been linked to SCC. Psoralen followed by exposure to UVA radiation, a combination known as PUVA used to treat a variety of dermatoses, increases the risk for developing squamous cell carcinoma as much as 35-fold [45–48]. Tanning beds, which primarily emit UVA radiation, have been implicated by multiple studies including a recent meta-analysis [49–52]. Therapeutic ionizing radiation, grenz rays, and gamma rays are all associated with the development of SCC [53].

SCC occurs more frequently in patients who are immunosuppressed after solid organ transplants [54–58] and disease tends to be more aggressive than in the immunocompetent [59, 60]. Immunosuppressive agents are believed to augment

UVR-related damage both directly [61] and through decreased immune surveillance [57], leading to an increased risk of multiple and recurrent lesions [62].

As previously mentioned, there is an increased risk of cutaneous SCC in chronically inflamed skin resulting from scars, burns, chronic ulcers, sinus tracts, or inflammation. It is estimated that 2 % of all SCCs arise within chronic scars and a staggering 95 % of all skin cancers arising in chronically inflamed skin are SCCs [63, 64]. Chronic inflammation is a particularly important risk factor in patients with dark-pigmented skin and thought to be responsible for almost half of SCC in this population [7].

SCCs arising in ulcers, also known as Marjolin's ulcers, occur more often in men. There is wide variation between the initial skin injury and appearance of malignancy, with reports of SCC appearing as early as 6 weeks or as late as 50 years after the traumatic event [65–67]. Mortality rate rises with increasing latency, and LE SCCs have a worse prognosis [63]. The healed burn injury, especially if healed by secondary intention, has compromised immune, lymphatic, and barrier function and is more at risk for continued injury. Like other forms of chronic scarring, most have latency periods of many years [68, 69].

Individuals with a family history of SCC may have an increased risk for developing the condition [70–72]. This may be due to genetic traits and inherited disorders similar to risk factors like sunlight [73, 74]. In general, SCC is thought to be more common in lower socioeconomic strata, primarily through occupational exposure to sunlight [75]. Multiple other toxins have been linked to SCC, including chronic exposure to arsenic, aromatic hydrocarbons, coal tar, petroleum-based oil, soot, and tobacco smoke [76–79].

22.2.2 Pathogenesis

Like many malignancies, SCC is not a solitary pathology defined by a single event that leads a cell toward carcinogenesis. Rather, SCC is the result of a collection of disparate acquired and genetic conditions which spawn the malignant transformation of suprabasal epidermal keratinocytes into a disease that ranges from easily managed, superficial tumors to metastatic, highly invasive lethal disease. This section reviews the etiology and pathogenesis of SCC, which shares many similarities with other non-melanoma skin cancers (NMSC).

22.2.3 Genetics of SCC

The genetic origins of SCC lie in three principal categories, regardless of primary etiology of the genetic alteration: *oncogenes*, *tumor-suppressor genes*, and *DNA-repair genes*. Oncogenes are a group of growth-promoting genes derived from normal genomic sequences (so-called proto-oncogenes) involved in the regulatory control of cell growth and proliferation [80]. These are normally tightly controlled; however if mutated, proto-oncogenes can become oncogenes, leading to unchecked

growth and malignant transformation. Mutations in the epidermal growth factor receptor (EGFR) proto-oncogene have been associated with SCC and are often linked to viral infection [81]. Human papillomavirus (HPV) is the most well-known cancer-inducing virus, linked to approximately 99.7 % of cervical SCC [82]. Despite this stalwart relationship, HPV's role in SCC arising from venous stasis ulcers is less clear. Baldursson et al. demonstrated that while ~30 % of patients harbored HPV in their venous stasis ulcer, none of the ulcers that ultimately developed SCC contained the virus [83], suggesting either HPV is not involved in ulcer-derived SCC pathogenesis or the ulcer is subject to "hit and run" HPV infections [84].

Tumor-suppressor genes comprise a class of regulatory sequences that inhibit cell division, downregulate growth, or induce apoptosis. When mutated, cell growth and division can go unchecked, leading to malignant transformation and tumor development. The tumor-suppressor gene TP53, which encodes the commonly known tumor protein p53, plays a central role in SCC pathogenesis and is mutated in over 90 % of patients [85]. While UV irradiation and subsequent CC→TT substitution is the most common cause of p53 mutations, studies suggest that the chronic inflammation and proliferative derangement in lower extremity ulcers may also play a role. In one report, 50 % of patients with chronic venous stasis ulcers who ultimately developed SCC demonstrated overexpression of nonfunctional mutated p53, a rate similar to that found in chronic scars [86, 87].

Finally, DNA-repair genes maintain the integrity of the genome by correcting missense or nonsense mutations that occur normally during the cell division process. Some inherited disorders such as xeroderma pigmentosum arise from mutations in DNA-repair genes, ultimately leading to widespread SCC, BCC, and melanoma. However, there is no direct link between DNA-repair gene mutations and ulcers of the lower extremity; therefore this text will defer discussion of this topic.

22.2.4 Chemical Carcinogenesis

The earliest association of chemical exposure and SCC was by Pott in 1775 in his report on the unusually high incidence of scrotal SCC among London's young chimney sweeps [1]. While first attributed simply to "soot," later studies confirmed that a chemical agent in soot, called benzo[a]pyrene, was responsible for the cancers [88]. Since then, dozens of chemicals have been associated with the development of SCC, many of which can cause ulceration of the extremities with topical exposure. Table 22.2 features carcinogenic agents linked to the development of SCC.

22.2.5 Photocarcinogenesis

UVR remains the primary etiologic agent for SCC (and all skin cancer) carcinogenesis. Both UVA and UVB play a role in the development of SCC, specifically through damage of genomic DNA [89, 90]. It is estimated that patients with greater

Table 22.2 Etiologic agents associated with SCC

Agent	At-risk population	Route of exposure
Ultraviolet radiation	General population	Topical
Cigarette smoke	Smokers	Topical/systemic
Soot	Chimney sweep	Topical
Coal tar, pitch	Coal/steelworker	Topical
Petroleum oils	Machinist, textile worker	Topical/systemic
Arsenic	Agricultural worker	Topical/systemic
4,4′-Bipridyl	Pesticide manufacturer	Topical
Psoralen (PUVA)	Psoriasis patient	Topical/systemic
Nitrogen mustard	T-cell lymphoma patient	Topical
Immunosuppressants	Transplant patients	Systemic

than 30,000 h of cumulative lifetime sun exposure are at higher risk for SCC development [42]. Given the protective nature of normal skin anatomy and its associated chromophores (most notably, melanin), it is reasonable to conclude that disruption of the normal protective layers of the skin through chronic wounds or ulceration would lead to higher susceptibility to UVR damage, though this specific question has not been studied. It is, however, important to understand the effect of UVR exposure on the development of chronic wounds, as the microvascular ablation and chronic inflammation in sun-damaged skin are significantly more prone to ulcerogenesis, regardless of the etiology [91].

22.2.6 Precancerous Lesions: Actinic Keratosis

While the concept of pre-SCC lesions has been intensely debated [92–94], it is now accepted that certain benign lesions are anatomic and genetic precursors to SCC [95, 96]. Chief among these is actinic keratosis (AK), which is thought to represent an early stage on the biologic continuum of SCC. After acne vulgaris, AK is the second leading cause for people to visit a dermatologist [38]. AK tends to appear on sun-exposed areas as the result of UVR exposure and appear as erythematous, rough, and scaly papules. Concerning physical findings that may indicate transition of AK to SCC include induration, pain, and ulceration. If a lower extremity cutaneous ulcer is biopsied and histopathology reveals AK, it is prudent to obtain additional sections of the biopsy sample as missed malignancies are common. Data from Carag et al. suggest that 33 % of tissue blocks initially revealing AK will yield further diagnoses if sectioned deeper, 3 % of which will demonstrate SCC [97].

22.2.7 Bowen's Disease

In situ SCC, also called Bowen's disease (BD), was one of the earliest described in situ precursors to invasive malignancy [98]. It can appear anywhere on the body,

including both sun-exposed and non-sun-exposed areas, notably on women's lower legs. Lesions may range from sub-centimeter to several centimeters in size and often present as oozing erythematous patches or plaques on the lower extremities. Histopathology typically demonstrates full-thickness atypia, which can reach from the stratum corneum to the basal cell layer, while preserving an intact basement membrane which distinguishes it from invasive SCC (Fig. 22.1). The likelihood that an untreated lesion will progress to SCC has been estimated at 3–5 % [99]. More importantly, the presence of BD indicates a patient's increased susceptibility in developing other NMSC. Kao reported that in patients with BD, the incidence of either previous or subsequent NMSC was between 30 and 50 % [100], indicating the need for heightened screening in these patients, particularly if lower extremity ulceration is present.

22.3 Clinical Presentation and Diagnosis

The primary role of the clinician is to evaluate whether a lesion is suspicious for SCC, as early detection decreases morbidity, mortality, and associated costs. This should be followed by evaluation for tumors that are at highest risk for aggressive behavior. Therefore a detailed history and thorough physical examination is directed at identifying the variety of clinical manifestations. Skin biopsies are required to confirm the diagnosis and are useful for staging.

22.3.1 Clinical Presentation

A thorough medical history can help determine the individual's demographics, occupational, and recreational exposure including trauma, personal and family history of SCCs, and contact with carcinogens. The physical examination provides clues to an individual's risk for skin cancer by revealing skin type, coexistence of photodamage, or chronic inflammation and may help determine the need for additional staging. Although sun exposure has been determined to be the primary significant environmental factor contributing to skin cancer, it is often difficult to obtain histories that accurately measure the amount of ultraviolet exposure.

Characteristics of fair complexion, light eyes, and light hair are associated with increased risk of SCC [101–103]. Light hair (blond or red) carries a relative risk of 12.5 for malignant disease and an individual's Fitzpatrick skin type also plays a significant role, as SCC arises disproportionately in individuals with skin types I and II [104]. Evidence of additional photodamage or known precursor lesions [26, 47, 105–107] may be helpful in sun-exposed areas, but may be less predictive in darker-pigmented individuals or in cases of LE SCC caused by chronic scarring.

The clinical appearance of cutaneous SCC is influenced by the lesion type and site. SCC in situ (BD) typically presents as a well-demarcated, scaly patch or plaque

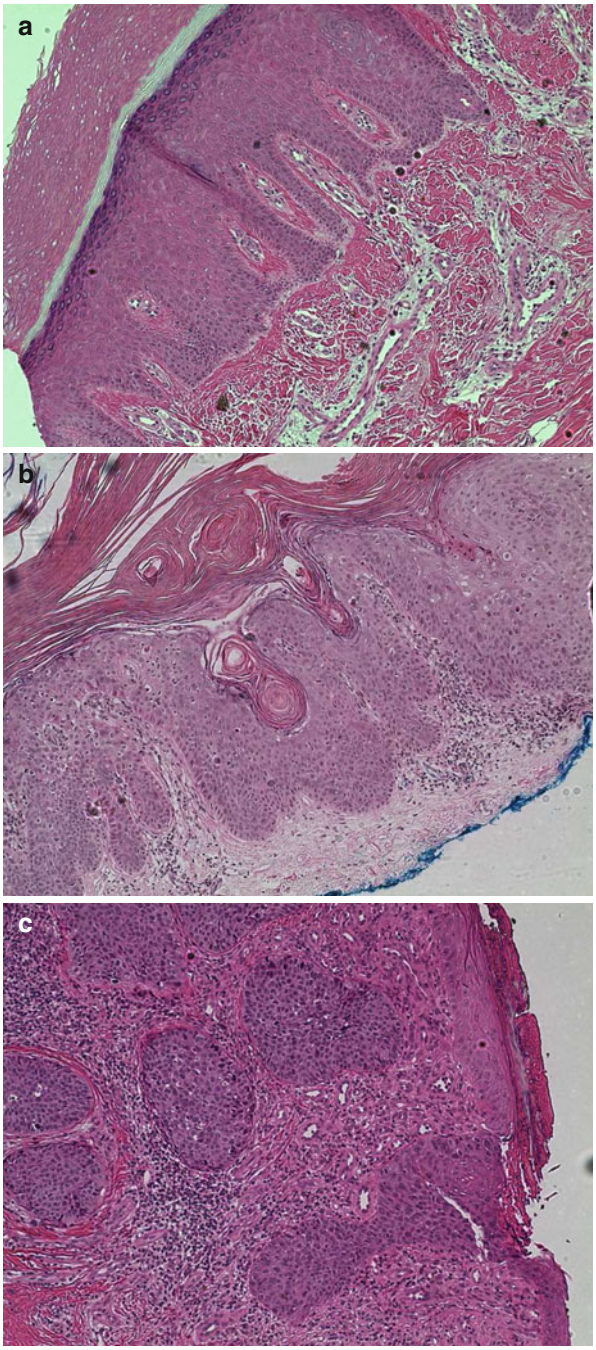

Fig. 22.1 Comparison of normal skin epithelium, squamous cell carcinoma (SCC) in situ, and invasive SCC. (**a**) Shows normal keratinizing stratified squamous epithelium of skin. (**b**) Shows SCC in situ: full-thickness keratinocytic atypia with a high degree of cellular and nuclear variation. (**c**) Shows invasive SCC: the invasive tumor islands in the dermis are surrounded by connective tissue with a brisk inflammatory cell infiltrate (H&E, ×100)

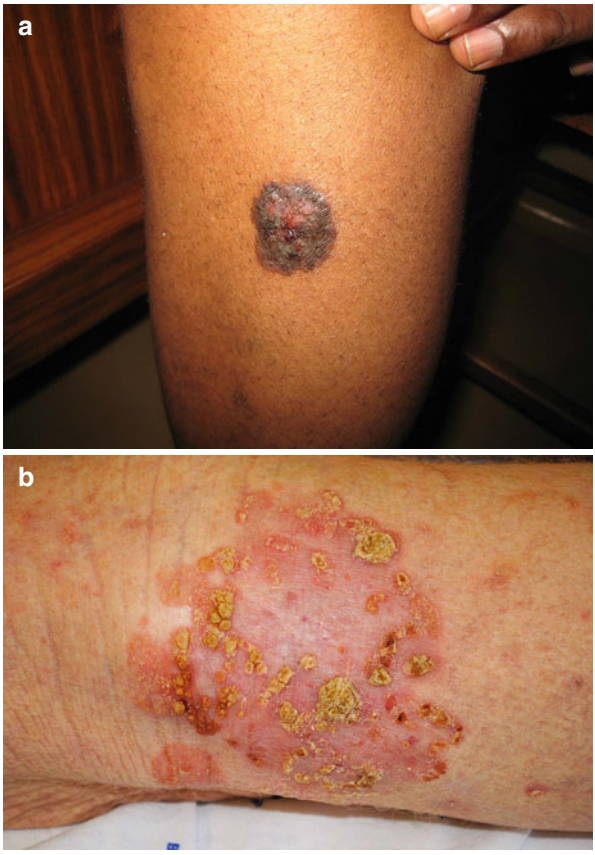

Fig. 22.2 Squamous cell carcinoma in situ. (**a**) Shows a pigmented sessile eroded well-demarcated plaque. (**b**) Shows a large erythematous thin plaque with hypertrophic scale and crusting

(Fig. 22.2). Though typically erythematous, lesions can also be skin colored or pigmented. SCC in situ lesions tend to grow slowly, enlarging over the course of years. They are typically asymptomatic, which distinguishes them from the inflammatory disorders that may resemble SCC in situ. Frequently, there is associated thickening of the epidermis (acanthosis), as well as hyperkeratosis and parakeratosis of the stratum corneum. BD is uncommon in dark-pigmented individuals. When present in these individuals, it tends to present as a scaly, sharply demarcated plaque that is often pigmented and may be velvety, flat, or verrucous. As with invasive tumors, BD in dark-pigmented individuals occurs predominantly on non-sun-exposed skin, particularly the LE [7].

The appearance of invasive SCC often correlates with degree of tumor differentiation. Well-differentiated SCCs tend to present as indurated or firm, hyperkeratotic papules, plaques, or nodules (Fig. 22.3). These lesions are typically smaller than 2 cm. In contrast, poorly differentiated SCC presents as fleshy, granulomatous

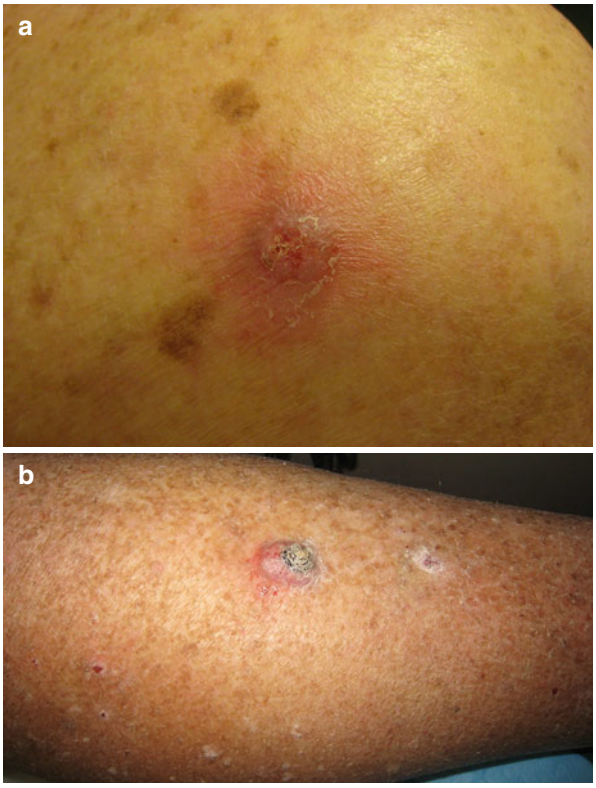

Fig. 22.3 Invasive squamous cell carcinoma. (**a**) Shows a nodule with erosion, scale, surrounding erythema, and induration. (**b**) Shows an erythematous nodule with central scale and crust

papules or nodules that lack the hyperkeratosis that is often seen in well-differentiated lesions. Poorly differentiated tumors are more likely to have ulceration, hemorrhage, or areas of necrosis. Lesions of invasive SCC are often asymptomatic, with neurologic symptoms (numbness, burning, paresthesias, or paralysis) occurring in approximately one-third of patients, suggesting potential perineural invasion and worse prognosis [108, 109].

SCC in setting of chronic wounds, scars, or other forms of inflammation may initially present as ulcerations that fail to heal, with nodularity developing as lesions progress (Fig. 22.4). Therefore, SCC should be suspected whenever chronic wounds fail with appropriate therapy. Because of the aforementioned predisposing factors for the development of SCC in dark-pigmented individuals, non-healing ulcers or nodules adjacent to an area of chronic scarring, inflammation, or abnormal pigmentation should undergo to biopsy to exclude malignancy [7]. The differential diagnosis for SCC manifesting as non-healing ulcers includes basal cell carcinoma, pyoderma gangrenosum, and venous stasis or traumatic ulcers.

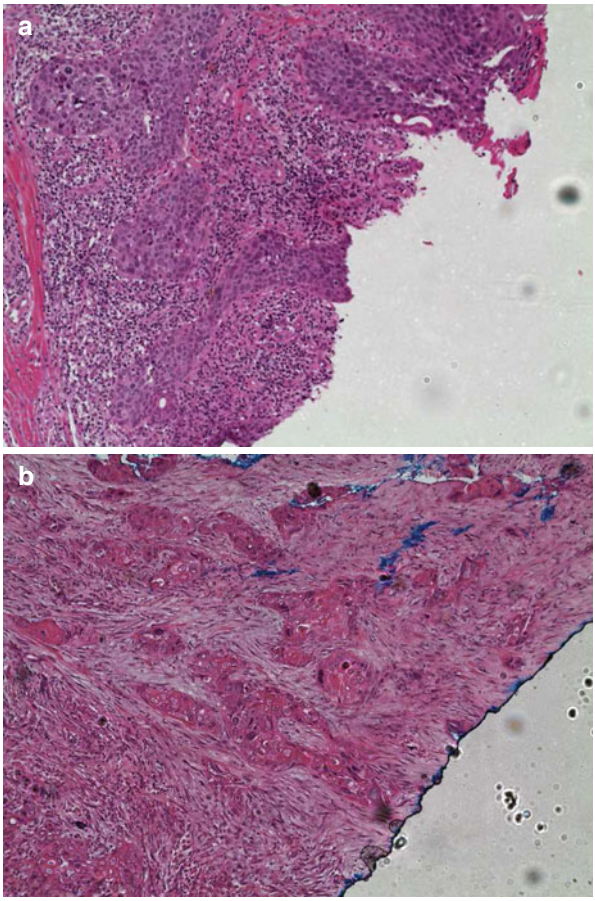

Fig. 22.4 SCC arising from abnormal tissue. Invasive squamous cell carcinoma developing in a background of ulcer with absence of surface epithelium and dense inflammatory cell infiltrate (**a**) and of wound with granulation tissue and fibrosis (**b**) (H&E, ×100)

22.3.2 Staging

Lesions suspicious for SCC should be sampled by shave, punch, or excisional biopsies. Biopsies should extend into the mid-reticular dermis to allow for adequate evaluation of invasive disease. In addition to tumor depth and differentiation, histopathologic examination is also useful for assessment for perineural invasion and other factors that are important for tumor staging and prognosis.

Patients diagnosed with SCC should be given a full-body skin examination (to evaluate for additional cutaneous malignancy) and palpation of regional lymph nodes for signs of metastatic disease. In addition to tumor size and lymph node status, other factors that affect prognosis, including lesion thickness, location, and

level of histopathologic differentiation, are included in the staging criteria. The updated TNM staging system of the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual is provided in (Table 22.3) [109, 110].

Untreated SCC can progress at variable rates, depending on a variety of factors including differentiation, continued exposure, and the patient immunologic status. SCCs not associated with UVR are considered high-risk tumors with a 20–40 % risk of metastasis in dark-pigmented individuals, compared with the 1–4 % metastatic rate of sun-induced SCC in whites [111–113, 7]. It is unclear if this disparity in metastatic rates can be explained by delayed presentation or inherently more aggressive tumors [68, 7]. The initial site of metastasis for cutaneous SCC is most frequently regional lymph node basins followed by distant sites including the lungs, liver, brain, skin, or bone.

Several variables are associated with the risk of local recurrence and metastasis, including location, size, depth, histologic differentiation, perineural involvement, immunosuppression status, and prior treatment [114–116]. SCCs with a diameter over 2 cm have three times the rate of metastasis of smaller tumors. Depth greater than 4 mm is considered higher risk. Poorly differentiated SCCs are associated with a twofold rate of local recurrence and threefold increase in metastatic rate. Local recurrence itself carries a metastatic rate of 25 %. Perineural invasion is a histologic indicator of a biologically aggressive tumor, with metastatic rates as high as 80 %. Immunosuppressed patients have a metastatic rate of almost 13 % [117]. Once SCC metastasizes, 5-year survival falls to 26.8 % [111–113]. Rates of recurrence and metastasis are also listed in Table 22.4.

SCCs developing in chronic wounds or scars are more likely to behave aggressively, with a metastatic rate as high as 38 % [63, 99]. Similarly, SCCs in the setting of prior radiation therapy are also considered high risk [118].

In patients with high-risk SCC, radiologic imaging should be used to assess advanced T staging for T3 or T4 staging (bone invasion) and determination of nodal and distant metastatic spread. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound have all been utilized for disease staging. CT appears to be most useful in the detection of bone and cartilage invasion, while MRI is better suited to assess extension into soft tissue and large nerves. Fine-needle aspiration or surgical excisional biopsy is recommended for clinically enlarged lymph nodes.

The optimal management of clinically node-negative patients with high-risk SCC remains unclear [119]. Various reports of sentinel lymph node (SLN) biopsy exist in the literature, but high-quality studies evaluating the effect of this procedure on survival are lacking. SLN positivity rate (14.1 %) [120] and failure rate, false-negative rate, and negative predictive value for SCC are similar to rates described in melanoma literature, where SLN biopsy is well established. However, the role of routine immunostaining with cytokeratin markers for SCC patients has not been established and the optimal treatment for microscopic lymph node metastases remains unclear with options including regional lymph node dissection, external radiation, or systemic chemotherapy. Presently, SLN biopsy is considered an investigational staging tool in the treatment of high-risk cutaneous SCC.

Table 22.3 AJCC TNM staging system for cutaneous squamous cell carcinoma

Primary tumor (*Tx*)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension with less than two high-risk features (see list of high-risk features below)
T2	Tumor greater than 2 cm in greatest dimension *or*
	Tumor any size with two or more high-risk features
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
High-risk features for the primary tumor (*T*) *staging*	
Depth/invasion	>2 mm thickness
	Clark level ≥IV
	Perineural invasion
Anatomic location	Primary site ear
	Primary site hair-bearing lip
Differentiation	Poorly differentiated or undifferentiated
Regional lymph nodes (*N*)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension
Distant metastasis (*M*)	
M0	No distant metastases
MI	Distant metastases

Anatomic stage/prognostic groups[b]			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0

(continued)

Table 22.3 (continued)

Anatomic stage/prognostic groups[b]			
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, Seventh Edition (2010) published by Springer New York, Inc

Note: *cTNM* is the clinical classification, *pTNM* is the pathologic classification

[a]Excludes cSCC of the eyelid

[b]Patients with primary cSCC or other cutaneous carcinomas with no evidence (clinical, radiologic, or pathologic) of regional or distant metastases are divided into two stages: stage I for tumors measuring ≤2 cm in size and stage II for those that are greater than 2 cm in size. In instances where there is clinical concern for extension of tumor into bone and radiologic evaluation has been performed (and is negative), these data may be included to support the stage I vs. II designation. Tumors that are ≤2 cm in size can be upstaged to stage II if they contain two or more high-risk features. Stage III patients are those with (1) clinical, histologic, or radiologic evidence of one solitary node measuring ≤3 cm in size or (2) tumor extension into bone: maxilla, mandible, orbit, or temporal bone. Stage IV patients are those with (1) tumor with direct or perineural invasion of skull base or axial skeleton, (2) ≥2 lymph nodes, or (3) single or multiple lymph nodes measuring >3 cm in size or (4) distant metastasis

22.4 Treatment

Once a premalignant or malignant lesion has been discovered, a variety of treatment options exist to effectively address the corresponding pathology. The specific level of screening, therapeutic modality, scope of treatment, and degree of posttreatment follow-up will depend on the extent and severity of disease.

22.4.1 Treatment of Premalignant Lesions

As reviewed earlier, AK is recognized as a precursor to SCC, though the vast majority of lesions will not become malignant. Because of the relatively low risk, some specialists regard the treatment of AK as unnecessary, though most dermatologists advocate treating AK because these therapies are relatively easy to perform, have low morbidity, and eliminate the risk of malignant transformation [121, 122]. Treatment for AK can be grouped into two main categories: *lesion-targeted* and *field* therapies.

Table 22.4 Factors associated with increased risk for local recurrence and metastasis of cutaneous squamous cell carcinoma

	Rate of recurrence (percent)	Rate of metastasis (percent)
Tumor factors [111, 148–150]		
Chronic wound or scar	N/A	26.2–37.9
Irradiated skin	N/A	20–26
Size [111, 151]		
≥2 cm	15.2	5.8–42.5
Depth [111, 151, 152]		
>4 mm/Clark IV, V	17.2	30.4–51
>6 mm	N/A	15.6
Recurrent tumor [111, 153]	10–27.5	16.3–30.3
Poorly differentiated histology [111, 151]	28.6	32.8–57.9
Perineural invasion [111, 154, 155]	16–47.2	10–50
Host factors		
CLL and SLL [156–158]	25–100	18–100
Organ transplantation [159, 160]	10–54	6–31

Original table modified for this publication. Copyright © 2006 by the American Society for Dermatologic Surgery, Inc. Published by Blackwell Publishing. Ross and Schmults [161]

Lesion-targeted therapies involve the physical destruction of the premalignant lesions and are the most common methods used to address AK [123]. The most ubiquitous of these destructive therapies is *liquid-nitrogen cryosurgery*, in which liquid nitrogen is directly applied to the lesion via a spray device or cotton applicator in order to destroy the lesion. Clearance rates are proportional to freeze times, with lesions treated for longer than 20 s demonstrating greater than 80 % complete response [124]. *Curettage*, with or without electrocautery, is the next most common lesion-targeted therapy and together with liquid-nitrogen cryosurgery comprises greater than 80 % of all treatments for AK [123]. In this modality abnormal cells are mechanically scraped away, with the judicious use of electrocautery to provide hemostasis as well as destroy an additional layer of underlying cells. If liquid nitrogen is not available, this is a relatively fast and effective method of treating AK, with the downside of additional patient discomfort and potential scarring.

In contrast, field therapies utilize medications to target larger areas of skin with either widespread or multiple AK to abrogate the need for isolated treatment of individual lesions. For decades, topical *5-flurouracil* (5-FU) has been the standard therapy for AK, selectively destroying damaged cells while preserving normal skin and completely eliminating AK in 75 % of lesions. More recently, the immunomodulator *imiquimod* has emerged as another viable topical AK agent. Imiquimod acts by stimulating interferon-α (IFN-α) and tumor necrosis factor-α (TNF-α) [125] in order to destroy abnormal cells, though efficacy appears to be inferior to 5-FU [126]. Another topical field therapy for AK is the nonsteroidal anti-inflammatory *diclofenac*. While the mechanism of action is not completely understood, treatment

is likely related to cyclooxygenase 2 (COX-2) inhibition reducing prostaglandins, which have been implicated in exacerbating UVR damage [127]. Diclofenac is at least as efficacious as imiquimod, with fewer local cutaneous side effects [128].

22.4.2 Treatment of Malignant Lesions

Treatments like curettage, liquid-nitrogen cryotherapy, and medical field therapies are often used because they are quick and less invasive and can be performed in the outpatient setting. However, these therapies are superficial and do not allow for histological margin assessment and are therefore inadequate for the treatment of BD or invasive carcinoma. These require more invasive therapies including *Mohs microscopically controlled surgery* (*MMCS*), *surgical excision*, and *chemoradiotherapy*.

22.4.3 Mohs Microscopically Controlled Surgery (MMCS)

In the 1930s at the University of Wisconsin, Dr. Frederic Mohs developed a method of preserving tumor tissue in situ prior to excision, thus allowing him to evaluate the surgical margin in real time and enabling him to take more tissue if necessary [129]. Because the technique was labor intensive and the tissue preservation process required the patient to leave and return every time a new margin required excision, Dr. Mohs' approach was not readily adopted. It was not until the 1970s when Dr. Theodore Tromovich at the University of California San Francisco utilized frozen sectioning in place of the original in situ fixation process that "Mohs Surgery" or MMCS became widely adopted by the dermatological community [130].

The basic technical principles of MMCS involve initial excision of the tumor with minimum required margins as evaluated by the performing clinician. At this stage the excised tissue is inked and oriented, and in real time the tissue margins are evaluated for residual malignant cells. If tumor is found at one of the margins, the specified marking and orientation of the specimen allow the clinician to further resect tissue only at the affected margin, not blindly across the entire wound bed. This allows for the minimum amount of tissue to be removed in order to achieve an oncologic resection. Across the board, MMCS has been shown to provide superior cure rates for both primary and recurrent disease over traditional treatment modalities [111]. In general, MMCS is used in areas where tissue preservation is paramount (e.g., face, genitals), in lesions with a high risk of local recurrence or with a high risk of metastasis [131]. It is not typically used in the lower extremities where larger and deeper simple excisions are more easily performed. Additionally, the presence of chronic inflammation in and around lower extremity ulcers can obscure intraoperative microscopic margin evaluation; therefore wide excision with or without flap reconstruction is recommended over MMCS in this setting.

22.4.4 Surgical Excision

Surgical excision has long been the mainstay of therapy and is still the standard of care for most SCCs of the lower extremity. The general recommendation for surgical margins for low-risk lesions less than 2 mm in depth is 4 mm. For lesions with higher-risk features or that are deeper than 6 mm, MMCS may be considered to enable intraoperative margin assessment, although surgical excision with wider margins and delayed pathologic evaluation is also appropriate, with the understanding that a return to the operating room for repeat excision may be necessary [132, 133]. On the lower extremity, the skin and subcutaneous tissue are incised to the level of the muscular fascia and removed en bloc for histologic analysis. The wound is typically closed primarily or through secondary intention; however in the setting of inflammation, scaring, or ulceration of the affected area, flap closure or skin grafting may be necessary. Tumors with concerning clinical characteristics (high mitotic rate, ulceration, etc.) and deeply invading tumors with involvement of nerve, bone, or muscle or occurrence in a previously irradiated field should all raise concern for the appropriateness of simple surgical excision, and therefore referral to MMCS is recommended.

Unlike in the case of melanoma, the role of sentinel lymph node biopsy for clinically N0 SCC is unclear [119]. If palpable regional nodes are present in the setting of SCC, fine-needle aspiration or core biopsy is recommended, followed by imaging and consideration of regional lymph node dissection [133]. If lymphadenectomy is performed and demonstrates nodal involvement, subsequent adjuvant chemoradiotherapy may be offered, as these patients are at highest risk of disease progression.

22.4.5 Chemoradiation

External-beam radiation is an important adjuvant therapy in patients with high-risk or refractory disease. In certain patient populations, it has been shown to improve 5-year disease-free and overall survival [134, 135]. For certain disease sites such as SCC of the auditory canal, it has shown particular utility [136], and while providing theoretical benefit in patients with high-risk lesions like a Marjolin's ulcer, this application has not been specifically studied.

Chemotherapy for SCC is typically reserved for recurrent or metastatic disease and its efficacy is highly variable. Cisplatin with or without 5-FU has been studied in a phase II setting, with a small minority of patients showing benefit [133, 137]. Cetuximab (Erbitux), an epidermal growth factor receptor (EGFR) inhibitor, has shown promise in a handful of case reports and possesses a far more attractive toxicity profile than cisplatin-based regimens [138–143]. Gefitinib (Iressa), an EGFR tyrosine kinase inhibitor, has also shown promise in clinical trials but is still considered investigative therapy at this time [144].

22.5 Follow-Up

The intensity of follow-up after treatment of premalignant or malignant lesions should be based on risk. Current National Comprehensive Cancer Network (NCCN) recommendations include a history and physical examination every 3–12 months for 2 years, every 6–12 months for 3 years, and then annually for life [133]. This is in addition to patient education regarding sun protection and skin self-examination. Patients with an elevated risk of metastases or local recurrence should be evaluated more frequently. Recommendations are based on two key factors in the natural history of SCC. First, once treated for SCC patients have a 30–50 % chance of developing another NMSC within 5 years [145], representing a 10-fold increase over the general population [146]. Second, 70–80 % of SCC recurrences occur within the first 2 years after treatment [147], emphasizing the need for increased surveillance during this time.

Conclusion

Squamous cell carcinoma represents a wide spectrum of disease with diverse etiologies and an oftentimes unpredictable clinical course. Despite its relatively low incidence, clinicians caring for patients with lower extremity ulcers should be aware of this often insidious malignancy, as early detection and treatment are crucial in the care of patients with this disease.

References

1. Pott P. Chirurgical observations relative to the cataract, the polyps of the nose, the cancer of the scrotum, the different kinds of ruptures, the mortification of the toes and feet. London: Hawes, Clarke and Collins; 1775.
2. Horton CE, Crawford HH, Love HG, Loeffler RA. The malignant potential of burn scar. Plast Reconstr Surg Transplant Bull. 1958;22(4):348–53.
3. Neubauer O. Arsenical cancer; a review. Br J Cancer. 1947;1(2):192–251.
4. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344(13):975–83.
5. Dabski K, Stoll Jr HL. Skin cancer caused by grenz rays. J Surg Oncol. 1986;31(2):87–93.
6. Traenkle HL. X-ray-induced skin cancer in man. Natl Cancer Inst Monogr. 1963;10:423.
7. Gloster Jr HM, Neal K. Skin cancer in skin of color. J Am Acad Dermatol. 2006;55(5):741–60.
8. Weinstock MA, Ultraviolet radiation and skin cancer: epidemiologic data from the United States and Canada. In: Young AR, Björn LO, Moan J, Nultsch W, editors. Environmental UV photobiology. New York: Plenum Press; 1993. p. 295.
9. American Cancer Society. Cancer Facts and Figures. 2014. Atlanta:American Cancer Society. 2014.
10. Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, Coldiron BM. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol. 2010;146(3):283–7.
11. Fleming ID, Barnawell JR, Burlison PE, Rankin JS. Skin cancer in black patients. Cancer. 1975;35(3):600–5.
12. Halder RM. Bang KM Skin cancer in blacks in the United States. Dermatol Clin. 1988;6(3):397–405.

13. Ishihara K, Saida T, Yamamoto A, Japanese Skin Cancer Society P, Statistical Investigation C. Updated statistical data for malignant melanoma in Japan. Int J Clin Oncol. 2001;6(3):109–16.
14. Koh D, Wang H, Lee J, Chia KS, Lee HP, Goh CL. Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968–97. Br J Dermatol. 2003;148(6):1161–6.
15. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol. 1994;30(5 Pt 1):774–8.
16. Amir H, Mbonde MP, Kitinya JN. Cutaneous squamous cell carcinoma in Tanzania. Cent Afr J Med. 1992;38(11):439–43.
17. Panda S. Nonmelanoma skin cancer in India: current scenario. Indian J Dermatol. 2010;55(4):373–8.
18. Chuang TY, Reizner GT, Elpern DJ, Stone JL, Farmer ER. Nonmelanoma skin cancer in Japanese ethnic Hawaiians in Kauai, Hawaii: an incidence report. J Am Acad Dermatol. 1995;33(3):422–6.
19. Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE, Fraumeni Jr JF. Recent cancer trends in the United States. J Natl Cancer Inst. 1995;87(3):175–82.
20. Gray DT, Suman VJ, Su WP, Clay RP, Harmsen WS, Roenigk RK. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch Dermatol. 1997;133(6):735–40.
21. Harris RB, Griffith K. Moon TE Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985–1996. J Am Acad Dermatol. 2001;45(4):528–36.
22. Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. Int J Cancer (Journal international du cancer). 1993;53(4):585–90.
23. Marks R. The epidemiology of non-melanoma skin cancer: who, why and what can we do about it. J Dermatol. 1995;22(11):853–7.
24. Hacker SM, Flowers FP. Squamous cell carcinoma of the skin. Will heightened awareness of risk factors slow its increase? Postgrad Med. 1993;93(8):115.
25. Baldursson B, Sigurgeirsson B, Lindelof B. Leg ulcers and squamous cell carcinoma. An epidemiological study and a review of the literature. Acta Derm Venereol. 1993;73(3):171–4.
26. Kricker A, Armstrong BK. English DR Sun exposure and non-melanocytic skin cancer. Cancer Causes Control. 1994;5(4):367–92.
27. Aubry F, MacGibbon B. Risk factors of squamous cell carcinoma of the skin. A case–control study in the Montreal region. Cancer. 1985;55(4):907–11.
28. Christenson LJ, Borrowman TA, Vachon CM, Tollefson MM, Otley CC, Weaver AL, Roenigk RK. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA. 2005;294(6):681–90.
29. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer (Journal international du cancer). 1999;81(4):555–9.
30. Gallagher RP, Ma B, McLean DI, Yang CP, Ho V, Carruthers JA, Warshawski LM. Trends in basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin from 1973 through 1987. J Am Acad Dermatol. 1990;23(3 Pt 1):413–21.
31. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63(1–3):8–18.
32. Osterlind A, Hou-Jensen K, Moller Jensen O. Incidence of cutaneous malignant melanoma in Denmark 1978–1982. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. Br J Cancer. 1988;58(3):385–91.
33. Kim C, Ko CJ, Leffell DJ. Cutaneous squamous cell carcinomas of the lower extremity: a distinct subset of squamous cell carcinomas. J Am Acad Dermatol. 2014;70(1):70–4.
34. Chakravorty RC, Dutta-Choudhuri R. Malignant neoplasms of the skin in Eastern India. Indian J Cancer. 1968;5(2):133–44.
35. Camain R, Tuyns AJ, Sarrat H, Quenum C, Faye I. Cutaneous cancer in Dakar. J Natl Cancer Inst. 1972;48(1):33–49.

36. Tada M, Miki Y. Malignant skin tumors among dermatology patients in university hospitals of Japan. A statistical survey 1971–1975. J Dermatol. 1984;11(4):313–21.
37. Yakubu A, Mabogunje OA. Squamous cell carcinoma of the skin in Africans. Trop Geogr Med. 1995;47(2):91–3.
38. Goldsmith LA, Fitzpatrick TB. Fitzpatrick's dermatology in general medicine. 8th ed. New York: McGraw-Hill Professional; 2012.
39. Halder RM, Bridgeman-Shah S. Skin cancer in African Americans. Cancer. 1995;75(2 Suppl):667–73.
40. Montagna W, Carlisle K. The architecture of black and white facial skin. J Am Acad Dermatol. 1991;24(6 Pt 1):929–37.
41. Kollias N, Sayre RM, Zeise L. Chedekel MR Photoprotection by melanin. J Photochem Photobiol B. 1991;9(2):135–60.
42. Vitaliano PP, Urbach F. The relative importance of risk factors in nonmelanoma carcinoma. Arch Dermatol. 1980;116(4):454–6.
43. Levi F, La Vecchia C, Te VC, Mezzanotte G. Descriptive epidemiology of skin cancer in the Swiss Canton of Vaud. Int J Cancer (Journal international du cancer). 1988;42(6):811–6.
44. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, Marks GC, Gaffney P, Battistutta D, Frost C, Lang C, Russell A. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet. 1999;354(9180):723–9.
45. Cockayne SE, August PJ. PUVA photocarcinogenesis in Cheshire. Clin Exp Dermatol. 1997;22(6):300–1.
46. Nijsten TE, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen + ultraviolet A: a cohort study. J Invest Dermatol. 2003;121(2):252–8.
47. English DR, Armstrong BK, Kricker A, Winter MG, Heenan PJ, Randell PL. Demographic characteristics, pigmentary and cutaneous risk factors for squamous cell carcinoma of the skin: a case–control study. Int J Cancer (Journal international du cancer). 1998;76(5):628–34.
48. Stern RS, Study PF-U. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. J Am Acad Dermatol. 2012;66(4):553–62.
49. Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstock MA. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst. 2002;94(3):224–6.
50. Lever LR, Lawrence CM. Nonmelanoma skin cancer associated with use of a tanning bed. N Engl J Med. 1995;332(21):1450–1.
51. Roest MA, Keane FM, Agnew K, Hawk JL, Griffiths WA. Multiple squamous skin carcinomas following excess sunbed use. J R Soc Med. 2001;94(12):636–7.
52. Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and nonmelanoma skin cancer: systematic review and meta-analysis. BMJ (Clinical research ed). 2012;345:e5909.
53. Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA, Greenberg ER. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Arch Dermatol. 2000;136(8):1007–11.
54. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation. 1990;49(3):506–9.
55. Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, Fauchald P. Simonsen S Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 1999;40(2 Pt 1):177–86.
56. Lampros TD, Cobanoglu A, Parker F, Ratkovec R, Norman DJ, Hershberger R. Squamous and basal cell carcinoma in heart transplant recipients. J Heart Lung Transplant. 1998;17(6):586–91.
57. Berg D, Otley CC. Skin cancer in organ transplant recipients: Epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47(1):1–17.

58. Silverberg MJ, Leyden W, Warton EM, Quesenberry Jr CP, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105(5):350–60.
59. Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). J Am Acad Dermatol. 1992;26(3 Pt 2):467–84.
60. Veness MJ. Aggressive skin cancers in a cardiac transplant recipient. Australas Radiol. 1997;41(4):363–6.
61. Parrish JA. Immunosuppression, skin cancer, and ultraviolet A radiation. N Engl J Med. 2005;353(25):2712–3.
62. Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D, Dierkhising RA, Kremers WK, McGregor CG, Otley CC. Incidence of and risk factors for skin cancer after heart transplant. Arch Dermatol. 2009;145(12):1391–6.
63. Phillips TJ, Salman SM, Bhawan J, Rogers GS. Burn scar carcinoma. Diagnosis and management. Dermatol Surg. 1998;24(5):561–5.
64. Jellouli-Elloumi A, Kochbati L, Dhraief S, Ben Romdhane K, Maalej M. Cancers arising from burn scars: 62 cases. Ann Dermatol Venereol. 2003;130(4):413–6.
65. Love RL, Breidahl AF. Acute squamous cell carcinoma arising within a recent burn scar in a 14-year-old boy. Plast Reconstr Surg. 2000;106(5):1069–71.
66. Akguner M, Marutcu A, Yilmaz M, Karatas O, Vayvada H. Marjolin's ulcer and chronic burn scarring. J Wound Care. 1998;7(3):121–2.
67. Friedman R, Hanson S, Goldberg LH. Squamous cell carcinoma arising in a Leishmania scar. Dermatol Surg. 2003;29(11):1148–9.
68. Gul U, Kilic A. Squamous cell carcinoma developing on burn scar. Ann Plast Surg. 2006;56(4):406–8.
69. Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns. 2005;31(4):403–13.
70. Hussain SK, Sundquist J, Hemminki K. The effect of having an affected parent or sibling on invasive and in situ skin cancer risk in Sweden. J Invest Dermatol. 2009;129(9):2142–7.
71. Milan T, Verkasalo PK, Kaprio J, Koskenvuo M, Pukkala E. Malignant skin cancers in the Finnish Twin Cohort: a population-based study, 1976–97. Br J Dermatol. 2002;147(3):509–12.
72. Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. BMJ (Clinical research ed). 2012;345:e8076.
73. Wallberg P, Kaaman T, Lindberg M. Multiple basal cell carcinoma. A clinical evaluation of risk factors. Acta Derm Venereol. 1998;78(2):127–9.
74. Hogan DJ, Lane PR, Gran L, Wong D. Risk factors for squamous cell carcinoma of the skin in Saskatchewan, Canada. J Dermatol Sci. 1990;1(2):97–101.
75. Robinson JK, Altman JS, Rademaker AW. Socioeconomic status and attitudes of 51 patients with giant basal and squamous cell carcinoma and paired controls. Arch Dermatol. 1995;131(4):428–31.
76. Everall JD, Dowd PM. Influence of environmental factors excluding ultra violet radiation on the incidence of skin cancer. Bull Cancer. 1978;65(3):241–7.
77. Guo HR, Yu HS, Hu H, Monson RR. Arsenic in drinking water and skin cancers: cell-type specificity (Taiwan, ROC). Cancer Causes Control. 2001;12(10):909–16.
78. Karagas MR, Stukel TA, Morris JS, Tosteson TD, Weiss JE, Spencer SK, Greenberg ER. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case–control study. Am J Epidemiol. 2001;153(6):559–65.
79. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. Arch Dermatol. 2012;148(8):939–46.
80. Balmain A. Cancer genetics: from Boveri and Mendel to microarrays. Nat Rev Cancer. 2001;1(1):77–82.
81. Lee JW, Soung YH, Kim SY, Nam HK, Park WS, Nam SW, Kim MS, Sun DI, Lee YS, Jang JJ, Lee JY, Yoo NJ, Lee SH. Somatic mutations of EGFR gene in squamous cell carcinoma of the head and neck. Clin Cancer Res. 2005;11(8):2879–82.

82. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Munoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–9.
83. Baldursson BT, Beitner H, Syrjanen S. Human papillomavirus in venous ulcers with and without squamous cell carcinoma. Arch Dermatol Res. 2000;292(6):275–8.
84. Iwasaka T, Hayashi Y, Yokoyama M, Hara K, Matsuo N, Sugimori H. 'Hit and run' oncogenesis by human papillomavirus type 18 DNA. Acta Obstet Gynecol Scand. 1992;71(3):219–23.
85. Brash DE. Roles of the transcription factor p53 in keratinocyte carcinomas. Br J Dermatol. 2006;154 Suppl 1:8–10.
86. Sakatani S, Kusakabe H, Kiyokane K, Suzuki K. p53 gene mutations in squamous cell carcinoma occurring in scars: comparison with p53 protein immunoreactivity. Am J Dermatopathol. 1998;20(5):463–7.
87. Baldursson B, Syrjanen S, Beitner H. Expression of p21WAF1/CIP1, p53, bcl-2 and Ki-67 in venous leg ulcers with and without squamous cell carcinoma. Acta Derm Venereol. 2000;80(4):251–5.
88. Kennaway EL. On the cancer-producing factor in Tar. Br Med J. 1924;1(3300):564–7.
89. Brash DE, Rudolph JA, Simon JA, Lin A, McKenna GJ, Baden HP, Halperin AJ, Ponten J. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88(22):10124–8.
90. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B. 2001;63(1–3):19–27.
91. Ulrich M, Ruter C, Astner S, Sterry W, Lange-Asschenfeldt B, Stockfleth E, Rowert-Huber J. Comparison of UV-induced skin changes in sun-exposed vs. sun-protected skin- preliminary evaluation by reflectance confocal microscopy. Br J Dermatol. 2009;161 Suppl 3:46–53.
92. Yantsos VA, Conrad N, Zabawski E, Cockerell CJ. Incipient intraepidermal cutaneous squamous cell carcinoma: a proposal for reclassifying and grading solar (actinic) keratoses. Semin Cutan Med Surg. 1999;18(1):3–14.
93. Heaphy Jr MR, Ackerman AB. The nature of solar keratosis: a critical review in historical perspective. J Am Acad Dermatol. 2000;43(1 Pt 1):138–50.
94. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol. 2000;42(1 Pt 2):11–7.
95. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet. 1988;1(8589):795–7.
96. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol. 1991;127(7):1029–31.
97. Carag HR, Prieto VG, Yballe LS, Shea CR. Utility of step sections: demonstration of additional pathological findings in biopsy samples initially diagnosed as actinic keratosis. Arch Dermatol. 2000;136(4):471–5.
98. Bowen JT. Pre-Cancerous Dermatoses — a Study of 2 Cases of Chronic Atypical Epithelial Proliferation. J Cutan Dis. 1912;20:241.
99. Reizner GT, Chuang TY, Elpern DJ, Stone JL, Farmer ER. Bowen's disease (squamous cell carcinoma in situ) in Kauai, Hawaii. A population-based incidence report. J Am Acad Dermatol. 1994;31(4):596–600.
100. Kao GF. Carcinoma arising in Bowen's disease. Arch Dermatol. 1986;122(10):1124–6.
101. Evans RD, Kopf AW, Lew RA, Rigel DS, Bart RS, Friedman RJ, Rivers JK. Risk factors for the development of malignant melanoma—I: Review of case–control studies. J Dermatol Surg Oncol. 1988;14(4):393–408.
102. Zanetti R, Rosso S, Martinez C, Navarro C, Schraub S, Sancho-Garnier H, Franceschi S, Gafa L, Perea E, Tormo MJ, Laurent R, Schrameck C, Cristofolini M, Tumino R, Wechsler J. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer. 1996;73(11):1440–6.

103. Bliss JM, Ford D, Swerdlow AJ, Armstrong BK, Cristofolini M, Elwood JM, Green A, Holly EA, Mack T, MacKie RM. Risk of c. utaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case–control studies. The International Melanoma Analysis Group (IMAGE). Int J Cancer (Journal international du cancer). 1995;62(4):367–76.
104. Fitzpatrick TB. Ultraviolet-induced pigmentary changes: benefits and hazards. Curr Probl Dermatol. 1986;15:25–38.
105. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, Ng SK, Munoz B, Emmett EA. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer. 1990;65(12):2811–7.
106. Gallagher RP, Hill GB, Bajdik CD, Coldman AJ, Fincham S, McLean DI, Threlfall WJ. Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer. II. Squamous cell carcinoma. Arch Dermatol. 1995;131(2):164–9.
107. Schwartz RA. Premalignant keratinocytic neoplasms. J Am Acad Dermatol. 1996;35(2 Pt 1):223–42.
108. Reule RB, Golda NJ, Wheeland RG. Treatment of cutaneous squamous cell carcinoma with perineural invasion using Mohs micrographic surgery: report of two cases and review of the literature. Dermatol Surg. 2009;35(10):1559–66.
109. Farasat S, Yu SS, Neel VA, Nehal KS, Lardaro T, Mihm MC, Byrd DR, Balch CM, Califano JA, Chuang AY, Sharfman WH, Shah JP, Nghiem P, Otley CC, Tufaro AP, Johnson TM, Sober AJ, Liegeois NJ. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. J Am Acad Dermatol. 2011;64(6):1051–9.
110. Buethe D, Warner C, Miedler J, Cockerell CJ. Focus issue on squamous cell carcinoma: practical concerns regarding the 7th edition AJCC staging guidelines. J Skin Cancer. 2011;2011:156391.
111. Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol. 1992;26(6):976–90.
112. North Jr JH, Spellman JE, Driscoll D, Velez A, Kraybill WG, Petrelli NJ. Advanced cutaneous squamous cell carcinoma of the trunk and extremity: analysis of prognostic factors. J Surg Oncol. 1997;64(3):212–7.
113. Veness MJ. Time to rethink TNM staging in cutaneous SCC. Lancet Oncol. 2008;9(8):702–3.
114. Miller SJ, Alam M, Andersen J, Berg D, Bichakjian CK, Bowen G, Cheney RT, Glass LF, Grekin RC, Kessinger A, Lee NY, Liegeois N, Lydiatt DD, Michalski J, Morrison WH, Nehal KS, Nelson KC, Nghiem P, Olencki T, Perlis CS, Rosenberg EW, Shaha AR, Urist MM, Wang LC, Zic JA. Basal cell and squamous cell skin cancers. J Natl Compr Cancer Netw. 2010;8(8):836–64.
115. Brantsch KD, Meisner C, Schonfisch B, Trilling B, Wehner-Caroli J, Rocken M, Breuninger H. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9(8):713–20.
116. Mullen JT, Feng L, Xing Y, Mansfield PF, Gershenwald JE, Lee JE, Ross MI, Cormier JN. Invasive squamous cell carcinoma of the skin: defining a high-risk group. Ann Surg Oncol. 2006;13(7):902–9.
117. Mullen DL, Silverberg SG, Penn I, Hammond WS. Squamous cell carcinoma of the skin and lip in renal homograft recipients. Cancer. 1976;37(2):729–34.
118. Edwards MJ, Hirsch RM, Broadwater JR, Netscher DT, Ames FC. Squamous cell carcinoma arising in previously burned or irradiated skin. Arch Surg. 1989;124(1):115–7.
119. Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: clinical experience and review of literature. World J Surg Oncol. 2011;9:80. doi:10.1186/1477-7819-9-80.
120. van Akkooi AC, Verhoef C. Eggermont AM Importance of tumor load in the sentinel node in melanoma: clinical dilemmas. Nat Rev Clin Oncol. 2010;7(8):446–54.

121. Drake LA, Ceilley RI, Cornelison RL, Dobes WL, Dorner W, Goltz RW, Graham GF, Lewis CW, Salasche SJ, Turner ML, et al. Guidelines of care for actinic keratoses. Committee on Guidelines of Care. J Am Acad Dermatol. 1995;32(1):95–8.
122. Boddie Jr AW, Fischer EP, Byers RM. Squamous carcinoma of the lower lip in patients under 40 years of age. South Med J. 1977;70(6):711–2.
123. Callen JP, Bickers DR, Moy RL. Actinic keratoses. J Am Acad Dermatol. 1997;36(4):650–3.
124. Feldman SR, Fleischer Jr AB, Williford PM, Jorizzo JL. Destructive procedures are the standard of care for treatment of actinic keratoses. J Am Acad Dermatol. 1999;40(1):43–7.
125. Lipper GM, Arndt KA, Dover JS. Recent therapeutic advances in dermatology. JAMA. 2000;283(2):175–7.
126. Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, Lee JH, Fox TL, Alomar A. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. J Am Acad Dermatol. 2004;51(4):547–55.
127. Lee PK, Harwell WB, Loven KH, Phillips TJ, Whiting DA, Andres KL, Lee JH. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. Dermatol Surg. 2005;31(6):659–64.
128. An KP, Athar M, Tang X, Katiyar SK, Russo J, Beech J, Aszterbaum M, Kopelovich L, Epstein Jr EH, Mukhtar H, Bickers DR. Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches. Photochem Photobiol. 2002;76(1):73–80.
129. Mohs F. Chemosurgery: a microscopially controlled method of skin cancer excision. Arch Surg. 1941;42(279):279.
130. Tromovitch TA, Stegman SJ. Microscopie-controlled excision of cutaneous tumors: chemosurgery, fresh tissue technique. Cancer. 1978;41(2):653–8.
131. Drake LA, Dinehart SM, Goltz RW, Graham GF, Hordinsky MK, Lewis CW, Pariser DM, Salasche SJ, Skouge JW, Turner ML, et al. Guidelines of care for Mohs micrographic surgery. American Academy of Dermatology. J Am Acad Dermatol. 1995;33(2 Pt 1):271–8.
132. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27(2 Pt 1):241–8.
133. NCCN Clinical Practice Guidelines in Oncology. Basal and Squamous Cell Skin Cancers (V 2. 2014). http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. Accessed Apr 22 2014.
134. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):748–55.
135. Shimm DS, Wilder RB. Radiation therapy for squamous cell carcinoma of the skin. Am J Clin Oncol. 1991;14(5):383–6.
136. Hashi N, Shirato H, Omatsu T, Kagei K, Nishioka T, Hashimoto S, Aoyama H, Fukuda S, Inuyama Y, Miyasaka K. The role of radiotherapy in treating squamous cell carcinoma of the external auditory canal, especially in early stages of disease. Radiother Oncol. 2000;56(2):221–5.
137. Shin DM, Glisson BS, Khuri FR, Clifford JL, Clayman G, Benner SE, Forastiere AA, Ginsberg L, Liu D, Lee JJ, Myers J, Goepfert H, Lotan R, Hong WK, Lippman SM. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. J Clin Oncol. 2002;20(2):364–70.
138. Suen JK, Bressler L, Shord SS, Warso M, Villano JL. Cutaneous squamous cell carcinoma responding serially to single-agent cetuximab. Anticancer Drugs. 2007;18(7):827–9.
139. Miller K, Sherman W, Ratner D. Complete clinical response to cetuximab in a patient with metastatic cutaneous squamous cell carcinoma. Dermatol Surg. 2010;36(12):2069–74.
140. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, Certain A, Duval X, Crickx B, Buffard V, Basset-Seguin N, Saez P, Duval-Modeste AB, Adamski H, Mansard S, Grange F, Dompmartin A, Faivre S, Mentre F, Avril MF. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011;29(25):3419–26.

141. Kim S, Eleff M, Nicolaou N. Cetuximab as primary treatment for cutaneous squamous cell carcinoma to the neck. Head Neck. 2011;33(2):286–8.
142. Bauman JE, Eaton KD, Martins RG. Treatment of recurrent squamous cell carcinoma of the skin with cetuximab. Arch Dermatol. 2007;143(7):889–92.
143. Arnold AW, Bruckner-Tuderman L, Zuger C, Itin PH. Cetuximab therapy of metastasizing cutaneous squamous cell carcinoma in a patient with severe recessive dystrophic epidermolysis bullosa. Dermatology. 2009;219(1):80–3.
144. Perez CA, Song H, Raez LE, Agulnik M, Grushko TA, Dekker A, Stenson K, Blair EA, Olopade OI, Seiwert TY, Vokes EE, Cohen EE. Phase II study of gefitinib adaptive dose escalation to skin toxicity in recurrent or metastatic squamous cell carcinoma of the head and neck. Oral Oncol. 2012;48(9):887–92.
145. Robinson J. Follow-up and prevention (Basal Cell Carcinoma). In: Miller S, Maloney M, editors. Cutaneous Oncology Pathophysiology, diagnosis and management. Malden, MA: Blackwell Science; 1998.
146. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol. 2000;136(12):1524–30.
147. Shin D, Maloney M, Lippman S. Follow-up and prevention (Squamous Cell Carcinoma). In: Miller S, Maloney M, editors. Cutaneous Oncology Pathophysiology, diagnosis, and management. Malden, MA: Blackwell Science; 1998.
148. Arons MS, Lynch JB, Lewis SR, Blocker Jr TG. Scar Tissue carcinoma. A clinical study with special reference to burn scar carcinoma. Ann Surg. 1965;161:170–88.
149. Fitzpatrick T, Eisen A, Wolff K, Stoll H, Schwartz R. Squamous cell carcinoma. In: Dermatology in General Medicine. New York: McGraw Hill; 1987. p. 746–58.
150. Martin H, Strong E, Spiro RH. Radiation induced skin cancer of the head and neck. Cancer. 1970;25(1):61–71.
151. Cherpelis BS, Marcusen C, Land PG. Prognostic factors for metastasis in squamous cell carcinoma of the skin. Dermatol Surg. 2002;28(3):268–73.
152. Kraus DH, Carew JF, Harrison LB. Regional lymph node metastasis from cutaneous squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 1998;124(5):582–7.
153. Clayman GL, Lee JJ, Hoisinger FC, Zhou X, Duvic M, El-Naggar AK, Prieto VG, Altamirano E, Tucker SL, Strom SS, Kripke ML, Lippman SM. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005;23(4):759–65.
154. Goepfeft H, dichtel JJ, Medina JE, Lindberg RD, Luna MD. Perineural invasion in squamous cell skin carcinoma of the head and neck. Am J Surg. 1984;148(4):5420547.
155. Garcia-Serra A, Hinerman RW, Mendenhall WM, amdur RJ, Morris CG, Williams LS, Mancuso AA. Carcinoma of the skin with perineural invasion. Head Neck. 2003;25(12):1027–33.
156. Weimar VM, Ceilley RI, Goeken JA. Aggressive biologic behavior of basal and squamous cell cancers in patients with chronic lymphocytic leukemia or chronic lymphoma. J Dermatol Surg Oncol. 1979;5(8):609–14.
157. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol. 2005;53(6):1067–71.
158. Frierson Jr HF, Deutsch BD, Levine PA. Clinicopathologic features of cutaneous squamous cell carcinomas of the head and neck in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Hum Pathol. 1988;19(12):1397–402.
159. Sheil AG, Disney AP, Mathew TH, Amiss N. De novo malignancy emerges as a major cause of morbidity and late failure in renal transplantation. Transplant Proc. 1993;25(1 PT 2):1383–4.
160. Euvrard S, Kanitakis J, Pouteil-Noble C, Disant F, Dureau G, Finazdevillaine J, Claudy A, Thivolet J. Aggressive squamous cell carcinomas in organ transplant recipients. Transplanat Proc. 1995;27(2):1767–8.
161. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systemic review of the English literature. Dermatol Surg. 2006;32:1309. doi:10.1111/j.1524-4725.2006.32300.x.

Melanoma of the Extremity

23

Suvro Ganguly and Diptendra K. Sarkar

23.1 Introduction

Ulcers of the foot have evolved as a subspecialty in itself. Though benign conditions comprise of the major causes, malignant ulcers are not at all a rare entity. Melanomas are defined as malignant neoplasms arising from the melanin-producing melanocytes of the skin (originally developed from the neural crests). Malignant melanoma is one of the most common malignant ulcers affecting the extremities in all age groups. Statistics from the Indian subcontinent is a scarcity, but in the United States, the annual incidence is close to 75,000 new cases per year with approximately 9000 deaths per year [1]. A surprising fact remains that females are mostly predisposed to melanomas of the extremities.

23.2 Cellular Classification of Melanoma

It is of historic importance and does not carry any major prognostic significance. It includes:

1. Superficial spreading
2. Nodular
3. Lentigo maligna
4. Acral lentiginous
5. Miscellaneous: mucosal lentiginous, verrucous, and desmoplastic [2]

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23.3 Molecular Classification of Melanoma

This classification is based on the identification of activating mutations which affects mutation in MAP kinase pathways. The role of this classification is not only to identify the mutagenic protein but also develop molecular targeted therapies against the subset. This includes:

1. BRAF (40–60 %)
2. NRAS (15–20 %)
3. C-KIT (6–7 %)
4. CDK-4 (4 %)

Other rare types: P13K, AKT, P53, PTEN, mTOR, Bcl-2, and MITF [3]

In addition, gene expression profiling of stage IV melanomas reveal four different molecular subtypes (each with BRAF/NRAS mutations) characterized by the expression of:

1. Immune response genes
2. Pigmentation differentiation gene subset
3. Proliferation genes
4. Stromal composition genes

The tumor with overexpression of proliferative genes has a particularly poor outcome compared with other subtypes. In addition, the cohort with underexpression of the immune response subsets also fare poorer compared with other subsets. This biological taxonomy is particularly helpful in prognosticating advanced disease (stage III and IV) and selecting candidates for targeted immune therapy [4].

23.4 Growth Pattern in Melanoma

Most melanomas except nodular variety are characterized by a preceding in situ phase where the growth pattern is radial. Subsequently, there is dermal invasion and the melanoma develops the potential to spread. Once the growth pattern changes from radial to horizontal phase, there is metastasis to lymph nodes and system [5].

23.5 Diagnostic Hallmark

A melanoma may be de novo or may arise from a preexisting mole. Early melanoma and dysplastic lesions can be suspected by the characteristic "ABCD" features. These are:

A. Asymmetry of a mole
B. Border irregularity of a mole
C. Color variability in a mole
D. Diameter increasing to more than 6 mm [6]

23.6 Characteristic Clinical Presentations [7]

1. *Superficial spreading type (70 %)*: It is the most common variety accounting for 70 % of cutaneous melanomas. Though it can occur in the trunk, a majority of the females develop ulcer in the extremities. They present as a flat or slightly elevated lesion with or without ulceration. It demonstrates the classical ABCD signs of melanoma.
2. *Nodular type (15–20 %)*: It can occur in the extremities and is characterized by the lack of radial growth phase, and therefore, the classical ABCD signs are usually missing. They present as thick lesions and therefore ulcerate very fast and tend to bleed upon touching. A large subset of such melanomas may be amelanotic (i.e., nonpigmented). The lack of radial growth phase, thicker lesions, and a nonpigmented appearance are responsible for late presentation and poorer prognosis.
3. *Lentigo maligna (5–15 %)*: Rarely occurs in the extremities. They occur in the elderly age group and are mostly distributed in the head and neck and back of the arm. They are mostly associated with solar degeneration.
4. *Acral Lentiginous*: Most common melanoma among dark-skinned persons accounting for 29–72 % of melanomas. They are rare in whites (2–4 %). They present in the palm, sole, and subungual region. Subungual lesions typically present as a blue-black discoloration of the posterior nail fold. The presence of pigmentation in the proximal or lateral nail folds is diagnostic of subungual melanoma (Hutchinson sign) (Figs. 23.1, 23.2, and 23.3).

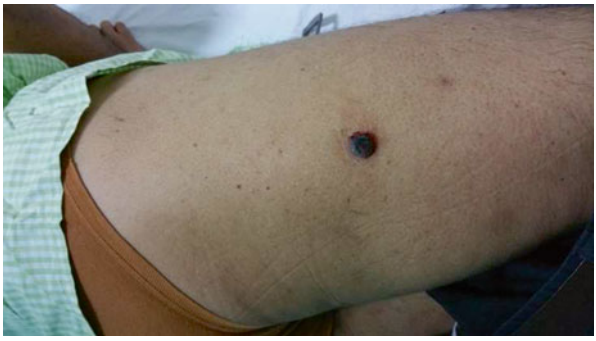

Fig. 23.1 Melanoma, back of thigh

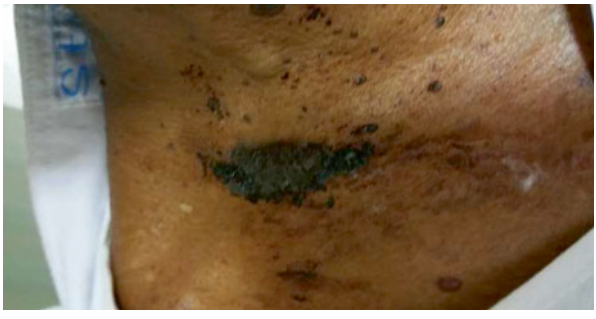

Fig. 23.2 Superficial spreading type

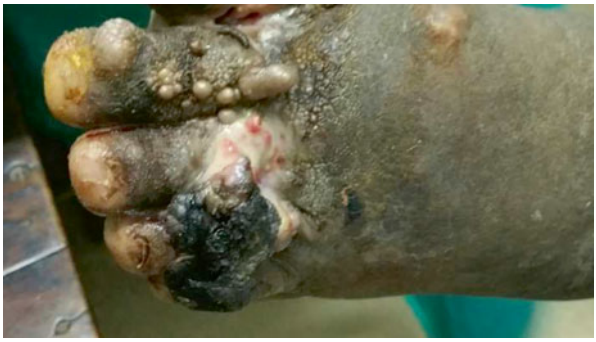

Fig. 23.3 Nodular melanoma with ulcer fixed to the bone

23.7 Staging of Melanoma

The clinical staging of melanoma is extremely important so as to describe the presentation stage. It involves:

(a) Melanoma confined to the primary site. Any satellite nodule within 2 cm from the primary is designated as part of the primary.
(b) Melanoma with metastasis to regional lymph nodes.
(c) Melanoma with systemic metastasis.

However, microscopic staging of melanoma is important particularly for melanomas apparently restricted to the primary site. The more is the depth of involvement, the higher is the chance of metastasis to regional nodes. The Breslow and the Clark staging are the two most commonly used types. Of these, Breslow is more reproducible as it involves absolute depth of invasion.

Breslow staging and its significance (vertical thickness of melanoma in millimeters)

Stage	Depth
I	Less than or equal to 0.75 mm
II	0.76–1.50 mm
III	1.51–2.25 mm
IV	2.26–3.0 mm
V	Greater than 3 mm

Clark staging (anatomical level of invasion)

Level of invasion	Description
Level I	Lesions involving only the epidermis (in situ melanoma); not an invasive lesion
Level II	Invasion of the papillary dermis; does not reach the papillary-reticular dermal interface
Level III	Invasion fills and expands the papillary dermis but does not penetrate the reticular dermis
Level IV	Invasion into the reticular dermis but not into the subcutaneous tissue
Level V	Invasion through the reticular dermis into the subcutaneous tissue

TNM staging

T (tumor size)	Depth	Subtypes
Tis	Melanoma in situ	
T1	<1.0 mm	(a) Without ulceration and mitosis <1/mm^2 (b) Without ulceration or mitosis >/=1/mm^2
T2	1.0–2.0 mm	(a) Without ulceration (b) With ulceration
T3	2.1–4.0 mm	(a) Without ulceration (b) With ulceration
T4	>4 mm	(a) Without ulceration (b) With ulceration
N (regional lymph nodes)		
N1	One lymph	(a) Micrometastasis (b) Macrometastasis
N2	2–3 nodes	(a) Micrometastasis (b) Macrometastasis (c) In-transit metastasis/satellite without metastatic nodes
N3	>/= 4 nodes	Matted LN/in-transit nodules with nodal metastasis
M (distant metastasis)		
M1a	Distant skin/subcutaneous/LN	LDH normal
M1b	Lung metastasis	LDH normal
M1c	All other visceral metastasis Any distant metastasis	LDH normal LDH elevated

23.8 Prognostic Factors

1. Depth of invasion
2. Lymph node metastasis
3. Anatomic location: Extremity melanomas have better prognosis than head and neck lesions (82 % versus 68 %).
4. Presence of ulceration: Carries poorer prognosis than nonulcerated form.
5. Sex: Females have better prognosis than males.
6. Histopathology types: Nodular and superficial spreading types have the same outcome when they are depth matched. But nodular lesions having more vertical progression tend to spread early. Lentigo maligna carries best prognosis, whereas acral lentiginous is the worst type.

23.9 Management

23.9.1 Diagnosis

1. *Biopsy*: All suspicious lesions must undergo full-thickness excision biopsy with 1–3 cm margin, provided the skin can be closed primarily. In large lesions, full-thickness incisional biopsy is taken from the margin. However, all biopsy incisions should be planned in a way that they can be encompassed during definitive surgery.
2. *Sentinel lymph node biopsy*: Detection and evaluation of draining lymph node.
3. *Metastatic workup*: USG of the regional lymph node to exclude regional metastasis. The change in the shape of nodes from a bean shape to a globular form with loss of fatty hilum on ultrasound is the hallmark of metastatic nodes.
4. *Systemic metastasis*: CT scan of abdomen and thorax is done to exclude metastasis.

23.10 Treatment

Stage 0 (melanoma in situ without lymph node or systemic metastasis): Excision only with minimum margin, but resection margin needs to be free microscopically (Figs. 23.4 and 23.5).

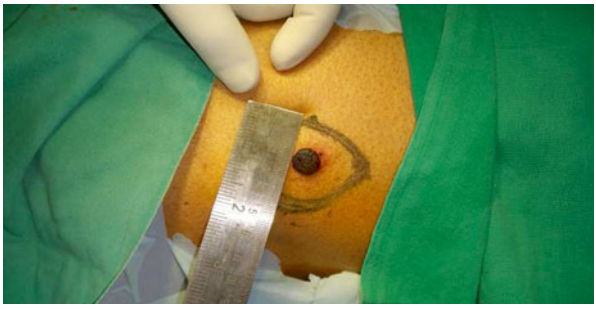

Fig. 23.4 Melanoma with wide local excision

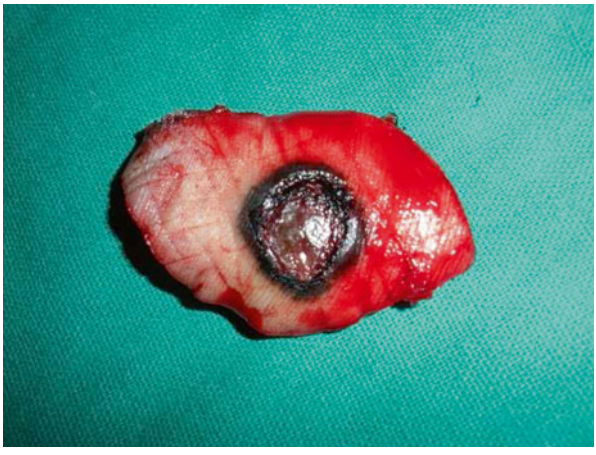

Fig. 23.5 Excision biopsy

Stage I

T1A: melanoma without ulceration Depth of invasion less than 1 mm Mitotic figures <1/mm^2	N0 M0	Excision with 1 cm radial margin is adequate. Wider margin is not associated with better OS or DFS The need for skin grafting is also reduced with 1 cm margin (Level 1 evidence) Lymph node Elective lymph node dissection or SLNB does not carry any survival advantage over observation only in intermediate-thickness lesions (Level 1 evidence)
T1B: melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2	N0 M0	
T2A: melanomas 1.01–2.0 mm in thickness without ulceration	N0 M0	

Stage 2

T 2B: melanomas 1.01–2.0 mm in thickness with ulceration	N0 M0	Wide local excision is recommended with a radial margin of 2–3 cm for intermediate-thickness lesions (2–4 mm) For lesions more than 4 mm, a 3 cm radial margin is mandatory Lymph node SLNB is the standard of care for these patients. Immediate nodal dissection for SLNB positive cases is done in most cases Elective nodal dissection does not improve survival Nodal dissection for microscopic disease does not improve survival
T 3A: melanomas 2.01–4.0 mm in thickness without ulceration	N0 M0	
T 3B: melanomas 2.01–4.0 mm in thickness with ulceration	N0 M0	
T 4A: melanomas >4.0 mm in thickness without ulceration	N0 M0	
T4B: melanomas >4.0 mm in thickness with ulceration	N0 M0	

Stage 3a or 3b (clinical or pathological which considers SLNB or CLD)

Any T	N > or = 1	Wide local excision using 3 cm margin with skin grafting is the standard of care Clinicoradiologically negative nodes should undergo SLNB Microscopically and macroscopically positive nodes need CLD Unresectable tumors need systemic treatment followed by palliative surgery
	N1 = 1 regional lymph node metastasis M0	
	N2 = 2–3 regional lymph node metastases M0	
	N3 = ≥4 regional lymph node metastases; or matted nodes; or in-transit metastasis/ satellite(s) with metastatic lymph node(s) M0	

Stage 4

Any T Any N	M1	Systemic treatment followed by palliative surgery

23.11 Systemic Therapy in Melanoma

No role in adjuvant setting. These are agents which are used in unresectable and metastatic diseases.

23.11.1 Immunotherapy

1. Check point inhibitors: This includes anti-cytotoxic antigen-4 (CTLA-4) and anti-programmed cell death (anti-PD-1) and anti-programmed cell death ligand (anti-PDL). Ipilimumab, an anti-CTLA-4 monoclonal antibody, stimulates T-cell activation, proliferation, and effector cell function.
   Pembrolizumab, an anti-BRAF inhibitor, is effective in BRAF-positive melanoma. It blocks PD-1 receptor site and is expected to improve OS and DFS.
2. High-dose interleukin-2 (IL-2): High-dose IL-2 demonstrated a 6–7 % CR rate. With a median follow-up time for surviving patients of at least 7 years, the median duration of CRs was not reached but was at least 59 months.
3. Dual immunomodulation: Combined blockade using anti-CTLA-4 and anti-PD agents is possibly more effective than single-agent therapy.
4. Interferon therapy: Though there was initial enthusiasm with this drug, long-term studies fail to demonstrate any major benefit [8, 9].

23.11.2 Signal Transduction Inhibitors

1. BRAF (V-raf murine sarcoma viral oncogene homolog B1) inhibitors (for patients who test positive for BRAF V600 mutation)
   Vemurafenib
   Dabrafenib
2. MEK inhibitors
   Trametinib
3. Combination therapy with signal transduction inhibitors
   Dabrafenib plus trametinib
   Multikinase inhibitors
4. KIT inhibitors

23.11.3 Chemotherapy

DTIC was approved based on OS in the 1970s, but RCT [8] demonstrates no survival advantage using DTIC therapy. The immunotherapeutic agents were found superior to chemotherapy in most of the trials.

23.11.4 Radiotherapy

No role except in cases of bone metastasis palliation.

23.11.5 Isolated Limb Perfusion

It is used in recurrent locally advanced inoperable melanomas.

It delivers high-dose regional chemotherapy and establishes a hyperthermic environment to the extremity. The circulation is isolated from the rest of the body. Retrospective meta-analysis has shown that single-agent therapy (melphalan) with mild hyperthermia induces complete response between 40 and 82 %. Adding TNF-alpha to melphalan has been suggested to improve CPR, but RCT fails to demonstrate any benefit (Figs. 23.6, 23.7, and 23.8) [9, 10].

Fig. 23.6 Amelanotic melanoma, improper surgery

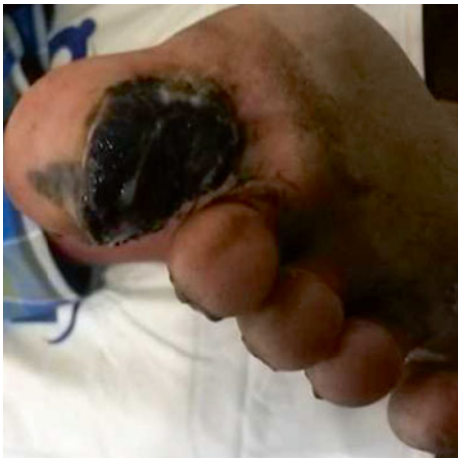

Fig. 23.7 Melanoma of the great toe, plantar aspect

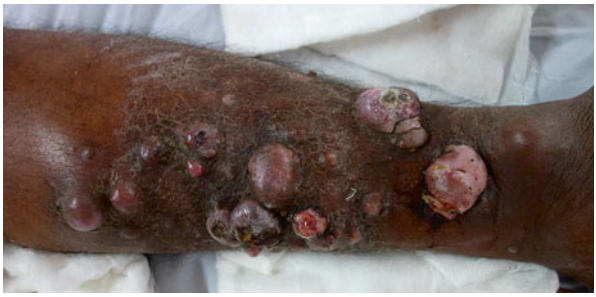

Fig. 23.8 In-transit nodules of melanoma

References

1. Williams NS, Bulstrode CJK, O'Connell PR, editors. Bailey and love short practice of surgery. 26th ed. London: Arnold, A member of the Hodder Headline group; 2000.
2. Brunicardi CF, Andersen DK, Billiar TR, Dunn DL, Hunter JJ, Pollock RE. Schwartz's text book of surgery. USA: McGraw-Hill Medical Publishing; 2005.
3. http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq.
4. Jönsson G, et al. Gene expression profiling-based identification of molecular subtypes in stage IV melanomas with different clinical outcome. Clin Cancer Res. 2010;16:3356–67.
5. Traugott L. Amber, Hall L Bruce. The Washington manual of surgery. 6th ed. St Louis: Wolters Kluwer-Lippincott Williams and Wilkins; 2012.
6. Cuschieri A, Steele RJC, Moossa AR. Essential surgical practice, higher surgical training in general surgery. 4th ed. London/New York: Arnold; 2002.
7. Kadison AS, Morton DL. Immunotherapy of malignant melanoma. Surg Clin North Am. 2003;83(2):343–70.
8. Zeiser R, Schnitzler M, Andrlova H, Hellige T, Meiss F. Immunotherapy for malignant melanoma. Curr Stem Cell Res Ther. 2012;7(3):217–28.
9. Taber SW, Polk Jr HC. Mortality, major amputation rates, and leukopenia after isolated limb perfusion with phenylalanine mustard for the treatment of melanoma. Ann Surg Oncol. 1997;4:440–5.
10. Brobeil A, Berman C, Cruse CW, et al. Efficacy of hyperthermic isolated limb perfusion for extremity-confined recurrent melanoma. Ann Surg Oncol. 1998;5:376–83.

Basal Cell Carcinoma

24

Chintamani and Megha Tandon

24.1 Introduction

Cutaneous carcinomas are classified into melanotic and non-melanotic cancers. Non-melanotic cutaneous carcinomas (NMCC) are the most common skin cancers worldwide and include squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). BCC is the most common human cancer, accounting for approximately 75 % of all NMCCs, followed by squamous cell carcinoma (SCC), which represents 20 % of all cutaneous malignancies. BCC consists of plugs and clusters of basal cells, with various clinical manifestations in accordance with various morphological features, which to a certain extent correspond with the various histological types [1].

24.1.1 BCC: Presentation as a Chronic Leg Ulcer (CLU)

Chronic ulceration of the lower limb is a frequent condition with the prevalence of 3–5 % in the population over 65 years of age, and this is despite the advancement in wound care. The association between malignancies and chronic ulcers is well known and includes two distinct entities, *primary ulcerating skin carcinomas* (often misdiagnosed as chronic ulcers) and the *secondary skin carcinomas* (those due to malignant transformation in long lasting ulcers [2]. The difference between these two entities is however not very clear in the literature [3, 4].

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24.2 Primary BCC

Skin cancers arising de novo and mimicking chronic limb ulcers in appearance are included in this category. Many cancers, including cutaneous metastases, can produce skin ulceration as their presenting feature like melanomas, Kaposi's sarcomas, and primary cutaneous B-cell or T-cell lymphomas. The two most frequently encountered malignancies causing ulcerations, i.e., squamous cell carcinoma [SCC] and basal cell carcinoma [BCC], can affect any part of the body with a preference for sun-exposed area. To confuse the picture further, BCC and SCC share their predilection in individuals above 60 years, i.e., the age when venous insufficiency as well as peripheral arterial diseases are also frequent. Furthermore, the indolent clinical course makes it a challenge to differentiate primary skin malignancies causing ulceration from CLU [3, 4].

Basal cell carcinoma is a slow-growing and locally destructive tumor arising from a subset of the basal cells in the epidermis. Initially it presents as a reddish, dome-shaped nodule that later expands to develop a central area of ulceration. This leaves a raised, rolled border, often mistaken for over-granulation, and this rarely involves deeper tissue, except at sites of chronic inflammation. It is characterized by a translucent pearly appearance, and the lesions tend not to be scaly as they do not produce keratin; however, occasionally there may be mild crusting and oozing. Variants of basal cell carcinoma include nodular carcinoma, cystic carcinoma, pigmented basal cell carcinoma, rodent ulcers, and sclerosing carcinoma, which have different appearances.

24.2.1 Pathogenesis of Primary BCC

The pathogenesis of primary BCC is multifactorial, and interaction between genes and the environment plays prominent role, but it is primarily attributed to ultraviolet light (UVL) exposure [5, 6]. BCC can arise sporadically, or it could be a part of multiple inherited syndromes like the following:

- Nevoid BCC syndrome (NBCCS)
- Bazex syndrome
- Rombo syndrome
- Unilateral basal cell nevus syndrome

High-risk individuals typically include light-colored (white) persons with light hair and eyes with the history of intermittent intense exposure to the sun resulting in sunburns rather than tanning [6]. UV-induced mutations in the p53 gene have been reported in up to 60 % of BCC [7]. Other important gene that plays a role in sporadic and probably inherited BCC is tumor suppressor gene known as the patched gene (PTCH) [6–8].

Pathogenesis of BCC fits in the "Knudson's two-hit theory." The first alteration or hit is inheritance of a mutation in a tumor suppressor gene, and the *second* one is inactivation of the normal homologue by environmental mutagenesis or random

genetic rearrangement. Inactivation of the PTCH gene is probably a necessary, if not sufficient step for BCC formation [9–13].

The first molecular step especially in sun-induced carcinogenesis is UVB-induced DNA photoproducts, most frequently involving adjacent pyrimidines. Absorption of UV photons at the double bond of pyrimidines damages the bond, allowing it to open up. This results in the formation of either the cyclobutane dimer or a pyrimidine-pyrimidone photoproduct, which further leads to abnormal DNA structures. During subsequent DNA replication, the DNA polymerase incorrectly inserts an adenine opposite a damaged cytosine. At the next replication, the adenine correctly codes for thymine opposite it. After UV exposure, these C®T mutations occur only where a cytosine lies next to a thymine or another cytosine, reflecting the specificity of the sites at which UV photoproducts occur [6–9].

24.3 Genetic Events

Two tumor suppressor gene mutations are mainly involved in the pathogenesis of BCC. *PTCH*, a component of a cellular signaling pathway, is mutated in perhaps 90 % of BCCs, and *p53*, which encodes a regulator of the cell cycle and cell death, is mutated in half of BCCs.

24.3.1 PTCH

PTCH was discovered as the gene mutated in nevoid basal cell carcinoma syndrome, an autosomal dominant disorder characterized by multiple BCCs, jaw cysts, and pits of the palms and soles. Most sporadic BCCs have inactivating *PTCH* mutations, and almost all tumors without *PTCH (patched)* mutations have activating mutations in its partner smoothened. Patched encodes a large transmembrane protein that along with smoothened (another transmembrane molecule) serves as the receptor for the secreted molecule hedgehog. When hedgehog binds, smoothened is released from inhibitory effects of patched and transduces a signal, while in hedgehog's absence, smoothened and patched form an inactive complex. However, mutations inactivating the patched switch on the hedgehog pathway without hedgehog, which is the early step in tumor development. No tumor may have loss on other chromosomes without involvement of the PTCH locusso PTCH functions as a "gatekeeper gene" in basal cell carcinogenesis. Inactivating this function is necessary before clonal expansion, and accumulation of other genetic hits can lead to BCC formation.

Nearly all hereditary BCCs have allelic loss as their second, somatic hit. Sun damage is usually the culprit for this allelic loss, since nevoid BCC syndrome tumors are most frequent on sun-exposed skin and are rare in Africans and African Americans. Mostly sporadic BCCs contain PTCH mutations that are UVB-like, with CC®TT mutations predominating. However, in approximately one-third of BCCs, mutations are clearly not UVB induced. These may include factors such as

UVA, oxidative damage, or arsenicals. Sunscreens may need to block both UVB and UVA to be completely protective against BCC [11–13].

Patched represses transcription of hedgehog target genes by inactivating smoothened. Hedgehog binds to patched, thereby activating smoothened and causing increased transcription of GLI, itself a transcription factor, and its downstream targets, such as WNT and transforming growth factor-b (TGF-b). In the absence of patched, smoothened may be constitutively activated, resulting in the overexpression of these genes.

24.3.2 p53

The distinctive mutations caused by UVB radiation identify a tumor suppressor gene critical for both BCC and SCC: p53. More than 90 % of SCC of the skin and 50 % BCC have this mutation. These are predominantly C®T and CC®TT base substitutions at sites of adjacent pyrimidines, directly implicating cytosine-containing cyclobutane dimers or (6–4) photoproducts and sunlight UVB as the mutagen. Each p53 mutation changes the amino acid, indicating that the mutation was selected for and contributed to tumor development, rather than being solely an indicator of sun exposure. p53 is a transcription factor that turns on or off the expression of other genes involved in the cell cycle, programmed cell death, and DNA repair. Most mutations inactivate p53's transcriptional activator function [11–13]. BCCs, though usually diploid and nonmetastasizing, also contain UV-induced p53 mutations. Approximately one-third of BCCs occur on body sites that are relatively sun shielded; p53 mutations from these tumors resemble those seen with UVA, ionizing radiation, or oxidative damage, rather than UVB. UVB-induced p53 mutations are frequent in skin cancers from XP patients and in carcinoma in situ. Non UV p53 mutations are common in keloids, as a result of dysregulated wound healing.

24.4 Cellular Events

Sunlight can act several times in skin carcinogenesis: first to mutate the p53 or PTCH gene and then afterward to select for clonal expansion of a p53-mutated cell. These two actions correspond to tumor initiation and tumor promotion. UVB is known to have tumor-promoting activity in mouse skin.

24.4.1 Clinical Behavior of Basal Cell Cancer

BCC is associated with extremely low metastatic potential, but it does invade/burrow locally, thus earning the name "rodent's ulcer." This biological behavior is based on angiogenic factors, stromal conditions, and the propensity for the cancer to follow anatomic paths of least resistance. The clinical behavior of larger BCCs is however different, and the recurrence rates in these cancers are higher.

24.4.2 Factors Responsible for the Biological Behavior of BCC

Angiogenic factors: These can be expressed by the tumor and lead to telangiectasis in vessels that are characteristically seen on the tumor surface. These factors also serve as prognostic markers that indicate the aggressive behavior. For these reasons, antiangiogenic factors are being tried in therapy and may have potential therapeutic role [14–16].
Stromal conditions: Tumor stroma is critical for both initiating and maintaining the development of BCC, and this concept of stromal dependence is supported by the low incidence of metastatic BCC (rates of metastatic BCC being 0.0028–0.1 %). Metastases, when reported, usually involve the lung, lymph nodes, esophagus, oral cavity, and skin and carry a poor prognosis [14–16].

Propensity for path of least resistance: BCC has a tendency to grow along the path of least resistance, and embryonic fusion planes are likely to offer little resistance. This can lead to deep invasion, tumor spread, and high rates of recurrence. The most susceptible areas for these cancers, therefore, include the inner canthus, philtrum, middle to lower chin, nasolabial groove, preauricular area, and the retroauricular sulcus [13–16]. Perineural spread is not common and occurs most often in recurrent, aggressive lesions. In a series, Niazi and Lamberty noted perineural invasion in 0.178 % of BCC. Perineural invasion may present with paresthesia, pain, and weakness or, in some cases, paralysis [17].

24.5 Clinical Subtypes of Basal Cell Carcinoma

Clinical variants of BCC include nodular, superficial, morpheaform (also termed aggressive-growth BCC or infiltrative BCC), pigmented, cystic BCC, and fibroepithelioma of Pinkus (FEP). The presentation of these forms can vary [17–21].

Nodular BCC: As the name suggests, it presents as a raised pearly nodule or a papule with visible vessels on the surface (Fig. 24.1).

Superficial BCC: Commonly presents as an erythematous scaly or eroded macule on the trunk and may be difficult to differentiate clinically from in situ cancer or a benign inflammatory lesion like eczema or psoriasis.

Morpheaform BCC: Presents as a flat, slightly firm lesion, without well-demarcated borders, and poses a challenge as it might be difficult to differentiate it from a scar. Symptoms of bleeding, crusting, and ulceration are often not present in these tumor subtypes, and this can lead to a delay in diagnosis.

Pigmented BCC: Is a variant of nodular BCC and may be difficult to differentiate from nodular melanoma. The pigment may help in determining adequate margins for excision (Fig. 24.2).

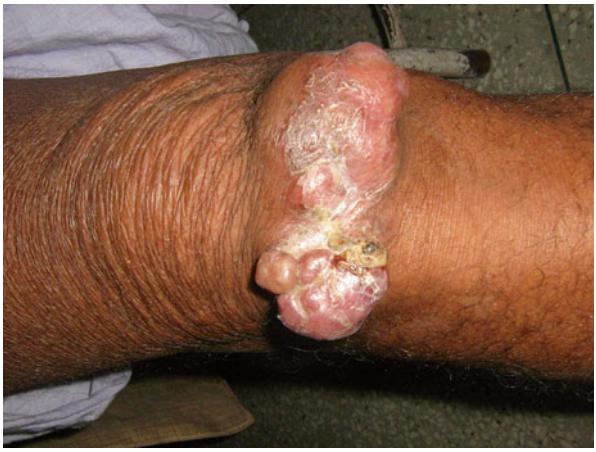

Fig. 24.1 Basal cell carcinoma of knee region

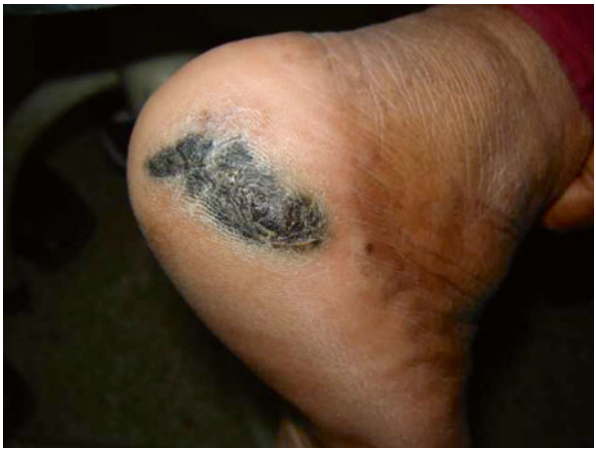

Fig. 24.2 Basal cell carcinoma (pigmented in sole)

Fibroepithelioma of Pinkus: It usually presents as a pink papule on the lower back. It may be difficult to distinguish clinically from amelanotic melanoma.

24.6 Histologic Subtypes of BCC

Histologic variants of BCC include *superficial, nodular, and infiltrative BCC,* and all of them share certain histologic characteristics, i.e., peripheral palisading of large basophilic cells, nuclear atypia, and retraction from surrounding stroma.

Superficial multifocal BCC accounts for approximately15% of BCCs and is characterized by basophilic buds extending from the epidermis. Retraction artifact is present, as is peripheral palisading within the buds.

Nodular BCC accounts for approximately 50 % of BCCs and is characterized by the presence of tumor cells in circular masses within the dermis. Peripheral palisading of nuclei is prominent, and surrounding retraction artifact may be present. Groups of cells may be solid or may have dermal necrosis or degradation, with formation of cysts or microcysts. The stroma is characteristically coarse and myxoid. If nodules measure less than 15 μm, the tumor may be called micronodular.

Infiltrative histology is seen in 15–20 % of BCCs and represents that subclass of BCCs referred to as aggressive-growth tumors. Tumor cells have irregular outlines with a spiky appearance. Palisading is characteristically absent. The stroma is less myxoid than in nodular form.

In the *morpheaform* variant, compromising approximately 5 % of BCCs, small groups or cords of tumor cells infiltrate a dense, collagenous stroma parallel to the skin surface.

FEP, which accounts for 1 % of BCCs, is characterized by a polypoid lesion in which basaloid cells grow downward from the surface in a network of anastomoses of cords of cells in loose connective tissue.

Mixed histology is apparent in approximately 15 % of BCCs.

The significance of histologic subtype lies in its correlation with biologic aggressiveness. The infiltrative and micronodular types are the most likely to be incompletely removed by conventional excision. Rates of incomplete excision vary from 5 to 17 % with a recurrence rates of 33–39 %. Recurrences after radiotherapy (RT) show a tendency toward infiltrative histology and evidence of squamous transformation, and even recurrent BCC after excision may become metatypical. In general, recurrences are more frequent in BCCs with infiltrative and micronodular histology, when clear margins are less than 0.38 mm, and in the presence of squamous differentiation. Incompletely excised BCCs should be removed completely, preferably by Mohs micrographic surgery (MMS), especially if they occur in anatomically critical areas [16].

Adequate treatment of BCC requires appreciation of the histopathologic pattern of the neoplasm. Though some BCCs are small and superficial and behave in essentially a "biologically benign" manner as long as they are conservatively removed, others behave more aggressively and thus require more aggressive treatment. Examples of the latter include clinical BCCs that ulcerate and those located in the central face or on the ear. Furthermore, BCCs that show an aggressive-growth pattern histologically require definitive treatment with confirmation of histologically negative margins. Occasionally, it may appear that a BCC has been adequately removed by biopsy alone, leading to the question of whether to render further treatment. In one study, 41 consecutive patients with 42 BCCs apparently removed by biopsy were treated by MMS, and blocks of tissue, sectioned consecutively until exhausted, were examined for the presence of residual tumor. In 28 of 42 cases (66 %), residual cancer was identified. The presence of residual cancer was not related to age, site, histologic subtype, or extent of surrounding inflammation. The results indicate that patients with small BCCs that appear to be completely removed by initial biopsy may be at risk for recurrence if not treated further [22].

24.7 Characteristics Related to Anatomic Site

BCCs may demonstrate unique characteristics based on anatomic site. The nose is the most common site for cutaneous malignancies (30 %), and BCCs involving the nose may be aggressive. A study of 193 cases of infiltrative BCC involving the nose confirmed that the majority of infiltrating and recurrent BCCs affect the ala. Analysis of the recurrences' aggressive local behavior indicated that recurrent lesions were subjected to inadequate therapy initially 23. In one study, 26 recurrences were identified in 71 nasal skin cancers at an average of 36 months after non-MMS excision. This suggests that MMS may be the treatment of choice for all BCCs involving the nose, especially those exhibiting aggressive-growth characteristics. Periocular BCC represents a significant therapeutic challenge. In one study, periocular BCC accounted for 7.3 % of 3192 BCCs treated over a 10-year period. Of these, 48.5 % involved the medial canthus, 22.35 % involved the lower eyelid, 10.7 % involved the upper eyelid, and 5.6 % involved the lateral canthus. BCC is the most common tumor affecting the eyelid. In a series of 97 cases of BCC involving the eyelid, 69 % were nodular, 13 % were infiltrative, 1 % were ulcerated, and 12 % were mixed (defined as having a significant nodular or ulcerative component in addition to an infiltrative component). Follow-up of 8 of 12 patients with mixed tumors revealed 3 recurrences. In one patient, orbital exenteration was required. This suggests that mixed tumors of the eyelid with aggressive-growth histology warrant thorough treatment with complete margin control. In a review of 24 eyelid tumors treated by MMS, high clearance rates were shown (100 %), although follow-up was short (14.6 months) [23, 24].

In addition, 50 % of patients were left with intact posterior lamellae, highlighting conservation of normal tissue. The results suggest that MMS followed by oculoplastic reconstruction, if necessary, is the preferred strategy in the management of periocular BCC.

Approximately 6 % of BCCs involve the ear, a site notable for high rates of recurrence. In a recent study, nine patients with BCC involving the conchal bowl were treated by an interdisciplinary approach. In each case, tumor extirpation was accomplished by MMS, and an otolaryngologist was available in the event of temporal bone involvement. There were no cases of recurrence at mean follow-up of 1 year. It must be stressed that BCC can occur anywhere, even in non-sun-exposed areas, and has been reported to occur on the vulva, penis, scrotum, and perianal area. In one series of vulvar BCC, mean age at presentation was 74 years. Patients have been seen with a history of local irritation that had been present for a few months to several years.

24.8 Basal Cell Carcinoma Developing in a Chronic Leg Ulcer (Secondary BCC)

In order to make a diagnosis of malignant transformation from a CLU (especially in the absence of a previous positive histology) and to differentiate it from a primary cutaneous carcinoma, the CLU should be present for at least 3 years. However, the definite guidelines are lacking and the subject is still debatable. Abnormal excessive granulation tissue at the wound edges has been appreciated as a sensitive parameter

for the diagnosis of CLU-associated malignancies in a recently published prospective study (done on CLUs that failed to improve even after 3 months of optimum treatment). Other specific parameters included abnormal bleeding and a high clinical suspicion of ulcerated skin malignancy or malignant transformation.

Basal cell carcinoma like many other malignancies may also develop secondary to the long-standing ulcers particularly squamous cell carcinomas developing in chronic venous ulcer or even a scar tissue (a burn scar). This can be explained by increased proliferative activity around the ulcer [2]. Carcinomas may arise in open wounds, but also at the site of remitting/relapsing ulcers. Ninety percent of the ulcers were found to be of venous origin or from mixed origin with a venous predominance in a published study. Exophytic irregular growth of the wound edges and/or bed, excess tissue granulation extending beyond the margins, increase in pain or bleeding, absence of healing despite adequate treatment, and unusual extension have also been reported as clinical features of malignant transformation [14, 15] .

24.9 Diagnosis

Although many NMSCs present with classic clinical findings such as nodularity and erythema, definitive diagnosis can only be made by biopsy. Adequate tissue obtained in a nontraumatic fashion is critical to histopathologic diagnosis. Skin biopsies may be performed by shave, punch, or fusiform excision. The type of biopsy performed should be based on the morphology of the primary lesion. A shave biopsy usually is adequate for raised lesions such as nodular BCC, SCC, or tumors of follicular origin. Punch biopsy is effective for sampling flat, broad lesions for which shave or fusiform excision would be technically inappropriate. An excisional biopsy may be used to sample deep dermal and subcutaneous tissue. Excision is appropriate when it is necessary to distinguish between a benign lesion such as a dermatofibroma and a malignant tumor such as a dermatofibrosarcoma protuberans.

24.9.1 Shave Biopsy

A shave biopsy is performed under clean conditions. Local anesthetic (lidocaine 1 % with epinephrine 1:100,000, unless contraindicated) is injected with a 30-gauge needle. The use of a sterilized razor blade, which can be precisely manipulated by the operator to adjust the depth of the biopsy, often is superior to the use of a No. 15 scalpel. After the procedure, adequate hemostasis is achieved with topical application of aqueous aluminum chloride (20 %) or electrocautery.

24.9.2 Punch Biopsy

A punch biopsy is performed under local anesthesia, using a trephine or biopsy punch. The operator makes a circular incision to the level of the superficial fat, using a rotating motion of the trephine. Traction applied perpendicularly to the

relaxed skin tension lines minimizes redundancy at closure. Hemostasis is achieved by placement of simple, nonabsorbable sutures that can be removed in 7–14 days depending on the anatomic site. If the punch biopsy is small and not in a cosmetically important area, the wound is likely to heal very well by secondary intention.

24.9.3 Excisional Biopsy

After local anesthesia has been achieved under sterile conditions, a scalpel is used to incise a fusiform ellipse to the level of deep fat. Hemostasis is obtained with cautery as needed, and the wound is closed in a layered fashion using absorbable and nonabsorbable sutures. In most cases, postoperative care involves daily cleansing with mild soap and water followed by application of antibiotic ointment and a nonstick dressing. Though popular in the past, it is now known that hydrogen peroxide may not have a favorable effect on wound healing.

Several biopsies from both the margins and the wound bed may be required to obtain a definitive diagnosis and may be repeated if clinical suspicion is high. The poor prognosis of malignant transformation of CLU is, at least, partly related to the delay in diagnosis, which is made at the metastatic stage in 30–34 % of cases.

24.10 Treatment

Surgery and radiotherapy appear to be the most effective treatment modalities, with surgery showing the lowest failure rates. Recurrent BCC is more difficult to cure than primary lesions, and surgical excision is the first line of treatment.

24.10.1 Surgical

Excision with primary closure, flaps and grafts: an excision margin of 4 mm around the tumor is recommended where possible, especially for all high-risk BCCs [25].

Mohs micrographic surgery (MMS) is a surgical technique that combines tumor extirpation and microscopic examination of tissue margins by the same surgeon. Beveled excision and careful mapping of the peripheral and deep margins of horizontal frozen sections permits a comprehensive examination of all the borders of the excised tissue and ensures excellent cure rates, exceeding 98 % for most skin cancers. In addition to the high cure rates, Mohs surgery is a tissue-sparing procedure. The need for wide, extensive excision is reduced because of the precise control of tumor margins. This has an important advantage in cosmetically and functionally sensitive areas [26].

24.10.2 History and Evolution of Technique

The Mohs technique is named after Dr. Frederic Edward Mohs, the inventor of the procedure. First introduced in 1936 at the University of Wisconsin, the procedure was initially met with much skepticism and resistance. Most of the early patients treated with Mohs surgery were patients with recurrent tumors who failed other treatments. In 1941, a physician with a mucoepidermoid carcinoma of the parotid gland was originally told that his tumor involved the facial nerve and it would have to be sacrificed. The patient was treated with the Mohs technique in an effort to surgically remove the tumor without losing the nerve. Preservation of the facial nerve was successful, and there was no recurrence of the carcinoma after a 17-year follow-up. The success of this case proved to be a landmark in establishing the legitimacy and usefulness of the Mohs technique.

The original technique involved the topical application of 20 % zinc chloride paste to malignant tissue for 12–24 h, enabling tissue fixation in situ. This was followed by excision of the tumor and histologic examination of frozen horizontal sections. If a margin was positive, the tissue was fixed with zinc chloride paste for an additional 12–24 h, and the tissue was removed for microscopic examination. Hence, the term Mohs chemosurgery was invoked to convey in situ tissue preservation with zinc chloride. Tissue fixation with zinc chloride had its limitations, however: It was time-consuming, laborious, and very painful for the patients. Dense inflammation from in situ fixation obscured tumor cells and made pathologic review of the tissue difficult. The intense inflammatory response caused by the chemical paste also prohibited immediate repair of the defect, and repairs were either delayed or left to heal by secondary intention. In 1953, the technique was changed to incorporate fresh tissue rather than tissue fixed with zinc chloride, which eliminated these problems and reduced the total treatment time to 1 day. There was also significantly less inflammation in the surrounding tissue, which reduced the overall surgical defect size and enabled immediate repair. Patients no longer required hospitalization between the stages of Mohs surgery, and local anesthesia could be used, making this an ambulatory procedure. The Mohs procedure became a more practical and comfortable procedure. This “fresh tissue technique” was later popularized by Drs. Theodore Tromovitch and Samuel Stegman in the early 1970s and is the standard practice today. Mohs micrographic surgery encompasses the key features of the procedure [27]:

- Microscopic control of 100 % of the tissue margin and meticulous cancer mapping of the excised specimen.
- Horizontal sectioning of the extirpated tumor in one plane (as opposed to vertical sections of paraffin-embedded tissue after standard excision).
- Detailed mapping enables the surgeon to have control of the entire tissue margin and re-excision of microscopic tumor extension.

24.10.3 Indications for Mohs Micrographic Surgery

Mohs micrographic surgery is an excellent technique for most cutaneous tumors of the face and body. It is the treatment of choice for primary skin malignancies such as basal cell carcinomas and squamous cell carcinomas that are recurrent, have aggressive features, or with ill-defined margins. Skin tumors in areas that are at high risk for recurrence and deep extension, often called the H-zone of the face, should be treated with Mohs surgery. These areas correlate with embryonic fusion plates and include sites such as the inner canthus, nasolabial fold, nose, periorbital, temple, upper lip and periauricular regions, retroauricular, and chin. The ear also has a high rate of recurrence and is suitable for treatment with Mohs surgery.

Tumors measuring >2 cm in diameter have higher rates of recurrence. Mohs surgery is the treatment of choice for these tumors. Recurrent tumors often have ill-defined margins given the presence of fibrosis from previous interventions. Tumors previously treated with other modalities, including radiation therapy, electrodesiccation and curettage, surgical excision, and cryotherapy, may have subclinical extension when they recur.

Recurrence rates of previously treated tumors are 18 % with excision, 10 % with radiation therapy, 40 % with electrodesiccation and curettage, and 12 % with cryotherapy. Mohs surgery yields the most favorable recurrence rates of 3.4–7.9 %, establishing it as the treatment of choice for recurrent skin tumors. For lesions in cosmetically or functionally important areas such as the nose, eyes, and lips, Mohs surgery is an excellent treatment choice because of the tissue-sparing advantage. The genitalia, digits, and the nipple area are locations with very little tissue laxity. Given the need for tissue preservation, Mohs surgery is the optimal treatment. Cutaneous tumors occurring in immunosuppressed patients should also be treated with Mohs surgery, as these tumors [25–27].

24.10.4 Curettage and Electrodessication

Common methods of skin cancer destruction include curettage and electrodesiccation (C&D) and cryotherapy using liquid nitrogen. C&D is performed under clean conditions with local anesthesia. Visible tumor is first removed by curettage. Curettage is extended for a margin of 2–4 mm beyond the clinical borders of the cancer. Electrodesiccation then is performed to destroy another 1 mm of tissue at the lateral and deep margins. Salasche recommended that C&D be performed for three cycles. Others report satisfactory results after a single cycle of C&D for tumors smaller than 1 cm. Although this leads to decreased scarring, it may lead to higher rates of recurrence, as suggested by Robins and Albom, who attributed to insufficiently aggressive treatment the higher rates of recurrence observed in young women with BCC. Tangential shave excision followed by gentle curettage and cauterization is an effective treatment approach for destruction of superficial BCCs [28].

24.11 Cryosurgery

Cryosurgery exposes skin cancers to subzero temperatures, which causes tissue destruction. Heat transfer occurs from the skin, which acts as a heat sink. Tissue damage is caused by direct effects initially and, subsequently, by vascular stasis, ice crystal formation, cell membrane disruption, pH changes, and thermal shock. Successful cryosurgery requires that temperatures reach −50 to −60 °C, including deep and lateral margins. The subsequent thaw leads to vascular stasis and failure of local microcirculation. The open-spray technique is used most often and requires liquid nitrogen spray delivery from a distance of 1 to 3 cm. With the confined-spray technique, liquid nitrogen is delivered through a cone that is open at both ends. With the closed-cone technique, one end of the cone is closed and a shorter delivery time is required. With the cryoprobe technique, a prechilled metal probe is applied to the tumor. Delivery time is determined via a depth dose estimation, which takes into account freeze time, lateral spread, and halo thaw time. Immediately after cryosurgery, local erythema and edema are apparent. An exudative phase ensues in 24–72 h, which is followed by sloughing at approximately day −7. Complete healing usually is seen with facial lesions at 4–6 weeks and in nearly 12–14 weeks in lesions on the trunk and extremities [29].

Cryosurgery and C&D both are limited by the inability to evaluate thoroughness of tumor eradication. The absence of margin control and the development of dense scar, which might obscure recurrence, make these methods valuable primarily in the care of histologically superficial NMSC. Close follow-up of the patient is necessary.

24.12 Nonsurgical

24.12.1 Topical Treatment

Imiquimod 5 % cream: It is an immune response-modifying agent that has recently been licensed for the treatment of small superficial BCCs. Imiquimod has been shown to achieve clearance rates ranging from 70 to 100 %, but relapse rates appear higher than with other conventional treatments, and there are some difficulties with side effects (e.g., pruritus). It is more effective for superficial than nodular tumors. Topical fluorouracil 5 % cream is useful in the management of multiple superficial BCC on the trunk and limbs with cure rates in the region of 80 %.

Photodynamic therapy (PDT): Involves the use of light therapy in combination with a topical photosensitizing agent to destroy cancer cells. Its use has been well described in the treatment of superficial BCC, and evidence of efficacy is adequate to support its use. The average clearance rate for superficial BCC is about 85 % but is lower in nodular BCC. Advantages of PDT include a low rate of adverse effects and good cosmetic outcome. The disadvantages are that the patient has to be available for a period of at least 3–4 h for treatment and that the photosensitizer and equipment are relatively expensive.

24.13 Radiation Therapy

Radiation therapy (RT) is a treatment option for NMSC but is also limited by the inability to confirm the tumor margins definitively. In addition, treatment of an excessively large area around the tumor carries risk. RT, in properly fractionated doses, generally is indicated when the patient's health or size or extent of the tumor precludes surgical extirpation. Consideration of the permanent tissue effects of RT must include anticipation and management of recurrence. After treatment for BCC or SCC, patients should be evaluated on an annual basis for the presence of skin cancers. In the case of a more aggressive tumor, evaluation should be more frequent and, in the case of squamous cell cancer, should include examination of draining lymph nodes. Laboratory evaluation, generally not indicated in uncomplicated cases of BCC and SCC, may be necessary for other types of particularly aggressive tumors. Imaging studies may be necessary in the case of aggressive tumors or in cases of long-neglected tumors impinging on vital structures. Magnetic resonance imaging allows visualization of the soft tissues, while computed tomography (CT) scan may be used to evaluate involvement of bone. In general, imaging studies have not proven helpful in definitive evaluation of the presence of perineural invasion by NMSCs [30].

References

1. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer: II. Squamous cell carcinoma. Arch Dermatol. 1995;131:164.
2. Chintamani, Shankar M, Singhal V, Singh JP, Bansal A, Saxena S. Squamous cell carcinoma developing in the scar of Fournier's gangrene – case report. BMC Cancer. 2004;27(4):16.
3. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58:185–206.
4. Voisard JJ, Lazareth I, Baviera E, Priollet P. Ulceres de jambe et cancer. A propos de 6 observations. J Mal Vasc. 2001;26:85–91.
5. Brash DE. UV mutagenic photoproducts in *E coli* and human cells: a molecular genetics perspective on human skin cancer. Photochem Photobiol. 1988;48:59.
6. Mitchell DL, Nairn RS. The biology of the (6–4) photoproduct. Photochem Photobiol. 1989;49:805.
7. Ananthaswamy HN, Pierceall WE. Molecular mechanisms of ultraviolet radiation carcinogenesis. Photochem Photobiol. 1990;52:1119.
8. Brash DE, Ziegler A, Jonason A, et al. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. J Invest Dermatol Symp Proc. 1996;1:136.
9. Black HS, deGruijl FR, Forbes D, et al. Photocarcinogenesis: an overview. J Photochem Photobiol B. 1997;40:29. Leffell DJ, Brash DE. Sunlight and skin cancer. Sci Am. 1996;275:52.
10. Zanetti R, et al. The multicentre south European study: skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer. 1996;73:1440.
11. Ziegler A, Leffell DJ, Kunula S, et al. Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. Proc Natl Acad Sci U S A. 1993;90:4216.
12. Hahn N, Woinbwski L, Miller U, Zimmer A. The patched signaling pathway in tumorigenesis and development: lessons from animal models. J Mol Med. 1999;77:459.
13. Ping XL, Ratner D, Zhang H, et al. PTCH mutations in squamous cell carcinomas of the skin. J Invest Dermatol. 2001;116:614.

14. Weninger W, et al. Differences in tumor microvessel density between squamous cell carcinomas and basal cell carcinomas may relate to their different biologic behavior. J Cutan Pathol. 1997;24:364.
15. Miller SJ. Biology of basal cell carcinoma (part I). J Am Acad Dermatol. 1991;24:1.
16. Robinson JK, Dahiya M. Basal cell carcinoma with pulmonary and lymph node metastasis causing death. Arch Dermatol. 2003;139:643.
17. Niazi ZB, Lamberty BG. Perineural infiltration in basal cell carcinomas. Br J Plast Surg. 1993;46:156.
18. Scherbenske JM, et al. A solitary nodule on the chest: fibroepithelioma of Pinkus. Arch Dermatol. 1990;126:955.
19. Muller P, Roul S, Mahe A, Roudier M, Vaque D, Strobel M. Carcinomeepidermoide sur ulcere de jambeaux Antilles. Ann Dermatol Venereol. 2004;131:347–50.
20. Combemale P, Bousquet M, Estival J, Dupin M, le groupe d'Angio-Dermatologie de la Societe Francaisede Dermatologie. Degenerescencecarcinomateuse des ulceres vasculaires de jambe: etude nationale retrospectivede 80 cas. Ann Dermatol Vénéréol. 2004;131:1S67.
21. Coulomb A, Agence Nationaled'Accreditation et d'Evaluation(ANAES). Recommandations pour lapratique clinique. Prise en charge ducarcinome basocellulaire de ladulte. Ann Dermatol Venereol. 2004;131:661–756.
22. Holmkvist KA, Rogers GS, Dahl PR. Incidence of residual basal cell carcinoma in who appear tumor free after biopsy. J Am Acad Dermatol. 1999;41:600.
23. Evans GR, Williams JZ, Ainslie NB. Cutaneous nasal malignancies: is primary reconstruction safe? Head Neck. 1997;3:182.
24. Kumar B, et al. A review of 24 cases of Mohs surgery and ophthalmic plastic reconstruction. Aust N Z J Ophthalmol. 1997;25:289.
25. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. Arch Dermatol. 1987;123:340.
26. Leslie DF, Greenway HT. Mohs micrographic surgery for skin cancer. Australas J Dermatol. 1991;32:159.
27. Rowe DE, Carroll RJ, Day Jr CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol. 1989;15:424.
28. Kopf AW, et al. Curettage-electrodesiccation treatment of basal cell carcinomas. Arch Dermatol. 1977;113:439.
29. Goncalves JC. Fractional cryosurgery. A new technique for basal cell carcinoma of the eyelids and periorbital area. Dermatol Surg. 1997;23:475.
30. Wilder RB, Kittelson JM, Shimm DS. Basal cell carcinoma treated with radiation therapy. Cancer. 1991;68:2134.

Sarcoma of Extremities Presenting as Ulceration

25

Carlo Perisano and Giulio Maccauro

25.1 Introduction

Sarcomas are relative rare malignant tumors arising from the mesenchymal tissue, which encompasses muscles, fat, bone, blood vessels, and fibrous or other supporting tissue [1]. An ulcer is a local defect or excavation of the surface of an organ or tissue characterized by a "full-thickness depth," which implies that there are no sources for reepithelialization left in the center of the ulcer, and a "slow healing tendency" [2].

25.2 Epidemiology

Soft tissue and bone sarcomas are a rare and heterogeneous group of tumors. Sarcomas display a wide variety of histological subtypes and frequently involve the limbs (55 % of cases), especially the lower extremities [3–5].

Although soft tissues and bone comprise 75 % of the average body weight, these neoplasms represent less than 1 % of all adult and 15–20 % of pediatric malignancies. The vast majority of diagnosed sarcomas will be soft tissue sarcomas, while malignant bone tumors make up just over 10 % of sarcomas [6, 7].

The annual incidence in the United States, which remains relatively constant, is approximately 6000–7000 soft tissue and 2500 bone sarcomas. In 2010, the National Center for Health Statistics (NCHS) projected that 10,520 and 2650 Americans, including all ages, will have been diagnosed with soft tissue and malignant bone tumors, respectively. Furthermore, it is also projected that 3920 and 1460 Americans will die in 2010 from soft tissue and malignant bone tumors, respectively [8].

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In SEER data (1973–2008), we observed that soft tissue sarcomas currently occur much more frequently than malignant bone tumors. In 2008, soft tissue sarcomas accounted for nearly 87 % of all sarcomas diagnosed, while the remaining 13 % of the diagnoses were malignant bone tumors. Osteosarcomas and chondrosarcomas were the most commonly diagnosed malignant bone tumors, accounting for over half of all the malignant bone tumor diagnoses. According to SEER, "other specified soft tissue sarcomas" accounted for roughly 51 % of all sarcomas diagnosed in 2008 and clearly lead soft tissue sarcoma occurrence. Fibrosarcomas and Kaposi sarcomas were the two distinct and individual soft tissue subtypes identified and predominantly diagnosed in 2008, accounting for roughly 7 and 9 % of all sarcoma diagnoses respectively. Although soft tissue sarcomas can arise anywhere in the body, the lower extremities are the most common site. Incidence is as follows: lower extremities, 46 %; trunk, 19 %; upper extremities, 13 %; retroperitoneum, 12 %; head and neck, 9 %; other locations, 1 % [9].

Lookingbill et al. retrospectively reviewed data accumulated over a 10-year period from the tumor registry at Hershey Medical Center of 7316 patients; 367 (5.0 %) had cutaneous malignancies. Of these, 38 patients had lesions as a result of direct local invasion, 337 had metastatic lesions, and 8 had both, and the histotype more common were breast, melanoma, lung, and colorectal while sarcomas were rare [10].

Instead a chronic ulceration of the extremities, especially of the lower limb, is a frequent condition, causing pain and social discomfort and generating considerable costs. Prevalence numbers (all ulcers) range from 1 % in the adult population to 3–5 % in the population over 65 years of age [11].

The prevalence of cancer wounds in patients treated for cancers in any anatomical location remain rarely documented [12]. In 2002, Clark estimated the prevalence to be between 5 and 10 % [13]. In one of the most recent studies conducted in Switzerland, the prevalence of metastatic cancers having skin expression was 6.6 % [14].

The presence of a chronic wound can be a significant burden to any person, but when it is related to cancerous infiltration of the skin, it can be a constant reminder of disease progression. It could be the result of a primary cancer or a metastasis to the skin from a local tumor or from a tumor in a distant site, and it most commonly arises from cancer of the breast or head and neck, melanoma, soft tissue sarcoma, and some cancers of the genitourinary system. As the tumor infiltrates the skin, ulcerating and fungating wounds develop. It may take the form of a cavity, an open area on the surface of the skin, skin nodules, or a nodular growth extending from the surface of the skin [15].

25.3 Etiology

Rarely many tumor types, including metastases, may present with skin ulceration as the first symptom. Inside this little group, the sarcomas of extremities presenting as ulceration are very few. Literature analysis does not show article about this topic except case series and cases related to Kaposi sarcoma [16].

The main causes are:

- Fibrosarcoma, primarily or that can also develop secondarily in chronic leg ulcers, especially in ulcers of longer duration, probably as a consequence of the continuously increased cell division in and around the ulcer
- Epithelioid sarcoma
- Lymphosarcoma
- Rhabdomyosarcoma
- Hemangiosarcoma
- MFH
- Synovial cell sarcoma
- Extraskeletal osteosarcoma
- Kaposi and pseudo-Kaposi sarcoma
- Dermatofibrosarcoma protuberans
- Cutaneous ewing sarcoma [16]

25.4 Differential Diagnosis

It's essential to underline that these are very rare causes, therefore the right approach toward patients with extremity ulcers is at the beginning to do a large differential diagnosis to choose the correct treatment because the most leg ulcers are caused by venous insufficiency (approximately 45–60 %), arterial insufficiency (10–20 %), diabetes (15–25 %), or combinations of these well-known etiological factors (10–15 %); decubitus, infection, vasculitis, and other rare underlying causes may exist as a venous insufficiency and dependency,an arterial occlusion,a microcirculatory disorders,a physical or chemical injury,an infectious diseases,a neuropathic diseases,an hematological disorders,a clotting disorders,a metabolic diseases,an ulcerating tumors,an ulcerating skin diseases and a drug reactions [2, 16, 17].

About tumor types that may present with skin ulceration as the first symptom, the two most frequent ulcerating tumors are basal cell carcinoma (ulcus rodens) and squamous cell carcinoma, which may occur anywhere on the body, with a preference for sun-exposed skin, followed by malignant melanoma, metastasis, pseudoepitheliomatous hyperplasia, epithelioma (Marjolin ulcer), lymphoma, leukemia, sarcomatoid renal cell carcinoma, and less frequently by sarcomas [16].

25.5 Pathophysiology and Methods of Dissemination

Unlike carcinomas, bone and soft tissue sarcomas disseminate almost exclusively through the blood. Hematogenous spread of extremity sarcomas is manifested by pulmonary involvement in the early stages and by bony involvement in later stages. Low-grade soft tissue sarcomas have a low (<15 %) rate of subsequent metastasis while high-grade lesions have a significantly higher (>15 %) rate of metastasis [18].

Metastases from sarcomas to regional lymph nodes are infrequent; the condition is observed in only 13 % of patients with soft tissue sarcomas and 7 % of bone sarcomas at initial presentation.

Most high-grade bone and soft tissue sarcomas are bicompartmental at the time of presentation (i.e., they involve the bone of origin as well as the adjacent soft tissues) [18].

The ulcerative extremity sarcomas are caused by infiltration of the epidermis by primary or metastatic tumor; cutaneous infiltration occurs via the lymphatics or bloodstream or as a result of direct invasion from a primary lesion [19].

Sarcomas respect anatomical borders. Local anatomy influences tumor growth by setting natural barriers to extension. In general, sarcomas take the path of least resistance and initially grow within the anatomical compartment in which they arose. In a later stage the walls of that compartment are violated (either the cortex of a bone or aponeurosis of a muscle), and the tumor breaks into a surrounding compartment. Most bone sarcomas are bicompartmental at the time of presentation; they destroy the overlying cortex and extend directly into the adjacent soft tissues. Soft tissue sarcomas may arise between compartments (extracompartmental) or in an anatomical site that is not walled off by anatomical barriers such as the intermuscular or subcutaneous planes. In the latter case, they remain extracompartmental and only in a later stage break into the adjacent compartment until they reach the skin and cause ulceration [20–22].

Local invasion may initially manifest as inflammation with induration, redness, heat, and/or tenderness. The skin may have a peau d'orange appearance and can be fixed to underlying tissue. As the tumor spreads and more tissue destruction occurs, the skin eventually ulcerates. These lesions may initially present as well-demarcated nodules ranging in size from a few millimeters to several centimeters with a changing in pigmentation or can appear are erythematous patches or plaques, violaceous papules and vesicles, or areas of alopecia [19].

Once the fungating or ulcerating wound develops, perfusion of tissues is altered and the mass expands; the center of the tumor becomes hypoxic and leads to tumor necrosis [20] that is an ideal environment for the overgrowth of anaerobic microorganisms, which may result in significant malodor, the vascular and lymphatic flow changing with edema and exudate. Additionally tumor cells secrete growth factors that support the growth of the tumor. The tumor may extend down into deeper structures with development of sinus or fistula formation, common in abdominal and peritoneal wounds [21]. The surrounding skin may be erythematous, fragile, and macerated in the presence of excessive wound exudate [20–22]. The degree of pain experienced by the patient will depend on wound location, depth of tissue invasion and damage, nerve involvement, presence of viable tissue with exposed nerve endings, and the patient's previous experience with pain and analgesia [20–22].

25.6 Symptoms and Signs

They symptoms and signs of sarcomas are nonspecific; they commonly present as a painless, slow-growing mass. These tumors may progress for long periods without causing overt symptoms. Their location deep within the body precludes palpation of

the tumor mass early in the course of the disease; consequently, these tumors often reach tremendous size prior to diagnosis [22].

Ulcerative sarcomas usually present as an ulcerated large solid mass associated with malodor, pruritis, exudate, bleeding, pain, functional limitation, and poor quality of life. Complications such as infection or massive hemorrhage may become life threatening, while fistulas or deep organ exposure may also be observed. Tumor wounds may present with different clinical characteristics, such as cavity wounds and cauliflower-like hypergranulating wounds [3, 22, 23].

25.7 Diagnosis

25.7.1 History and Clinical Examination

To make a correct diagnosis it is essential to know the complete history, underlying etiology-cancer type, past and current treatment of cancer and wounds, the physical status, the psychosocial and quality of life concern, and the nutritional assessment because a poor nutritional status (a common finding in patients with cancer) impairs the ability to maintain skin integrity and to heal wounds. Adequate nutrition with energy, protein, micronutrient, and fluid requirements is essential for healing and plays a pivotal role in the success or failure of the treatment plan [3, 22, 23].

The clinical exam is typical showing the ulcerative lesion especially the neurovascular bundle to avoid the risk of bleeding and compression, the presence of bleeding, infection, malodor, and dimension [3, 22, 23].

25.7.2 Imaging

Advances in imaging technology have significantly changed the way to do diagnosis of bone and soft tissue sarcomas, and some techniques such as X-ray or ultrasonography to study the ulcerated extremity sarcomas have a marginal role [3, 23].

25.7.3 Radiographs

Radiographs have lost the key role that have in the past but it is important for the evaluation of bone tumors and it lets an accurate diagnosis of bone tumors in more than 80 % of cases but as such do not have any value in the evaluation of soft tissue sarcoma [3, 23].

25.7.4 Computerized Tomography (CT)

CT is the imaging modality of choice to evaluate the extent of bone destruction and reaction. In ulcerated sarcomas it has a role to define bone sarcoma and its extension, the extent of bone resection. It is essential to look up pulmonary nodules, masses, and lymphadenopathy or other signs of metastatic disease [24].

25.7.5 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging is the best tool in the evaluation of soft tissue tumors, of the medullary and soft tissue components of bone tumors, of the margins and to stage and characterize the lesion. The signal intensity of a tumor is assessed by comparing it with that of the adjacent soft tissues, specifically skeletal muscle and subcutaneous fat. MRI is useful in evaluating the relationship of a tumor to the adjacent blood vessels and nerve. The presence of orthopedic hardware or surgical clips is not a contraindication to MRI; however, if a lesion is immediately adjacent to the location of the hardware, the local field may be distorted [25]. MRI has been proven to be superior to CT to detect size, extent of a tumor, muscle involvement, and recurrent soft tissue sarcomas [26].

25.7.6 Positron Emission Tomography (PET)

Positron emission tomography (PET) offers a combination of concurrent anatomical and functional imaging findings and in sarcomas have a role for detection of local recurrence and metastatic disease as well as for evaluation of response to neoadjuvant chemotherapy [27].

25.7.7 Radionuclide Bone Scans

Bone scan is currently used to determine the presence of metastatic bone disease and skin metastasis and the involvement of a bone by an adjacent soft tissue sarcoma. In addition, the appearance of a bone lesion in the flow and pool phases of a three-phase bone scan reflects its biological activity and may be helpful in its diagnosis [3, 23].

25.7.8 Angiography

Angiography is useful in these lesions prior to surgery because usually these are high-grade sarcomas with a large involvement of surrounding tissues and extraosseous component, so the vascular displacement or involvement is common. It helps the surgeon to plan the anatomical approach and to avoid excessive bleeding during surgery [18].

25.7.9 Biopsy

An incisional biopsy is gold standard for diagnosis and must be always done before any treatment. In ulcerated sarcoma, it can be very simple to do it. It is useful to repeat

in case of suspected recurrence [3, 23]. All recent skin lesions occurring on a scar or leg ulcer should be biopsied in a repetitive manner when clinical doubt is raised [3].

25.8 Treatment

An ulcerated sarcoma can be an emotional and physical challenge for patients, families, and physician. An interdisciplinary team is required. The treatment usually consists of chemotherapy, radiotherapy, and surgery, with need to do an amputation when not possible to do large excision and reconstruction. Node excision is often deliberated, depending on the histological form and the presence of an invaded sentinel node [28–30].

The treatment of the ulcerated sarcomas consists to treat the primary causes, the patient and family concern and the wound when an excision is not possible; therefore the aim of treatment can be curative or palliative [28]. In this palliative context, wound care should be personalized and reevaluated depending on the needs and the consequences of the wound and the general condition of the patient [29, 30]. Palliative care should be realized by a multidisciplinary approach, combining wound-healing expert nurses, physicians specialized in cancer, pain specialists, and surgeons. Surgeons may adapt the local strategy and propose an adapted closure technique, such as skin grafting for temporary coverage when the wound bed may allow it; or the surgeon can propose a secondary cosmetic surgery for social exigence. Also a palliative intralesional procedure surgery may be performed [31].

25.8.1 Treat the Primary Causes: Medical Options

Radiation, chemotherapy, and hormonal therapy may help to reduce the symptoms associated with malignant wounds and need to be considered. Chemotherapy can relieve tumor symptoms and decrease mass, but the effectiveness depends on the tumor's responsiveness to chemotherapy. Radiotherapy should destroy malignant tumor cells, thereby reducing the size of the wound and alleviating symptoms such as exudates, bleeding, and pain. With radiation treatment wound may initially deteriorate as malignant cells die and skin reactions occur. Hormonal blocking agents are used for hormone-sensitive tumors. The response to these treatments are slow and may take 4–6 weeks before decrease in progression and size of wound is noted [15, 18, 20, 22].

25.8.2 Treat the Primary Causes: Surgery

Surgery can be used occasionally to reduce tumor mass, to debride wound, to extend symptom-free period, and to improve cosmetic appearance. Usually all

ulcerated sarcoma would need to be amenable to complete excision and defect repair, but anytime this may not be possible due to the extent of the disease, health status, healing ability, hemorrhage, and/or involvement of surrounding structures and organs [32].

The improvement in chemotherapy, radiotherapy, imaging, and surgical option in the recent years has led to earlier diagnosis and better preoperative staging and treatment of these patients; these have made limb salvage the procedure of choice than amputation in 85–90 % of patients with limb sarcoma without affecting the survival [32] (Fig. 25.1). Limb salvage surgery is also recommended after a previous surgical procedure although it is associated with a higher rate of inadequate marginal and, consequently, higher local recurrence rates than amputation but should still be attempted whenever possible, as local control is not the primary determinant of survival [33].

Therefore primary amputations as the treatment choice in lower extremity sarcomas are now reduced to <5 % of all patients and <15 % among recurrences while demonstrating a comparable long-term survival. Primary amputation is however investable in extensive circumferential limb sarcoma, multicomponent proximal thigh tumors, extensive skeletal involvement, compromised general condition for a longer procedure, local unfavorable conditions like PVD, or technically difficult reconstructions [34, 35].

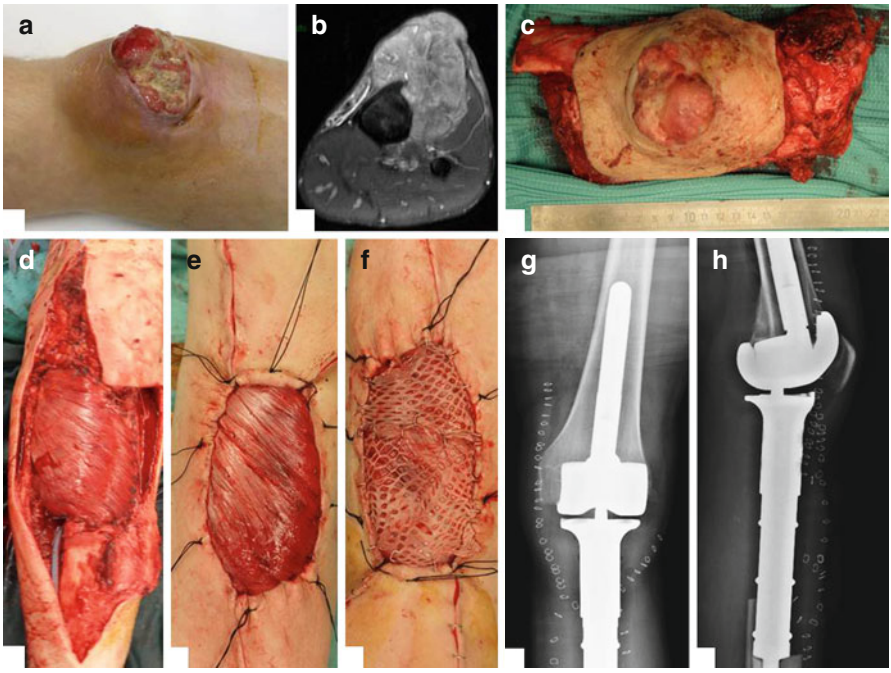

Fig. 25.1 The figure showing the ulcerative pleomorphic sarcoma of the knee (**a**) with its MRI imaging (**b**). The patient underwent an intra-articular resection (**c**) and reconstruction with tibial and femoral mega-prosthesis and gemellus muscle flap with skin graft (**d**–**f**). Anteroposterior and latero-lateral postoperative X-ray of the leg (**g**, **h**)

The surgical management of bone sarcomas is a real challenge to the orthopedic surgeon, owing to the diversity of sites in which tumors arise, combined with the extension of the tumor into adjacent soft tissues and their proximity, in many cases, to major neurovascular structures. The aim of treatment is local control and if possible the salvage of the limb and its function [32–35].

A wide (en bloc) resection entails removal of the tumor and its pseudocapsule, and a cuff of normal tissue peripheral to the tumor in all directions should be the objective. The adequate thickness of the normal tissue cuff is a controversy and it is generally believed to be a few centimeters, while an amputation is required when a wide resection is not possible [36].

The choice of the method of reconstruction should be individualized based upon many factors including the patient's age, the extent and location of the tumor, the wishes of the patient, and the availability of surgical facilities and expertise, as well as the cost of the procedure. There's a lot of choice including expandable and nonexpandable tumor prostheses, vascularized fibula, autograft, and allograft [37–40].

In the ulcerative sarcoma, performing a wide resection is needed lose skin and soft tissue, but an adequate soft tissue cover is cardinal in restoring function and should obliterate the dead space, tension-free skin closure, supporting the preserved skin with underneath muscle flaps and provide adequate cushion for exposed bony prominences or amputation stumps [41] (Fig. 25.2).

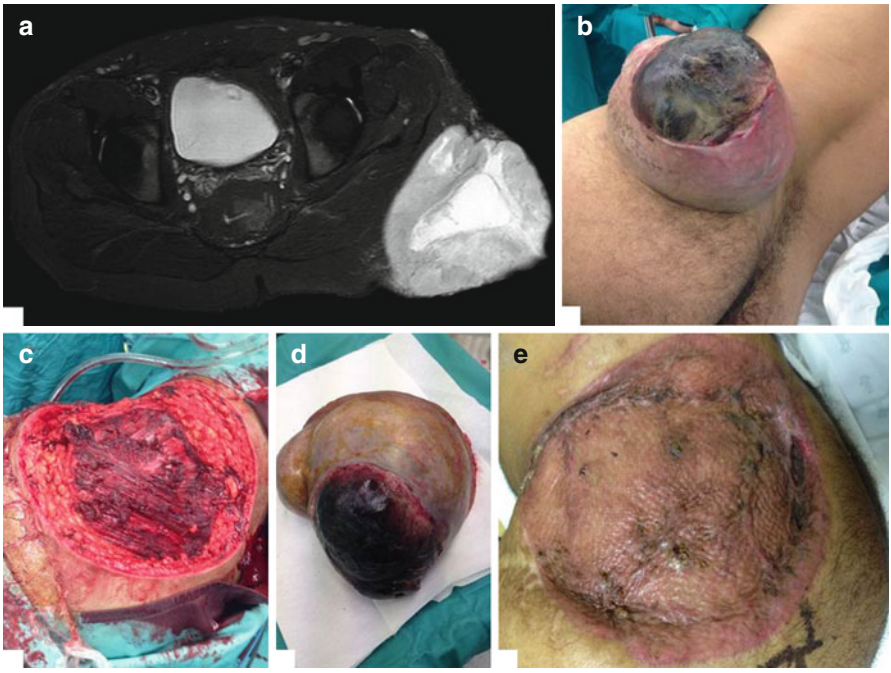

Fig. 25.2 Figure showing a huge ulcerative synovial sarcoma of the pelvis with its MRI imaging (**a**, **b**) treated with an en bloc resection (**c**, **d**) VAC therapy and skin graft (**e**)

Standard procedures that are available include skin grafting for superficial defect closure, whereas vacuum-assisted closure therapy poses an option for temporary defect closure. Immediate coverage is the preferred choice, but it is not a must [41].

A wide variety of pedicled or free vascularized flaps are available for reconstruction in the whole musculoskeletal system. These include the lateral arm flap, scapula/parascapular flap, radial forearm flap, anterolateral thigh flap, free fibula flap, latissimus dorsi flap, rectus abdominis flap, gracilis flap, free filet flap, the medial femoral condyle periosteal bone flap, or various perforator flaps [42, 43]. Perforator or fasciocutaneous flaps are superior to skin grafts but inadequate to cover large defects, and donor site skin graft in the immediate vicinity is a disadvantage [41].

Unfortunately a patient with ulcerated sarcoma needs neoadjuvant and adjuvant chemotherapy and radiotherapy that can higher the rate of failure of the skin graft and flap because it reduces the vascularization and increases the fibrosis and inelasticity of the surrounding skin [21].

25.8.3 Treat Patient/Family Concerns

It is important for a right management of the pain, to value the impact on the patient and on his family of the pathology and to address psychological issues and coping strategies.

25.8.4 Treat the Wound

The aim of this treatment is to manage with primary dressing symptoms such as odor, bleeding, and pain and with secondary dressings to contain exudate. It is important for the right management of the ulcer that these medications are accessible and easy to use with a few dressing changes and an appropriate social support to decrease stress and anxiety at home [44–46].

25.8.5 Cleansing

Cleansing may be proposed in cancer wounds, as in any wound type, using water or physiological saline solution. Showering under tap water is also encouraged for the comfort of the patient and to decontaminate the wound and the surrounding skin. Low-pressure hydrojets may provide a more efficient cleansing, without causing pain or discomfort [47, 48].

25.8.6 Exudate Management

When exudates are moderate and the skin lesion is fresh (ulcerated nodules), the medication have the aim to prevent dressing adherence, bleeding, and crust formation or to hydrate skin which is fragile by the underlying tumor; nonadherent contact layers,

amorphous hydrogels, sheet hydrogels, hydrocolloids, and semipermeable films may be useful [49]. When exudates are more excessive, we must absorb and contain exudates to prevent dressing adherence; this can be obtained using hydrofiber or alginate dressings, foams, starch copolymers, gauze, soft cotton pads, or multilayer dressings to increase the absorption capacity [49]. In the terminal phase, negative pressure therapy may be of interest, with a minimal pressure of 40–50 mmHg, in order to increase the drainage capacities and limit the number of dressing changes. Apart from this exceptional situation, negative-pressure therapy is contraindicated in tumor wounds as it has been reported to promote proliferation of tumor cells [50].

25.8.7 Bleeding Control

A slow capillary bleeding can be treated with alginates, silver nitrate, topical thrombin, gel foam, oxidized cellulose, collagen materials, tranexamic acid, sulfracrate paste, fibrinolytic inhibitors, or adrenalin diluted in saline (1:10) applied over the surface of the wound. When bleeding is provoked by dressing removal in spite of the gel formed by hydrofibers or alginate, Vaseline interface dressings or non-Vaseline interfaces, such as Mylar film, may be applied. If the lesion is associated to a major bleeding, then hemostatic radiotherapy, surgery cauterization or ligation, and embolization may be used. It is important to monitor hemoglobin to ensure anemia has not developed with persistent moderate to heavy bleeding [51, 52].

25.8.8 Infection and Odor Control

Infection and odor control is achieved by managing local bacterial colonization with an accurate wound cleansing and debridement, use of topical (efficacy only for superficial bacteria) and oral metronidazole or other antimicrobial agents, charcoal dressings placed above the primary dressing to adsorb the offensive volatile compounds, and Iodosorb gel [53]. Topical preparations may be most effective due to the decreased perfusion and vasculature throughout malignant wounds which decreases the effectiveness of systemic therapy. The silver sulfadiazine is used to control pseudomonas infection. Avoid antiseptics such as hydrogen peroxide, povidone iodine, and sodium hypochlorite, as they may cause tissue damage and pain. Consider use of slow-release iodine products, i.e., Iodosorb. Consider use of specialized antimicrobial dressing to control infection at site [13, 54–56].

25.8.9 Perilesional Skin Care

It is essential to preserve peri-wound skin integrity with an attention prevention of pruritus, maceration, irritation and an adequate hydration using non-adherent fixing systems, or silicone adhesives applied without any tension over a limited surface [44, 45].

25.8.10 Pain Control

Pain management cannot be limited to local treatments. Pain has to be managed with oral therapy such as morphine or hydromorphone. There is also limited evidence to support the use of topical opioids and other analgesics because peripheral opioid receptors should be present [12, 15].

Secondary pain has to be avoided during the dressing changes. Hypnoanalgesia, MEOPA (mélange équimolaire d'oxygène et de protoxyde d'azote), general anesthesia, and techniques of local anesthesia for dressing changes may be used [57].

Locally, combined lidocaine/prilocaine or lidocaine is used with limited effect, linked to the low penetration of the product. In clinical practice, morphine mixed with hydrogel at a dosage between 10 and 30 mg for 15 g of gel can be applied and has been reported to be beneficial [58–60].

References

1. Perisano C, et al. Misdiagnosis of soft tissue sarcomas of the lower limb associated with deep venous thrombosis: report of two cases and review of the literature. BMC Musculoskelet Disord. 2013;14:64.
2. Baker SR, et al. Epidemiology of chronic venous ulcers. Br J Surg. 1991;78:864–7.
3. Ilaslan H, et al. Clinical presentation and imaging of bone and soft-tissue sarcomas. Cleve Clin J Med. 2010;77 Suppl 1:S2–7.
4. What is sarcoma? http://www.sarcoma.org.uk/what-is-sarcoma
5. Simon MA, Springfield D. Surgery for Bone and Soft-Tissue Tumors. Philadelphia, PA: Lippincott-Raven; 1998. p. 198–200.
6. Burningham Z et al. The epidemiology of sarcoma. Clin Sarcoma Res. 2012. doi: 10.1186/2045-3329-2-14.
7. SEER*Stat Database: incidence – SEER 9 regs research Data, Nov 2010 Sub (1973–2008)<Katrina/Rita Population Adjustment>– Linked To County Attributes – Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission. Surveillance, Epidemiology, and End Results (SEER) Program (http://www.seer.cancer.gov)
8. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK, editors. SEER cancer statistics review, 1975–2008. National Cancer Institute. Bethesda; http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site. 2011.
9. Perisano C, et al. Soft tissue metastases in lung cancer: a review of the literature. Eur Rev Med Pharmacol Sci. 2012;16(14):1908–14.
10. Lookingbill DP, et al. Skin involvement as the presenting sign of internal carcinoma. J Am Acad Dermatol. 1990;22:19–26.
11. Ryan TJ. The epidemiology of leg ulcers. In: Westerhof W, editor. Leg Ulcers: Diagnosis and Treatment. Amsterdam: Elsevier Science Publishers BV; 1993.
12. Dowsett C. Malignant fungating wounds: assessment and management. Br J Nurs. 2002;7:394–400.
13. Clark J. Metronidazole gel in managing malodorous fungating wounds. Br J Nurs. 2002;11(6 Suppl):S54e–60.
14. Probst S, et al. Malignant fungating wounds: a survey of nurses' clinical practice in Switzerland. Eur J Oncol Nurs. 2009;13:295–8.

15. Haisfield-Wolfe ME, Rund C. Malignant cutaneous wounds: a management protocol. Ostomy Wound Manage. 1997;43(1):56–60.
16. Mekkes JR, et al. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148:388–401.
17. Khan AF, et al. Prevalence and presentation of chronic venous disease in Pakistan: a multicentre study. Phlebology. 2013. doi:10.1258/phleb.2012.011122.
18. Shmookler B et al. Bone and soft-tissue sarcomas: epidemiology, radiology, pathology and fundamentals of surgical treatment. Musculoskeletal cancer surgery. 2001. p. 3–35. doi: 10.1007/0-306-48407-2_1
19. Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol. 1995;33:161–82.
20. Collier M. The assessment of patients with malignant fungating wounds – a holistic approach: part 1. Nurs Times. 1997;93(suppl):1–4.
21. Grocott P, Cowley S. The palliative management of fungating malignant wounds – generalising from multiple case study data using a system of reasoning. Int J Nurs Stud. 2001;38:533–45.
22. Naylor W. Assessment and management of pain in fungating wounds. Br J Nurs. 2001;10 Suppl 22:S33–6.
23. Eary JF, Conrad EU. Imaging in sarcoma. J Nucl Med. 2011. doi:10.2967/jnumed.111.092999.
24. White LM, Buckwalter KA. Technical considerations: CT and MR imaging in the postoperative orthopedic patient. Semin Musculoskelet Radiol. 2002;6:5–17.
25. Wu JS, Hochman MG. Soft-tissue tumors and tumorlike lesions: a systematic imaging approach. Radiology. 2009;253:297–316.
26. Chan WP. Magnetic resonance imaging of soft-tissue tumors of the extremities: a practical approach. World J Radiol. 2013;5(12):455–9.
27. Blodgett TM, et al. Issues, controversies, and clinical utility of combined PET/CT imaging: what is the interpreting physician facing? AJR Am J Roentgenol. 2005;184 Suppl 5:S138–45.
28. Grocott P. The management of fungating wounds. J Wound Care. 1999;8:232–4.
29. Maida V. Wound management in patients with advanced illness. Curr Opin Support Palliative Care. 2013. doi:10.1097/SPC0b013e32835c48e5.
30. Ferris FD, et al. Palliative wound care: managing chronic wounds across life's continuum: a consensus statement from the International Palliative Wound Care Initiative. J Palliat Med. 2007;10:37–9.
31. Meaume S, et al. Neoplastic wounds and degenerescence. J Tissue Viability. 2013. doi:10.1016/j.jtv.2013.07.001.
32. Wafa H, Grimer RJ. Surgical options and outcomes in bone sarcoma. Expert Rev Anticancer Ther. 2006;6(2):239–48.
33. Gaston CL, et al. Is limb salvage surgery safe for bone sarcomas identified after a previous surgical procedure? Bone Joint J. 2014;96-B(5):665–72.
34. Papagelopoulos PJ, et al. Current concepts for management of soft tissue sarcomas of the extremities. J Surg Orthop Adv. 2008;17:204–15.
35. Daigeler A, et al. Proximal major limb amputations: a retrospective analysis of 45 oncological cases. World J Surg Oncol. 2009;7:15.
36. Dion N, Sim FH. The use of allografts in musculoskeletal oncology. Instr Course Lect. 2002;51:499–506.
37. Capanna R, et al. A new technique for reconstructions of large metadiaphyseal bone defects: a combined graft (allograft shell plus vascularized fibula). Orthop Traumatol. 1993;2:159–77.
38. Scoccianti G, et al. The use of osteo-articular allografts for reconstruction after resection of the distal radius for tumour. J Bone Joint Surg Br. 2010;92(12):1690–4.
39. Chang DW, Robb GL. Recent advances in reconstructive surgery for soft-tissue sarcomas. Curr Oncol Rep. 2000;2:495–501.
40. Chen CM, et al. Reconstruction of extremity long bone defects after sarcoma resection with vascularized fibula flaps: a 10-year review. Plast Reconstr Surg. 2007;119:915–24.
41. Kadam D. Limb salvage surgery. Indian J Plast Surg. 2013;46(2):265–74.

42. Saint-Cyr M, et al. Free tissue transfers and replantation. Plast Reconstruct Surg. 2012;130:858e.
43. Choudry UH, et al. The vascularized medial femoral condyle periosteal bone flap for the treatment of recalcitrant bony nonunions. Ann Plast Surg. 2008;60(2):174–80.
44. BC Cancer Agency. Malignant wound care guidelines. 2001; http://ww.bccancer.bc.ca.
45. Barton P, Parslow N. Caring for oncology wounds- management guidelines. 1998. http://www.worldwidewounds.com.
46. Cartwright A. Nutritional assessment as part of wound management. Nursing Times. 2002;98(44):62–3.
47. Collier M. Management of patients with fungating wounds. Nurs Stand. 2000;15(11):46–52.
48. "Care of malignant wounds" BCCA guidelines. 2004. http://www.bccancer.bc.ca/.
49. Seaman S. Dressing selection in chronic wound management. J Am Podiatr Med Assoc. 2002;92:24–33.
50. Ford-Dunn S. Use of vacuum assisted closure therapy in the palliation of a malignant wound. Palliat Med. 2006;20(4):477–8.
51. Cihoric N, et al. Clinically significant bleeding in incurable cancer patients: effectiveness of hemostatic radiotherapy. Radiat Oncol. 2012;7:132.
52. Lund-Nielsen B, et al. Qualitative bacteriology in malignant wounds – a prospective, randomized, clinical study compare the effect of honey and silver dressing. Ostomy Wound Manage. 2011;57:28–36.
53. Seaman S. Management of malignant fungating wounds in advanced cancer. Semin Oncol Nurs. 2006;22:185–93.
54. Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010;19(208):210–2, 214–5.
55. Ashford RFU, et al. Metronidazole in smelly tumours. Lancet. 1980;1:874–5.
56. Patterson DR, et al. Hypnotherapy as a treatment for pain in patients with burns: research and clinical considerations. J Burn Care Rehabil. 1987;8:263–8.
57. Greengrass RA, Duclas Jr R. Paravertebral blocks. Int Anesth Clin. 2012;50:56–73.
58. Krajnik M, et al. Potential uses of topical opioids in palliative care – report of 6 cases. Pain. 1999;80:121–5.
59. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. J Pain Symptom Manage. 2003;25:547–54.
60. Vernassier C, et al. Study to determine the efficacy of topical morphine on painful chronic skin ulcers. J Wound Care. 2005;14:289–93.

Grafts and Flaps for the Lower Limb

26

V. Bhattacharya and Siddhartha Bhattacharya

26.1 Introduction

The major defects of lower limb of different magnitude are frequently encountered, and majority of them require reconstruction. Such wounds fall into two categories, acute deep wounds and those which have not healed within 6 weeks, i.e., chronic wounds. The common causes are trauma, infection, postexcisional defect, venous ulcer, trophic ulcer, etc. For the consideration of resurfacing, they are divided into those requiring split skin grafts (SSG) and the others which need a flap. Before coverage, an acute wound needs to be free of devitalized tissue and foreign bodies through adequate surgical debridement and cleaning with normal saline under proper light in the operation theater. Similarly a chronic defect should be free of infection which can be achieved by debridement and regular dressing. The wound swab is sent for culture and sensitivity, and accordingly a suitable antibiotic is administered. The defect is then assessed in terms of size, contour, and exposed vital structures. It is also necessary to evaluate whether the defect needs only SSG, flap, or combination of them. Accordingly the decision is made regarding the type of reconstruction. The aim is to have functional and aesthetic outcome preferably in a single stage with minimal donor site morbidity. If it is noncontoured surface defect, split skin graft is indicated. If the underlying vital structures are exposed, e.g., bone and joints, tendons, neurovascular bundle, exposed hardware following bony fixation, etc., a flap cover is needed. Sometimes part of the wound requires a flap and the rest can be managed by SSG (Fig. 26.1).

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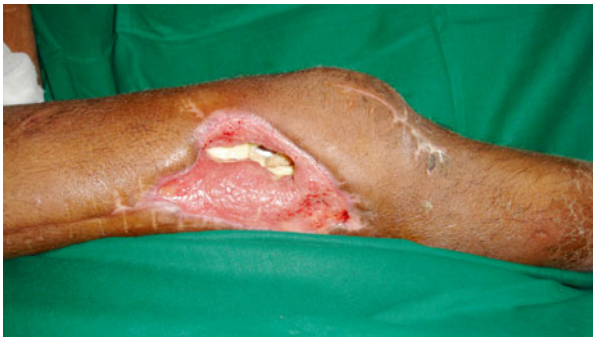

Fig. 26.1 Wound around knee where exposed bone require a flap and rest can be managed by split skin graft

26.2 Split Skin Graft

For below-knee defect, ipsilateral thigh is the preferred donor site as the patient can use the other limb for routine work during the immediate postoperative period. If only one sheet of graft is necessary, it should be harvested from the posterior aspect of the thigh. This will avoid any scar in the future on the more visible areas of the thigh. After cleaning and draping, the SSG is first harvested if the size of the wound is known. A chronic wound is thoroughly scraped by the back of the knife till punctate bleeding appears. Long-standing ulcers should be excised judiciously till the healthy tissue all around to ensure proper "take" of the graft. A hot swab is kept to maintain hemostasis. After few minutes it is removed using normal saline sprinkle. Multiple perforations are made on the graft with No. 15 surgical blade to prevent hematoma underneath. The wound is finally washed with normal saline. The graft is secured over the wound by catgut/Vicryl stitches or stapler. In contoured defect it is preferred to apply several quilting stitches through the graft to the bed to obliterate the dead space and to avoid tenting of the graft. Through the perforations, saline is pushed with a syringe to remove micro clots. A nonadhesive firm dressing is applied for proper contact between the graft and the bed. The first dressing is opened after 2–3 days. A pink graft without hematoma and infection confirms the "take" of the graft. The donor site is opened around 3 weeks once it has epithelialized.

26.3 Flaps

The indications for resurfacing a wound with a flap are as follows: exposed (a) vital structures, e.g., bone and joint, tendon, neurovascular bundle, etc., (b) exposed hardware following orthopedic surgery for fracture fixation, and (c) contour defect. There could be two types of flaps, locoregional flap and free flap through microvascular transfer. This chapter deals with the former procedures. The choice of nature

and constituent of the flap also depend upon the abovementioned types of defect and the availability of healthy adjacent tissue [1].

The available flaps are fasciocutaneous, adipofascial, fascial, muscle, musculocutaneous, and a combination of them [2]. Fasciocutaneous flap is the commonest choice as it is reliable and stable. It consists of skin, subcutaneous tissue, and deep fascia. The adipofascial flap consists of adipose tissue and deep fascia [3]. The fascial flap has only deep fascia. As the flap becomes thinner, the incorporation of vascular arcades is reduced. Therefore, their safe dimension is also reduced. Hence, the planning of the flap prior to surgery is of utmost importance. The planning includes decision regarding the constituent, vascular basis, plane of dissection, mode of transfer, donor site morbidity, and postoperative care.

For the choice of flap, the non-weightbearing areas of the limb and weightbearing areas of the heel and sole should be considered separately because the requirements are different. For defects over the non-weightbearing areas from the knee to foot, fasciocutaneous flap is preferred as larger dimension of tissue can be transferred and it is most stable. The donor site usually needs skin graft. For noncontoured defects and exposed Achilles tendon, adipofascial flap provides good result. The donor area is sutured primarily. For defects over the areas where subcutaneous tissue is less, e.g., shin of tibia, malleoli, etc., fascial flap is considered so that the flap does not look bulky. Both the adipofascial and fascial flaps require SSG over them, and the donor site is sutured primarily. The gastrocnemius muscle flap is useful for contour defects of upper third of the leg and knee. Sometimes a split muscle flap is a choice to reduce the bulk and to preserve the functional unit in an already traumatized leg. Soleus muscle is also used for upper and middle third defects. These muscle flaps require SSG to cover them. Myocutaneous flaps can also be designed based on either head of gastrocnemius; however, they are bulky and not aesthetic. Any flap which proves to be bulky can be debulked in a secondary procedure after few months.

For weightbearing areas of heel and sole, the requirement is different. The adipofascial and fascial flaps are not suitable as they do not withstand the wear and tear of daily life. The flap is decided on the location of the defect, its dimension, and condition of the adjacent tissue. If it is around 2–4 cm, a local flap of similar tissue is ideal with primary closure of the donor site. It can be rotation, transposition, V–Y advancement, or bilobed flap. If it is a deep posttraumatic or trophic ulcer at the heel up to 4 cm, muscle flaps of the first layer of the sole can be turned over and SSG is applied. These muscles are abductor digiti minimi, flexor digitorum brevis, and abductor hallucis. The donor site of muscle exposure is closed primarily. If the defect is larger, more than one muscle can be transferred. If the defect over the heel involves whole of the heel, an inferiorly based fasciocutaneous flap is designed from the proximal calf area and rotated 180° to cover the defect. Large inferiorly based fasciocutaneous flap can resurface almost two third of the sole or dorsum of foot. The sural neurocutaneous flap is the other choice for the heel and other adjacent defects. If ipsilateral calf tissue is not available, a cross-leg flap can be designed.

26.4 Vascular Basis of the Flaps

It has two aspects: (a) vascular arcades within the different constituents of flap and (b) perfusing vessels through which blood reaches to the tissue from the main vascular trunk. Earlier main vascular trunk used to be sacrificed to transfer the tissue to the defect. Now with better understanding of vascularity, the tissue is transferred based on the small vessels arising from the main vessel called "perforators." These perforators are of two types: (a) musculocutaneous, when it courses through the muscle, e.g., gastrocnemius, and then enters the subfascial surface of the deep fascia, and (b) septocutaneous, when it traverses through the septum in between the muscle bellies before entering the deep fascia [4]. The third type of vessel is the (c) direct cutaneous artery which arises from the main vascular trunk and directly enters the subcutaneous tissue. The perforators then arborizes into the rich vascular network on the subfascial surface of the deep fascia which subsequently passes through the deep fascia in the intrafascial course to form the suprafascial plexus [5]. Further it communicates with the subcutaneous plexus and then with the subdermal and dermal network [6]. Thus, it is a continuous rich arcade through different layers of tissue. This is the vascular basis of different constituent of flap [7].

26.5 Hemodynamics of Flaps

It is of utmost importance to understand the hemodynamic of flap for the successful tissue transfer. Vascular plexuses of different layers of tissue play important part in the success of flap transfer. Earlier the deep fascia was supposed to be an avascular structure with only function of covering the muscle underneath to prevent herniation. Now the vascular anastomosis of the deep fascia in one of the dominant systems is well established. The musculocutaneous and septocutaneous perforators first make rich plexus at the level of deep fascia as they perforate on their way to the superficial layers of anastomotic channels. That is why incorporation of deep fascia provides significant enhancement to vascularity. Each perforator has a territory of anastomotic network called "angiosome." The perforators of different dimensions are present at regular interval of 3–4 cm [8]. Their angiosomes communicate freely to form a continuous vascular arcade throughout the limb [9]. The amount of blood flowing through a perforator is directly proportional to the internal diameter [10]. Depending upon the perfusion pressure of a perforator, blood is pushed in to the vascular network. Thus, several adjacent angiosomes will be perfused by a single perforator. It is important to understand this mechanism because while dissecting a flap, several perforators are severed and the flap gets its blood supply through one or two perforators those have been incorporated in the pedicle of the flap.

26.6 Vascular Axis

There are three major vascular axes in the lower limb, namely, anterior tibial, posterior tibial, and peroneal. Several perforators arise from them. With the advancement of technology in the form of audio Doppler, color Doppler,

two-dimensional and three-dimensional CT angiography, etc., these perforators can be precisely identified and measured from fixed bony landmarks. Their internal diameter can be gauged based on which they are classified into three categories: group-1, up to 1 mm; group 2, 1.1–2 mm; and group 3, more than 2 mm. The constituent of the flap decides which vascular networks have been incorporated. For example, fasciocutaneous flap contains subfascial, suprafascial, subcutaneous, subdermal, and dermal plexus [11]. In adipofascial flap, subdermal and dermal network are not included. In fascial flap, only the subfascial and suprafascial network remains. Therefore, the fasciocutaneous flap has larger safe dimension followed by adipofascial flap and then fascial flap. In myocutaneous flap, the underlying muscle is also incorporated and the overruling fasciocutaneous unit receives the blood supply through the musculocutaneous perforators. Muscle flap is used based on the blood supply of a particular muscle. Regarding mobility of the flap, it is necessary to understand that the thicker the flap, the less is the mobility. Accordingly transfer of tissue has to be calculated. Therefore, it has bearing on the measurement of flap while planning. Similarly flap with broader base will have less mobility. With advanced knowledge of the perforators, the base can be substantially narrowed with much greater mobility. This allows increased reach of the flap to reconstruct distant defects.

After deciding the blood supply, the dimension of the flap is calculated depending upon the defect. For small to moderate size defect, a single flap may be sufficient. For larger defect, two or three flaps can be designed perfused by different perforators of the same vessel or different vessels. All these decisions are based on accurate planning and measurement of the defect and flap; otherwise, the flap may fall short. If the calculation is compromised, then the surgeon dissects toward the base of the flap, endangering the vascularity due to probable damage to the perforator and sutures under tension. It may also cause acute kinking at the base. Thus, the vascularity may be compromised leading to part or complete necrosis of the flap.

26.7 Practical Techniques for Flaps

The following steps need to be followed in every type of tissue transfer:

(a) If it is a perforator-based flap, then the location of the perforators should be identified preoperatively which is most commonly done by audio Doppler.
(b) A meticulous “planning in reverse” is done so that the transferred tissue does not fall short of defect in every dimension. It is done with the help of a piece of lint prior to surgery. The lint is kept as if the flap has been transferred over the defect. The pedicle is held by the assistant, and the lint representing the flap is moved to the donor site. The outline of the flap is marked on the donor site one centimeter beyond on the three sides of the proposed flap. This is to take into account the tissue contractility. The transfer is then rechecked holding the pedicle fixed. This certainly ensures correct planning.
(c) The incision is beveled outward specially where multiple tissue constituents are incorporated. Following such incision, all the layers come to the margin at the

same level. Then they are secured by 3/0 chromic catgut interrupted stitches as one unit. For example, in fasciocutaneous flap, the deep fascia is sutured to the dermis. This prevents shearing movement between individual planes during dissection and transfer of the flap. Thus, the composite vascular network within the flap is preserved allowing free flow of blood without interruption.

(d) The plane of dissection needs to be identified in the initial phase of dissection which should be maintained throughout.

(e) Several perforators will be encountered as the flap is raised. They need to be severed. While doing so, low coutary may be used toward the main vascular trunk but the end toward the flap should be ligated using 4/0 chromic catgut/Vicryl. Even apparently small looking charring on the flap surface due to cautery may prove to be detrimental for a small segment of flap.

(f) Whenever a flap is moved more than 90° over a pivot point, acute twist should be prevented. This can be achieved by narrowing the pedicle or by raising little longer flap or skeletonizing the perforator.

(g) Avoid suturing under tension. It is preferred to keep a drain under the flap to avoid hematoma.

(h) Low molecular weight dextran is infused during flap elevation and continued for 2 days to enhance microcirculation.

(i) The limb is kept elevated by 30° for better venous drainage.

26.8 Few Common Flaps

26.8.1 Fasciocutaneous Flap

Constituent wise it consists of skin, subcutaneous tissue, and deep fascia. Majority of moderate-sized defects from knee to foot can be resurfaced by these procedures. For simple understanding of the reconstructive options, the lower limb is divided into upper, middle, and lower third. For upper and middle third, superiorly based (antegrade) flaps based on the perforators of the posterior tibial artery (on medial side) or from the anterolateral aspect based on the perforators of the peroneal artery are used. These flaps are transferred to the defect by rotation or transposition or combination of both. Inferiorly based flaps (retrograde) perfused by the distal perforators of the abovementioned vascular trunks are used for distal third leg (Fig. 26.2), ankle (Fig. 26.3), heel (Fig. 26.4), midsole, and dorsum of foot defects [12]. It is essential to incorporate at least two sizable perforators in the pedicle to ensure adequate blood supply, irrespective of the nature of the flap, that is, how a flap of nonconventional dimension can be transferred with safety. Sometimes there may be intervening normal tissue, and the flap has to reach the defect crossing over this bridge of tissue. It is called "interpolation flap." In such situation, the pedicle is detached after 3 weeks under local anesthesia, and proximal insetting of the flap is done.

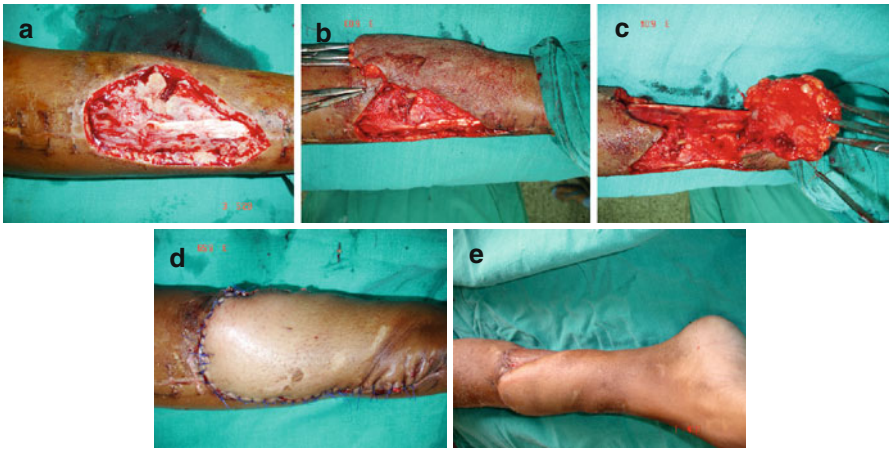

Fig. 26.2 (**a**) Mid and distal third defect with exposed tibia. (**b**) and (**c**) Flap dissected on distal posterior tibial perforatord. (**d**) Flap transfered to the defect. (**e**) Followup of healed flap at 3 months

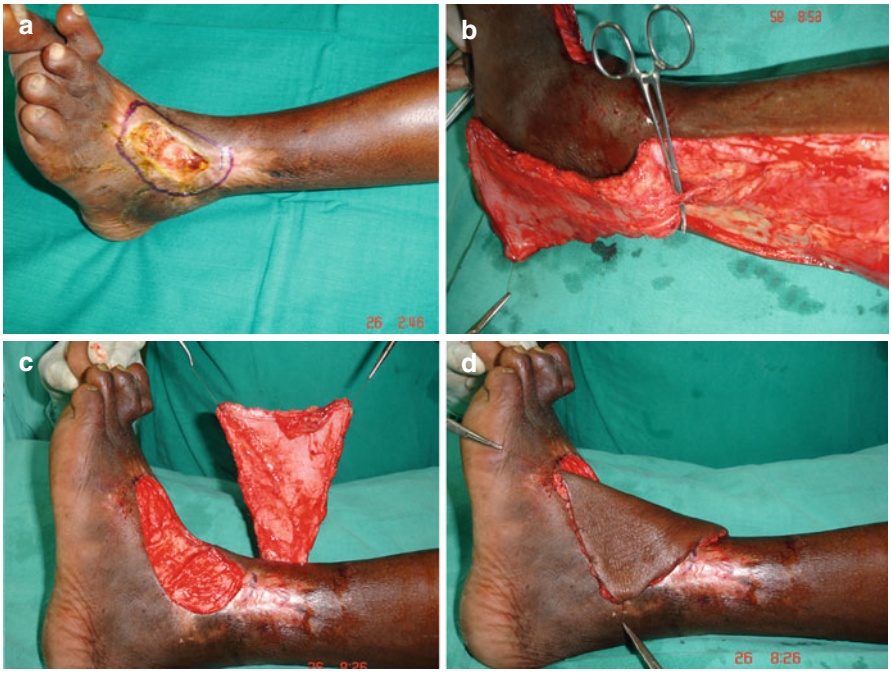

Fig. 26.3 (**a**) Post traumatic anterior ankle defect. (**b**) Reconstructed by distal posterior tibial perforator perfused fasciocutaneous flap. A sizable distal perforator has been isolated. (**c**) Allowing narrowing of the pedicle. (**d**) Enhancing the mobility of flap transfer

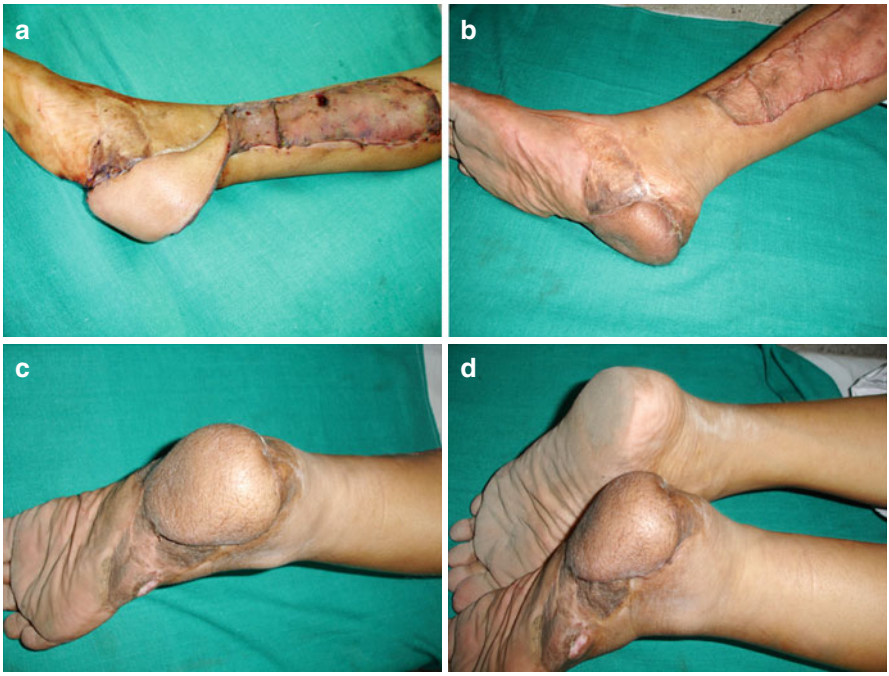

Fig. 26.4 (**a**) A retrograde interpolation fasciocutaneous flap. (**b**) Flap transferred to the post traumatic heel defect. The pedicle has been narrowed allowing 180° rotation. (**c**) After detachment. (**d**) The contour has been well achieved as compared to the normal heel

26.8.2 Adipofascial Flap

They are usually defect-based turnover flap. When the skin of the fasciocutaneous unit is not incorporated, it becomes an adipofascial flap. So it is composed of subcutaneous tissue and deep fascia. Thus, it will have two plexuses less than that of a fasciocutaneous flap, i.e., dermal and subdermal plexuses. Only the vascular plexus associated with the deep fascia and subcutaneous tissue supply this flap. The skin is undermined by a lazy "S" incision. It is important to keep two to three fat globules with the skin to protect the subdermal plexus [13]. This prevents marginal desquamation of the sutured donor site. After adequate undermining, the incision is made on three sides of the proposed flap through the subcutaneous tissue and deep fascia. This composite tissue is dissected through the subfascial plane toward the defect. The dissection stops at a distance of about equal to the width of the defect or at least 2 cm from the proximal margin of the defect. This is to protect the perforators at the base. The flap is then gently hinged to the defect [14]. To prevent acute kink during base turnover, a plane rubber catheter is placed at the base to ensure smooth rolling over. The flap is sutured to the margins of the defect. Thus, the subfascial surface faces on the surface. A perforated thin split skin graft is used to resurface it. The donor site is sutured primarily (Fig. 26.5). It is the flap of choice on many occasions.

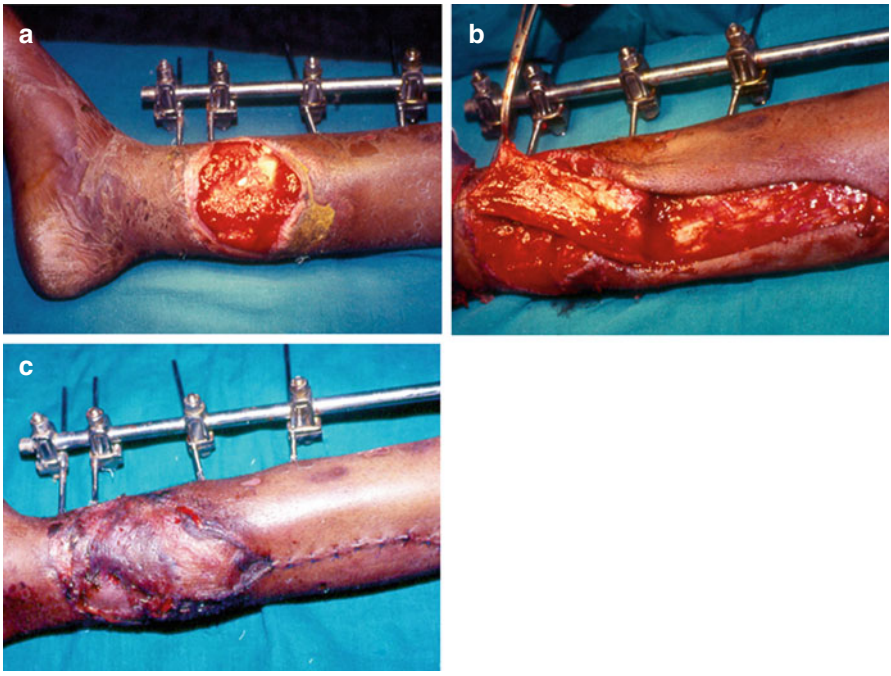

Fig. 26.5 (**a**) Distal leg defect. (**b**) Adepofascial flap has been turned over from the proximal calf region. (**c**) Flap split skin grafted and donor area closed primarily

It has several advantages, e.g., provides well-vascularized tissue, it is a thin flap and does not look bulky, dissection is easy, reliable and durable. Postoperative management is simple and provides good gliding surface for the underlying tendons; there is minimal donor site morbidity with a linear scar, nonhairy tissue is transferred, no major vascular trunk is sacrificed, it does not require any special training or setup, it can be transferred in various ways, and the option for free flap remains open.

26.8.3 Propeller or Skeletonized Perforator Flap

The flaps of the above constituents can be transferred with complete isolation of the perforators with their venae comitantes leaving only a small cuff of tissue around them. A large dimension of tissue is transferred in a single stage. These are specifically advantageous for distal defects. The flap is marked at the proximal calf. An initial exploratory incision is made along one of the proposed margins that is closure to the vascular axis. Subfascial dissection is done toward the main vascular trunk to identify the perforators [15]. Then the rest of the flap is dissected leaving the distal perforators nearest to the defect. Such critical dissection should be done using loupe magnification (3×/4×). The flap is totally islanded. This will allow easy transfer of the flap to cover the defect (Fig. 26.6). The prime advantages of these

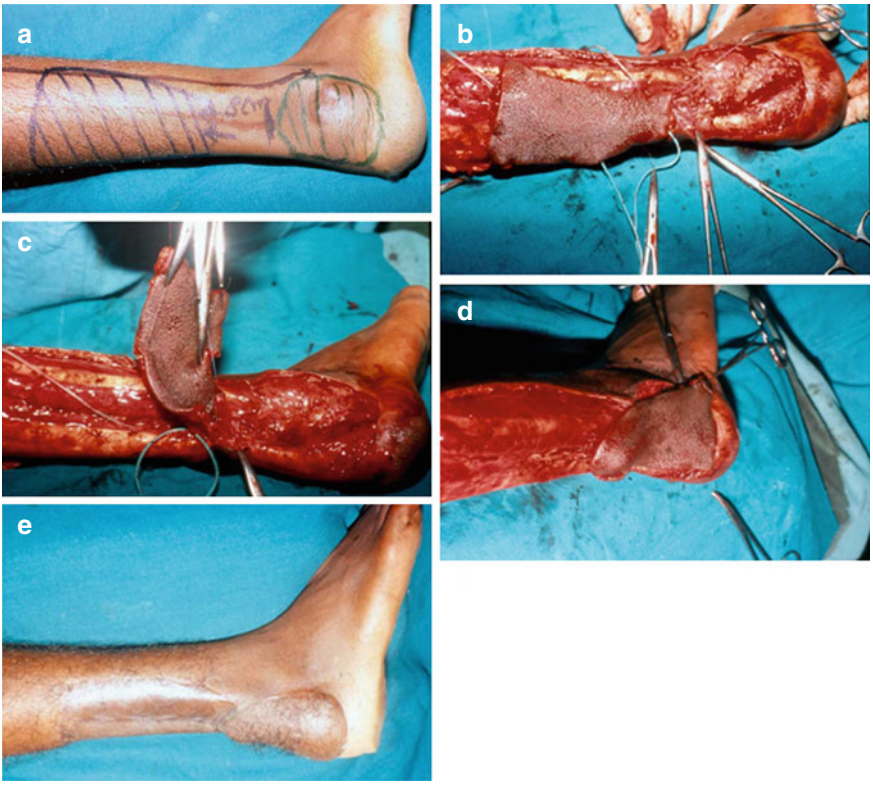

Fig. 26.6 (**a**) Planning of scalitonized distal peroneal perforator based fasciocutaneous flap. (**b**) Post excisional defect of lateral malleolar and posterior heel region with dissected flap. (**c**) Isolated distal peroneal perforator. (**d**) Flap transferred with 180° rotation. (**e**) Follow up at 6 months

flaps are greater flexibility in rotating the flap with enhanced reach as compared to a peninsular flap and the procedure being done in a single stage. Excessive manipulation should be avoided as it may result in perforator spasm or even their avulsion. Kinking, torsion, or pressure due to hematoma may be detrimental. Even though the skeletonization of the perforator allows the flap to move freely 180° on either side, overstretching of the flap while insetting must be avoided.

26.8.4 Sural Neurocutaneous Flap

This is one of the popular flaps for distal limb defects. The flap is perfused by two sources: neurocutaneous arteries from the supramalleolar vascular network and distal septocutaneous perforators of the peroneal artery [16]. The proximal limit of the flap is 8 cm from the popliteal crease; the lateral boundaries are formed by lateral border of the fibula and medial border of the tibia [17]. The incision is made up to the deep fascia, and the dissection is continued in the subfascial plane preserving the

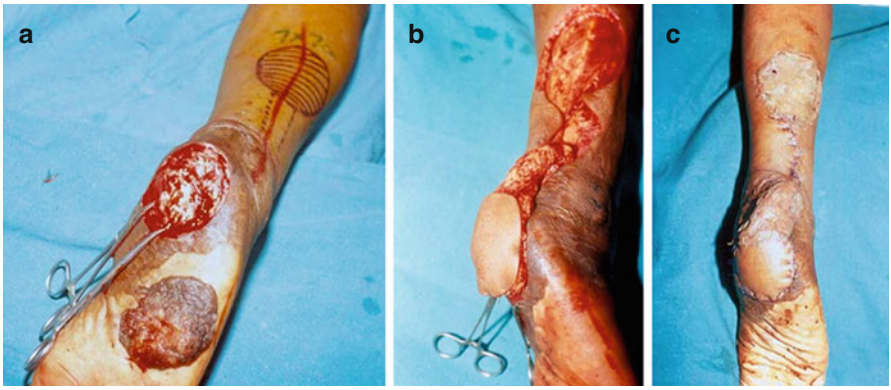

Fig. 26.7 (**a**) Planning of sural neurocutaneous flap with heel defect. (**b**) Flap transferred to the defect with adepofascial pedicle. (**c**) Insetting of flap and donor area skin grafted

sural nerve. The constituent of the pedicle is sural nerve, its accompanying arterial branches, lesser saphenous vein, and the surrounding adipofascial tissue. The pedicle is usually split skin grafted. Sometimes it may be tunneled to the defect, but it is risky as the intervening tissue at the distal leg is not loose and therefore difficult to adequately undermine. Hence, if the pedicle is passed under this tunnel, there is every possibility of compression. The pivot point is 5 cm above the lateral malleolus which is the location of the distal peroneal artery perforator. This is the source of blood supply which perfuses the flap through the arcade of vessel surrounding the sural nerve up to the dermis. The flap is used to resurface defects over the Achilles tendon and concomitant wounds around heel (Fig. 26.7), ankle, and distal tibia. Advantages are as follows: Long pedicle enables great arc of rotation and no major artery is sacrificed.

26.8.5 Fascial Flap

It is indicated for noncontoured defects, e.g., over shin of the tibia, exposed Achilles tendon, distal tibia, etc. The adjacent donor site is explored by a lazy "S" incision. Margins are undermined in the subcutaneous plane exposing the deep fascia. One distal horizontal and two vertical incisions are made through the deep fascia. The flap is dissected toward the defect in the subfascial plane leaving adequate base for vascularity. Then the flap is hinged to the defect and sutured at the margins (Fig. 26.8). They are usually defect-based turnover flap, or they can be tunneled to the defect. Larger flap can be safely used by incorporating one or two perforators at the base. However, it is not necessary to visualize the perforators during dissection. A thin skin graft is applied over the subfascial surface of the transferred flap, and the donor area is closed primarily (Fig. 26.9). It is a simple and reliable method. The maximum safe length of the distal perforator-based flap is 14 cm. In case of a random flap, the safe limit is 8–10 cm depending upon the length of the base. It has

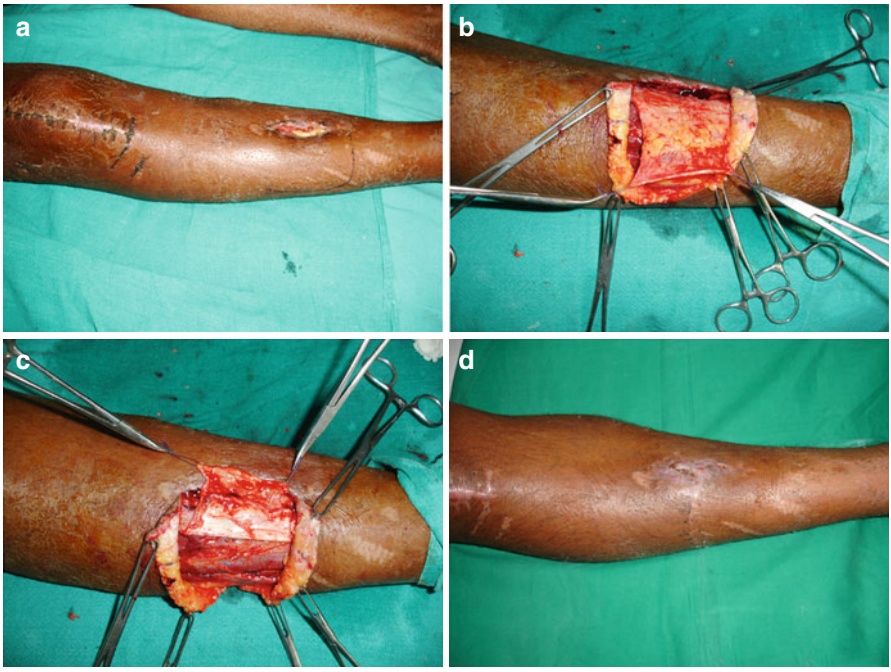

Fig. 26.8 (**a**) Defect over the shin of tibia. (**b**) Defect based fascial flap dissected. (**c**) Flap turned over to the defect and grafted. (**d**) Desirable result

several advantages being a well-vascularized tissue, single-stage procedure, thin flap, dissection is easy. It is reliable and durable provides good gliding surface over the tendon. It can be tailored to the dimension of the defect, postoperative management is simple, and it has minimal donor site morbidity with a linear scar.

26.8.6 Muscle/Myocutaneous Flap

When there is a deep contoured defect with exposed knee, tibia, or fibula at the upper two third of the leg, the application of a muscle flap is considered. Depending upon the location and extent of the defect, either the medial or the lateral head of the gastrocnemius muscle is used. The supplying vessel enters the muscle at the popliteal fossa. The muscle belly is detached at the musculotendinous junction distally and dissected proximally till the muscle lie easily over the defect (Fig. 26.10). The vascular pedicle need not be visualized most of the time. It is a large muscle belly with adequate width for tibial defect. The muscle can be transposed or rotated to the defects from the knee to upper two third of the tibia. However, it is not a frequently preferred tissue as it is bulky and need not be sacrificed as a functional unit in an already traumatized limb. A myocutaneous unit is bulkier and not aesthetic. To reduce the bulk and to maintain the functional unit, the gastrocnemius can be split

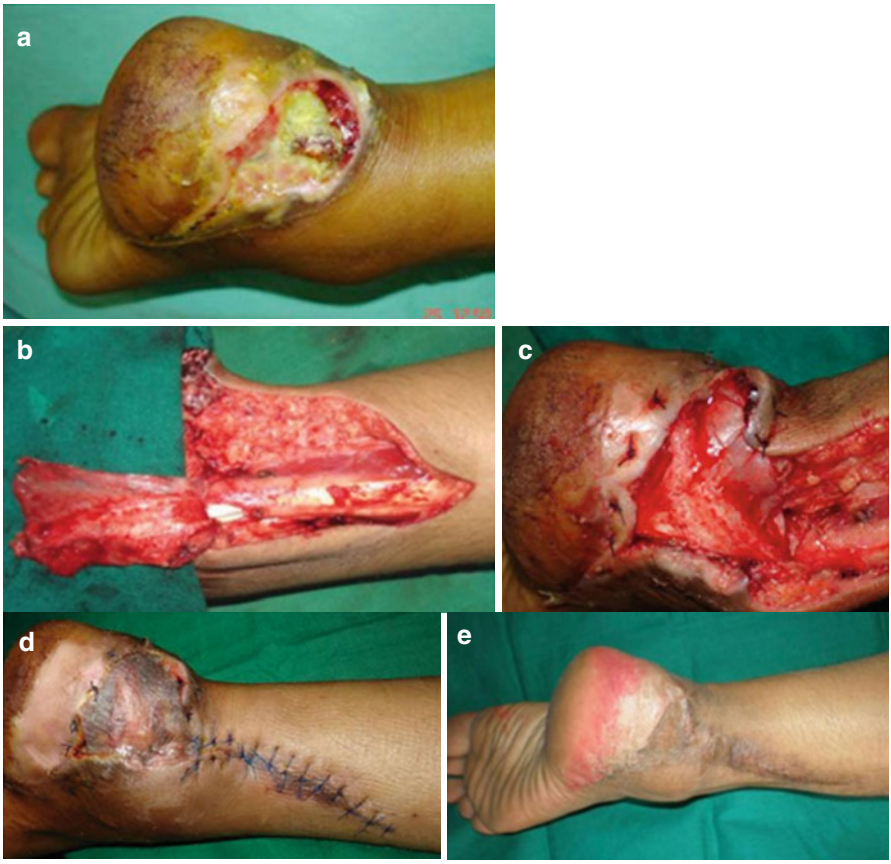

Fig. 26.9 (**a**) Non weight bearing posterior heel defect. (**b**) Distal peroneal perforator perfused retrograde fascial flap. (**c**) Insetting of the flap. (**d**) Flap skin grafted and donor site closed primarily. (**e**) Follow up at 8 months

sagittally. The superficial portion can be transferred as a split muscle flap (Fig. 26.11). Thus, the bulk of the transferred muscle mass is also reduced with better aesthetic result. The other muscle available is soleus. It can be easily identified and dissected from the medial head of the gastrocnemius. It can also resurface the upper two third of the tibia and is less bulky. However, it is supposed to be the peripheral heart and should be used selectively.

26.8.7 Flaps for Heel and Sole Defects

The skin of this area is unique in nature. Therefore, for smaller defects up to 3–4 cm diameter, local flaps are designed in the form of rotation (Fig. 26.12), transposition, V–Y advancement, bilobed flap (Fig. 26.13), or a medial planter artery

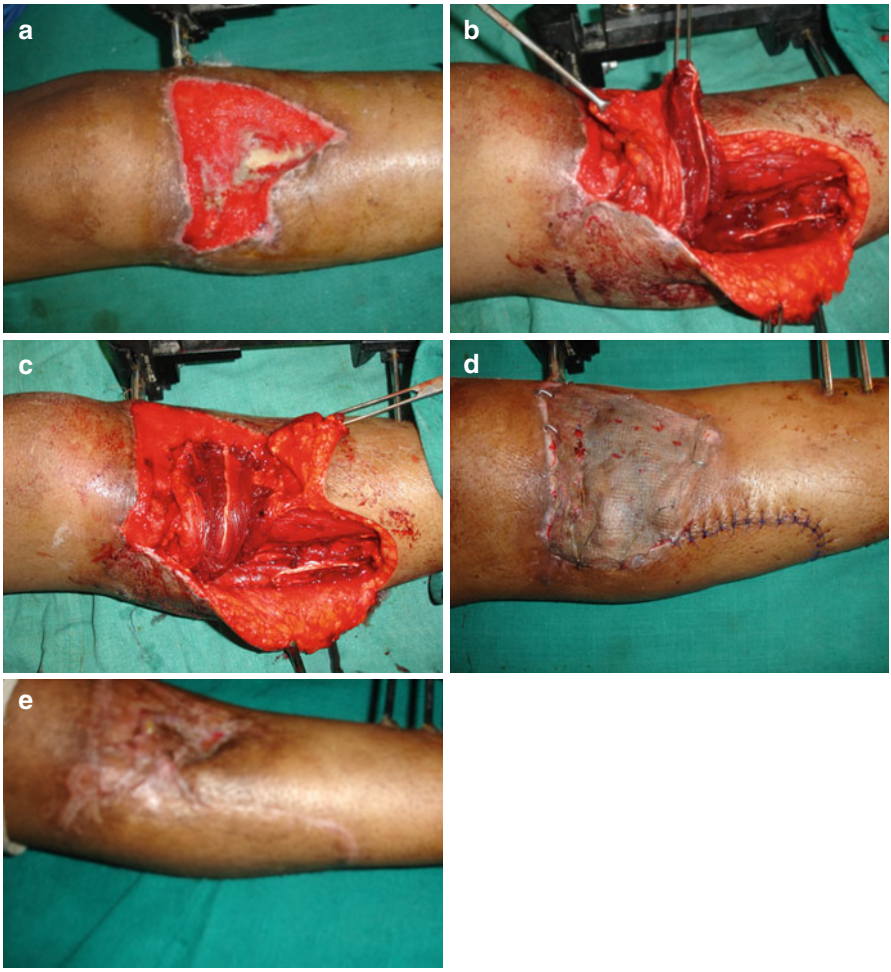

Fig. 26.10 (**a**) Proximal third contoured defect. (**b**) Dissected lateral head of gastrocnemeus muscle. (**c**) Flap transposed to the defect. (**d**) Flap covered with SSG. (**e**) Follow up at 6 moths providing suitable result

flap. If the local tissue is not suitable, the three muscles of the first layer of the sole are very useful for defects of the heel and proximal sole. They are abductor digiti minimi (Fig. 26.14), flexor digitorum brevis, and abductor hallucis. They can be detached from their insertion distally and transferred to the proximal defect to adequately fill up the contoured trophic ulcers and posttraumatic defects. For larger defect, two muscles can be transferred (Fig. 26.15). Subsequently split-thickness graft is applied over the muscle. The donor incision is placed on the non-weight-bearing area and sutured primarily. Thus, there is no morbidity while wearing shoe or during ambulation.

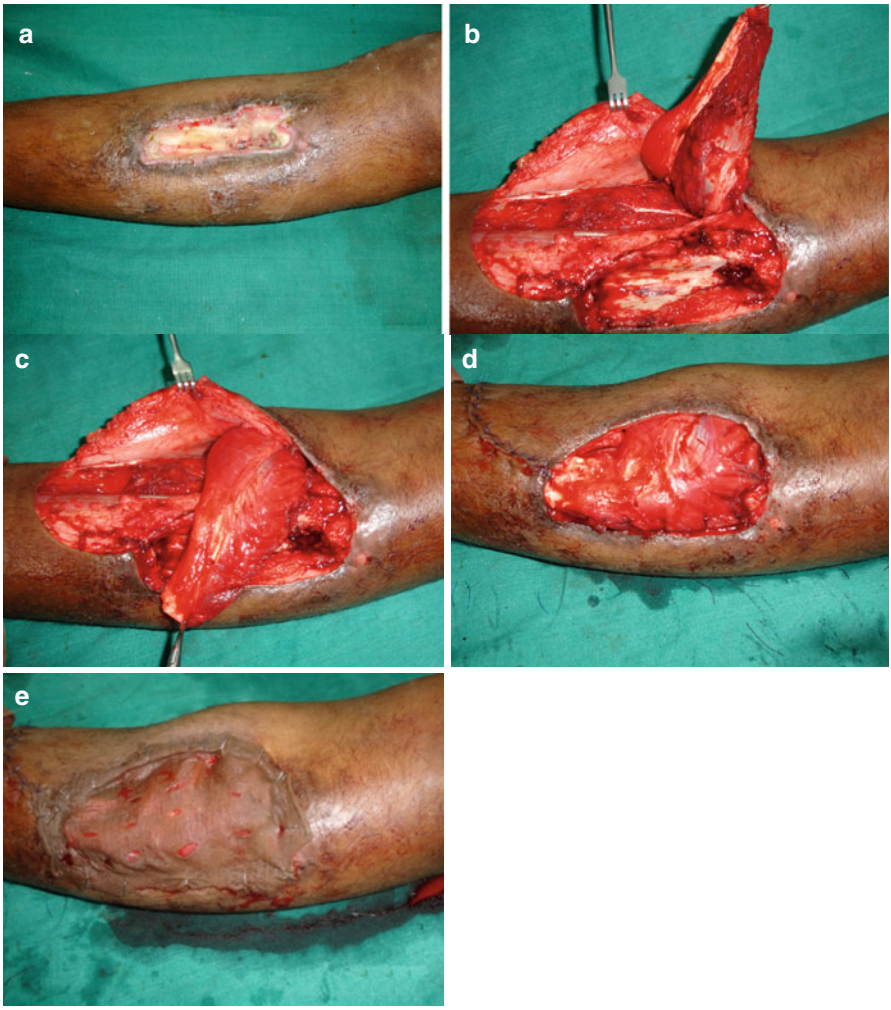

Fig. 26.11 (**a**) Mid tibial defect. (**b**) Split medial gastrocnemeus muscle flap dissected. (**c**) Flap transposed to the defect. (**d**) Insetting of the flap. (**e**) Flap covered with perforated SSG

26.8.8 Combination of Different Techniques

When we assess a defect for choosing the technique of resurfacing, two aspects are considered: (a) which area requires a flap and which requires only a skin graft. There are occasions when large area of the same wound is graftable and portion of the wound with exposed underlying vital structure require a flap. (b) Sometimes there may not be adequate adjacent healthy tissue to design a single flap to cover a large defect. In such situation one should think combination of two or more flaps of same or different constituents. It could be one antegrade and one retrograde

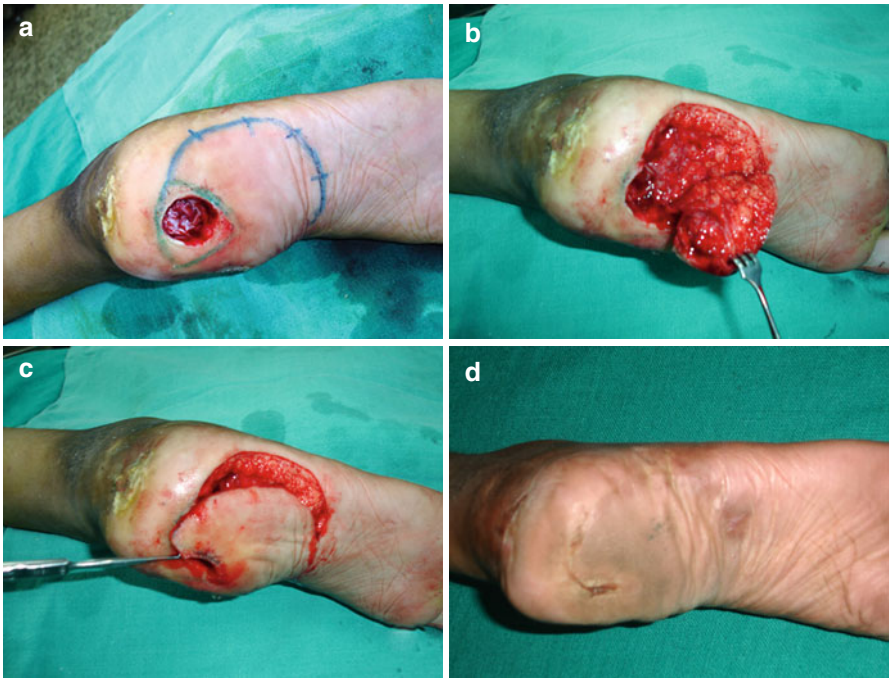

Fig. 26.12 (**a**) Trophic ulcer of heel. (**b**) Rotation flap dissected. (**c**) Flap transferred to the defect. (**d**) Final outcome

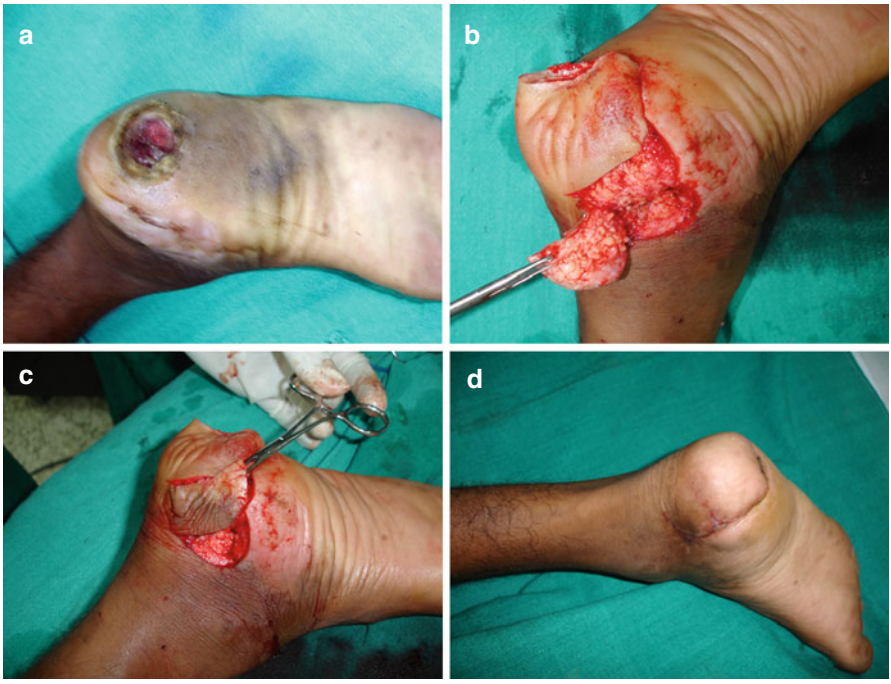

Fig. 26.13 (**a**) Trophic ulcer of heel. (**b**) Proximal heel bilobed flap dissected. (**c**) Transferred to the defect. (**d**) Predictable result

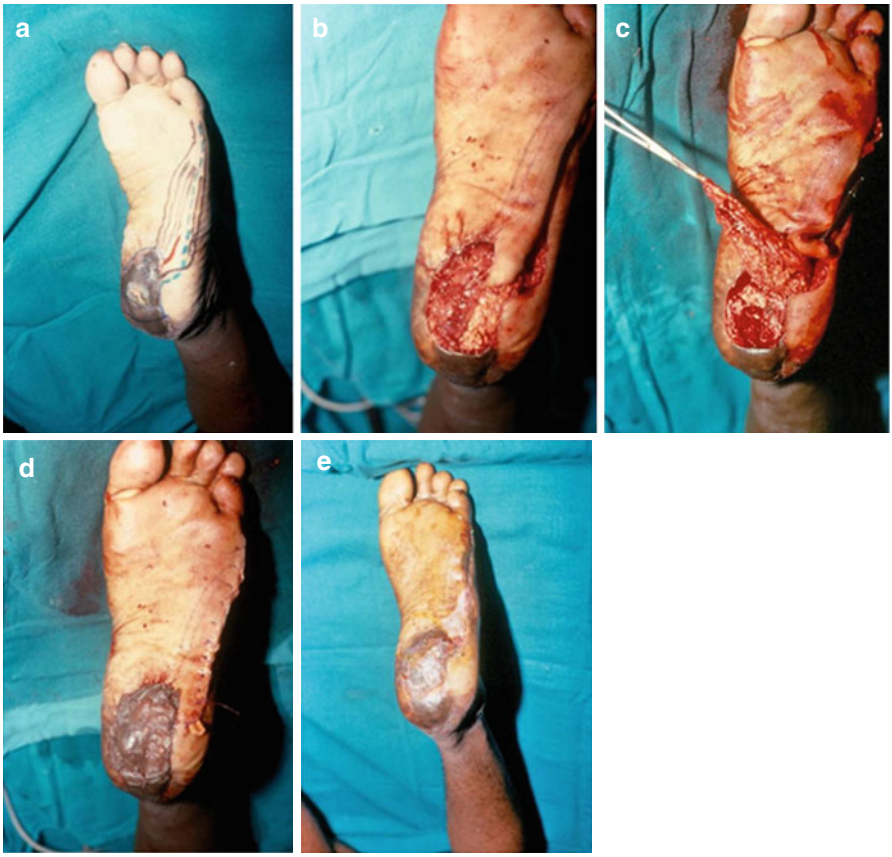

Fig. 26.14 (**a**) Post traumatic heel defect. (**b**) Exposure for abductor digiti minimi muscle flap. (**c**) Muscle dissected. (**d**) Insetting of Flap to the defect with SSG. (**e**) Follow up at 6 months

fasciocutaneous flap based on the perforator of the same vessel (Fig. 26.16) or different vessels (Fig. 26.17). These flaps are sutured together at their distal margin. It can be a combination of muscle flap with fasciocutaneous flap (Fig. 26.18).

26.8.9 Free Flaps

Free flaps are considered when the defect is extensive or the adjacent soft tissue is so grossly damaged that no local flap can be harvested with safety. These flaps are either fasciocutaneous in nature or a muscle flap with SSG. For moderate defects, radial artery forearm flap, parascapular, medial arm flap, etc., are used. For larger defect, anterolateral thigh (ALT) flap is used. The commonest muscle used is the latissimus dorsi, gracilis, serratus anterior, etc. The recipient vessel for anastomosis is either one of the main vascular trunks with end-to-side anastomosis or one of the

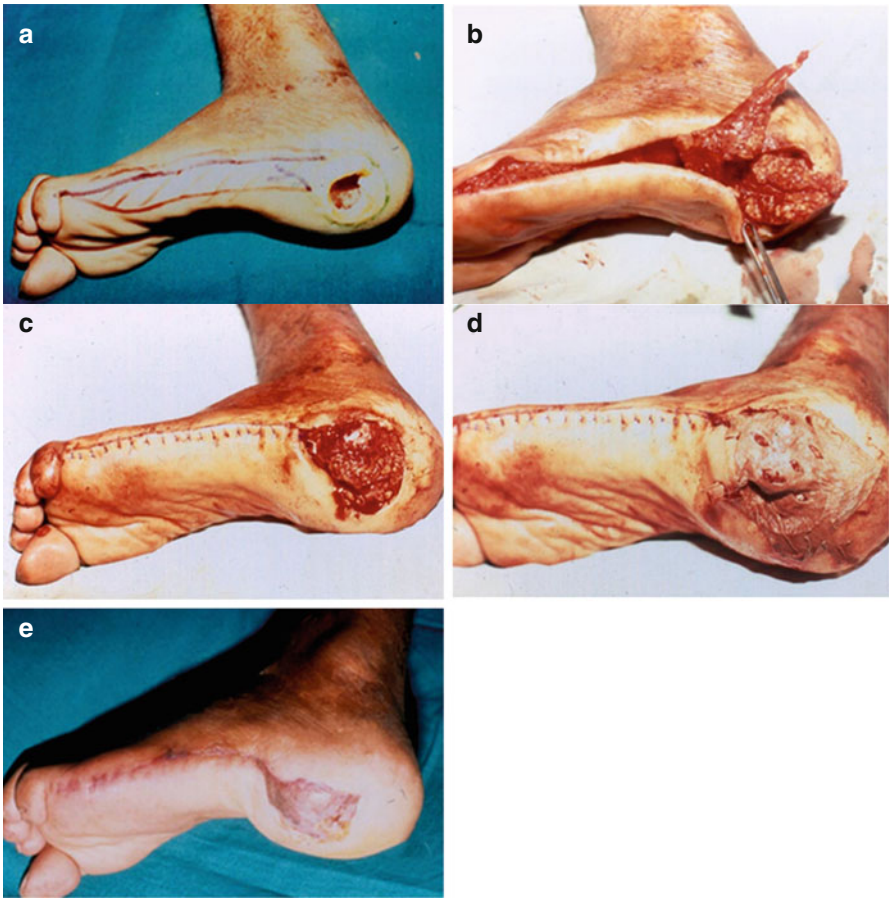

Fig. 26.15 (**a**) Larger heel defect. (**b**) Abductor digiti minimi and flexor digitorum brevis muscle flap dissected. (**c**) Insetting of muscle flaps. (**d**) Covered with SSG and donor site closed primarily. (**e**) Follow up at 8 months

sizable perforators. That is why it is advisable to perform a preoperative angiographic evaluation of the vascular tree of the lower limb in extensive trauma to identify and plan the site of the anastomosis. If no suitable vessel is available adjacent to the defect for anastomosis, a vein graft is used for a more proximal anastomosis with a normal vessel.

26.9 Postoperative Care

It is as important as surgery. The flap needs to be inspected every day. The aspects to be ensured are as follows: (a) light dressing, (b) avoiding pressure over the pedicle, (c) limb to be kept elevated by 20–30°, and (d) stitches to be removed around

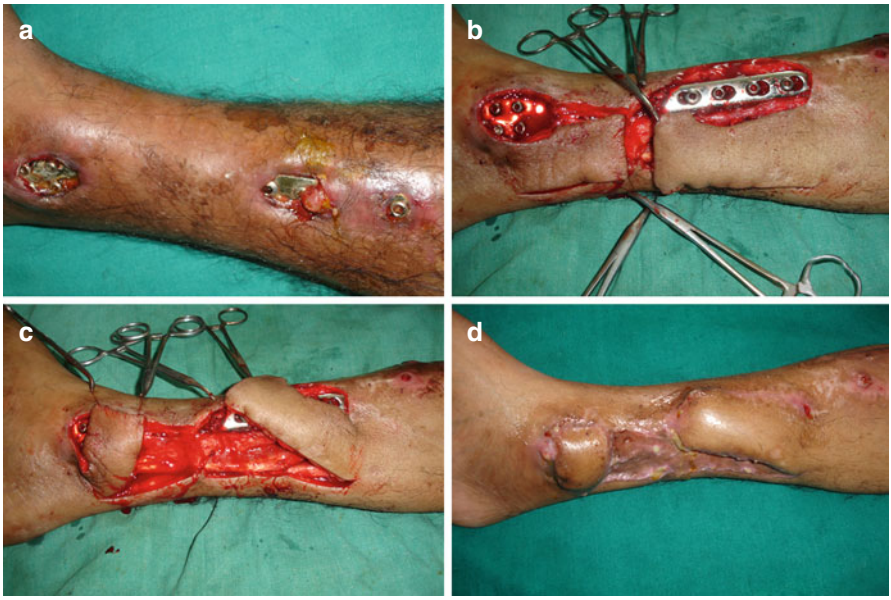

Fig. 26.16 (**a**) Exposed hard ware at multiple level. (**b**) Antegrade and retrograde flaps based on the perforators of the posterior tibial artery. (**c**) Flaps transferred to the defects. (**d**) Healed wound at 4 months

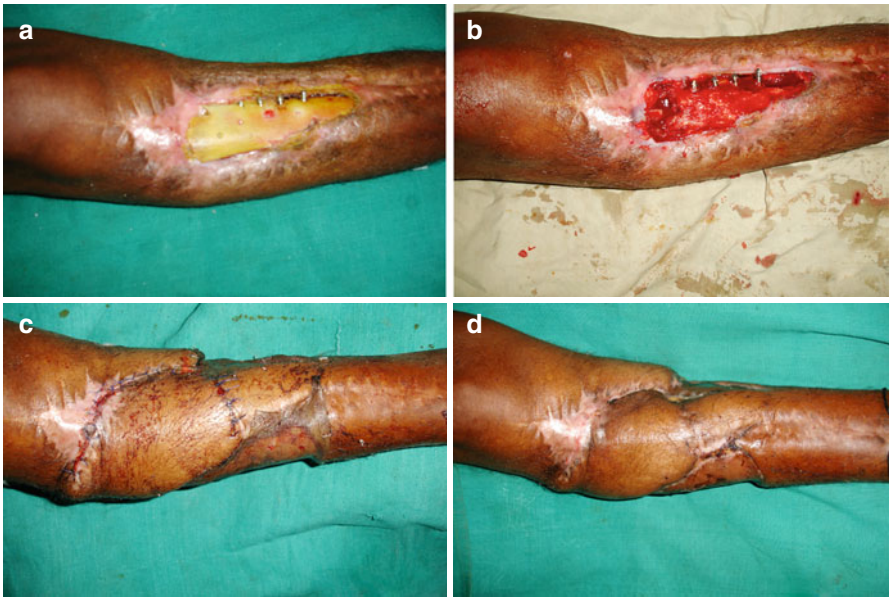

Fig. 26.17 (**a**) Large tibial defect with surface sequestrum. (**b**) Sequestrum deroofed. (**c**) Resurfaced by peroneal perforator antegrade flap and posterior tibial perforator retrograde flap joined together. (**d**) Follow up at 6 months

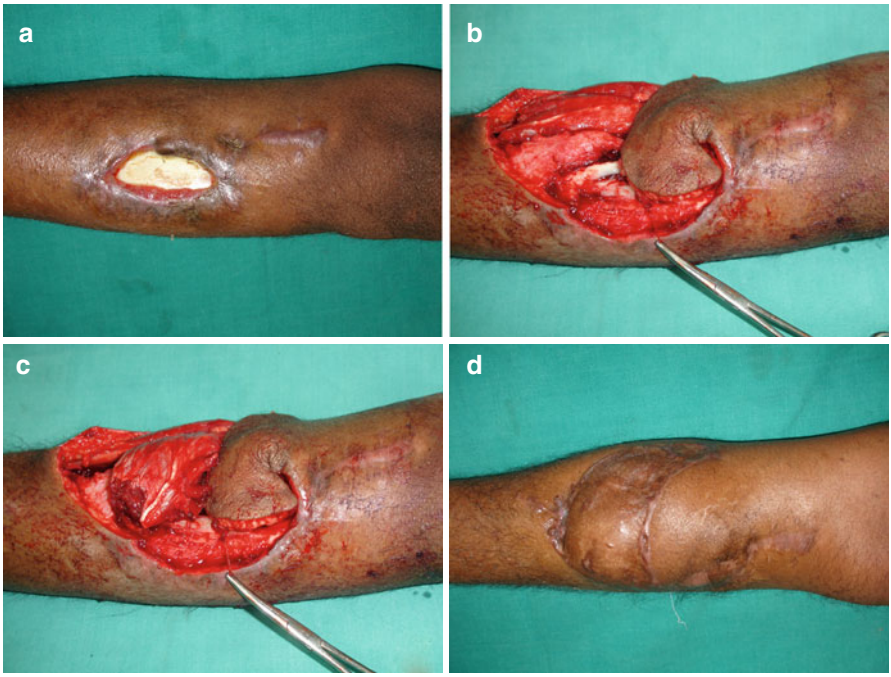

Fig. 26.18 (**a**) Mid tibial defect. (**b**) Combination of split medial gastrocnemeus muscle flap and medial antegrade fasciocutaneous flap. (**c**) Insetting of flaps. (**d**) Follow up at 6 months

10–12th day. If one suspects compromise with the vascularity, immediate measure should be taken to salvage the flap. The early indications of compromised vascularity are change of color at the distal margin and low temperature. If allowed to progress, blisters will appear which is an alarming sign. In such occasion, remove the whole dressing and check for the pressure over the pedicle by posture of the limb or pressure due to dressing. Evacuate hematoma if any. Remove few distal stitches to prevent traction on the flap.

26.10 Complications

Complications can happen in the immediate postoperative period in the form of hematoma under the flap which may compromise with the vascularity. Infection will have detrimental effect and increase the morbidity, poor take of the skin graft, partial or complete flap necrosis.

In late follow-up, if the instructions are not followed by the patient, there may be infection and trophic changes around the margins of the flap specially at the heel and sole. There may be sequestrum under the flap which will cause sinus requiring sequestrectomy. The part or whole flap may require debulking depending upon the type of flap and the location. Most of these complications are avoidable.

26.11 Instructions to the Patient During Follow-Up

Keep the flap clean to avoid infection, keep it moist using moisturizer, protect it from trauma, and inspect it twice a day. Explain that different types of sensation will appear after at least 6 months starting with protective sensation. Therefore, till then one has to be careful. The other sensations appear around 1 year or later. Use soft shoe in case of flaps on the ankle, dorsum of foot, heel, and sole. Visit for monthly checkup to the first 6 months and then every 3 months for 2 years. Functional and aesthetic aspect is considered both for the recipient and donor sites.

Conclusion

Acute and chronic wounds of different etiologies pose significant challenge to the reconstructive surgeons. It is of utmost importance to choose the appropriate procedure for resurfacing a given defect keeping in mind its nature and location. A meticulous preoperative "planning in reverse" must be done for suitable flap design. Definitive understanding of vascularity of different flaps and fault less execution is the key to the success. The locoregional flaps of different constituents and combinations are of enormous value and popular in managing moderate-sized defects. These procedures can be simultaneously performed with the orthopedic care in acute and chronic stages. If any future surgery is to be performed in the same area, one can approach through the flap safely after 3 months.

References

1. McCarthy JG. Plastic surgery, General principles, vol. 1. Philadelphia: WB Saunders Company; 1990.
2. Bhattacharya V, Arora R. Fasciocutaneous flap with adipofascial extension in contour defects of leg. Ind J Plast Surg. 2002;35:70.
3. Ponten BC. The fasciocutaneous flap: it's use in soft tissue defects of the lower leg. Br J Plast Surg. 1981;34:215–20.
4. Carriquiry C, Costa A, Vasconez LO. An anatomic study of the septocutaneous vessels of the leg. Plast Reconstr Surg. 1985;76:354–61.
5. Tolhurst DE, Haeseker B, Zeeman RJ. The development of fasciocutaneous flap and its clinical applications. Plast Reconstr Surg. 1983;71:597.
6. Haertsch PA. The blood supply to the skin of the leg. A post-mortem investigation. Br J Plast Surg. 1981;34:470–7.
7. Bhattacharya V, Goyal S, Jain P. Angiographic evaluation of fasciocutaneous flaps. Int Surg. 2006;91:326–31.
8. Bhattacharya V, Watts RK, Reddy GR. Live demonstration of microcirculation in deep fascia and its implication. Plast Reconstr Surg. 2005;115(2):458–63.
9. Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg. 1987;40:113–41.
10. Bhattacharya V, Deshpande SB, Watts RK, et al. Measurement of perfusion pressure of perforators and its correlation with their internal diameter. Br J Plast Surg. 2005;58:759–64.
11. Cormack GG, Lamberty BGH. The fasciocutaneous system of vessels. The arterial anatomy of skin flap. Edinburgh: Churchill Livingstone; 1986.

12. Bhattacharya V, Watts RK. Ipsilateral fasciocutaneous flaps for leg and foot defects. Ind J Plast Surg. 2003;36:30–5.
13. Bhattacharya V, Sunish G, Adil BS. Reconstructive implications of adipofascial flaps in limb defects. Eur J Plast Surg. 2007;30:169–75.
14. Lee S, Estella CM, Burd A. The lateral distally based adipofascial flap of the lower limb. Br J Plast Surg. 2001;54:303–9.
15. Bhattacharya V, Reddy GR, Goyal S, Kumar U. Skeletonised retrograde distal perforator island fasciocutaneous flaps for leg and foot defects. J Plast Reconstr Aesthet Surg. 2007;60:892–7.
16. Bullocks JM, Hickey RM, Basu CB, Hollier LH, Kim JY. Single-stage reconstruction of Achilles tendon injuries and distal lower extremity soft tissue defects with the reverse sural fasciocutaneous flap. J Plast Reconst Aesth Surg. 2008;61:566–72.
17. Vergara-Amador E. Distally-based superficial sural neurocutaneous flap for reconstruction of the ankle and foot in children. J Plast Reconstr Aesth Surg. 2009;62:1087–93.
18. Lees V, Townsend PLG. Use of pedicled fascial flap based on septocutaneous perforators of the posterior tibial artery for repair of distal lower limb defects. Br J Plast Surg. 1992;45:141.

Amputation of the Lower Extremity

27

Shyam Kumar Saraf

27.1 Introduction

Chronic leg ulcers are defined as those that show no tendency to heal after 3 months of appropriate treatment or are still not fully healed at 12 months [1]. Various treatment modalities have been suggested for the management of nonhealing ulcers. The amputation is done as a last resort, when all other methods of treatment have exhausted or when it is felt that amputated limb will provide a better functional result as compared to limb with persistent chronic nonhealing ulcers. The amputation rate in diabetics can be reduced with good care of the foot. The last decade saw a marked decline in the lower extremity amputation in the Medicare population in the USA [2].

27.2 Indications

The various indications where amputation may be the choice in patients presenting with ulcers are:

(a) Ulcer with gangrene changes
(b) Ulcer with atherosclerosis
(c) Ulcer with uncontrolled infection
(d) Ulcers after traumatic conditions
(e) Miscellaneous causes

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27.2.1 Ulcer with Gangrene Changes

The typical example is diabetic foot (Fig. 27.1); however, in nondiabetics too, there can be ulcers with gangrenous changes. The ulcers in diabetics develop due to multiple reasons. The reduced blood supply to the tissues as a result of atherosclerosis means less supply of factors responsible for healing of a wound. The foot all the time is susceptible of sustaining injury due to loss of sensations. When an ulcer in diabetics is compounded further by infection, the cumulative effect may lead to gangrenous changes since the infection is likely to further restrict blood supply (Fig. 27.2). With gangrenous changes, it becomes necessary to amputate the affected limb to prevent the spread of infection and further damage to healthy tissue. According to Izumi et al., the risk of reamputation in patients with diabetes is high [3]. The cumulative risk of reamputation noticed was 27 % after 1 year, 48 % after 3 years, and 61 % after 5 years. We have noticed that 30–50 % of amputee will undergo reamputation within 1–3 years

27.2.2 Ulcer with Atherosclerosis

Ulcers develop in atherosclerosis due to compromised blood supply. The ulcers as a result of trauma or infection are difficult to heal or may not heal at all. Depending upon the severity of the block, there can be gangrenous changes. Smoking, obesity, and hyperlipidemia are the risk factors.

27.2.3 Ulcers in Infective Conditions

There can be single or multiple sinuses in chronic osteomyelitis. Occasionally these sinuses may not respond to prolonged antibiotics and even to multiple surgeries. Osteomyelitis of the calcaneum may lead to ulcer formation, as heel is a weight-bearing area. Necrotizing fasciitis is yet another serious infection where an early intervention in the form of amputation may be necessary. In advanced uncontrolled infective ulcers, open amputation is indicated (Fig. 27.3). It can be guillotine amputation with revision to more proximal level after control of infection.

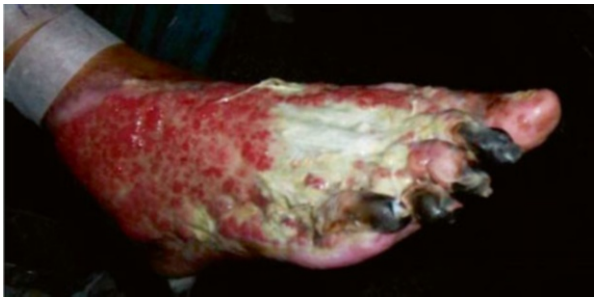

Fig. 27.1 Gangrene of multiple toes requiring amputation in diabetic foot ulcer

27.2.4 Ulcers in Traumatic Conditions

In a severely injured limb, the amputation may be the only treatment available. For unsalvageable crush injuries of the limb, the functional results after amputation are better than continuing with prolonged therapy. The various complications associated with a severely injured limb resulting in ulcer formation are uncontrolled soft tissue infection as well as osteomyelitis and infective arthritis and may be gangrene. Preserving such disabling parts of body is more frustrating to patients than getting

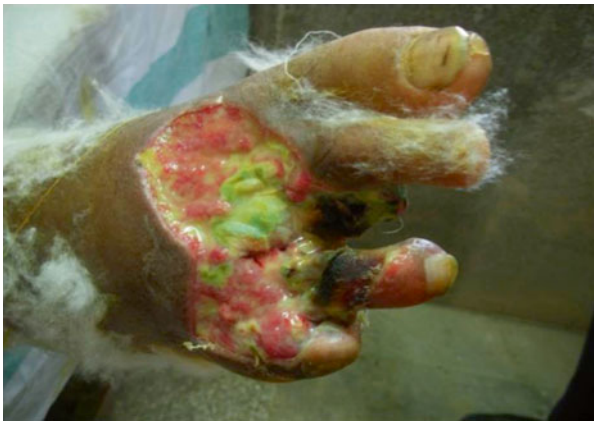

Fig. 27.2 Gangrene of toes with infection and tissue necrosis

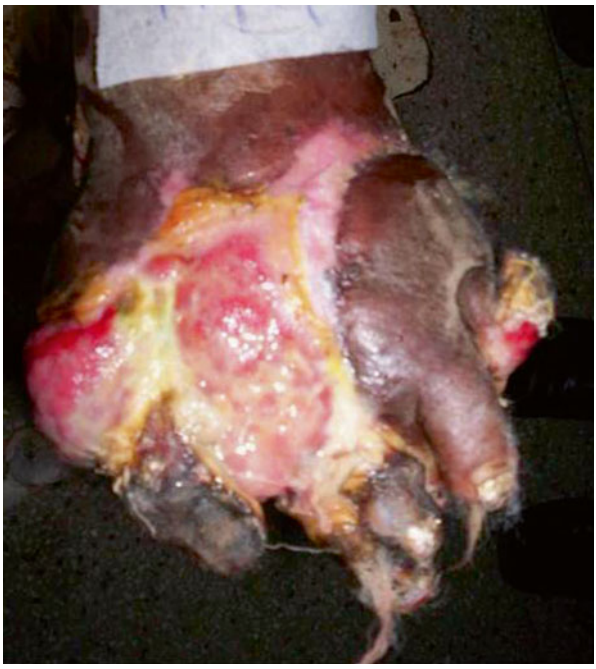

Fig. 27.3 A case of extensive tissue necrosis with infection is indicated for open amputation

rid of it followed by fitting of prosthesis. Blast injuries and burns are other examples which may result in nonhealing ulcers refractory to treatment.

27.2.5 Miscellaneous

Pressure ulcers are common and challenging in patients with spinal cord injury. Proximal amputations of the lower limbs can be considered as part of the treatment for complicated pressure ulcers as it would reduce the number of hospital stay and improve the quality of life and functional outcome [4]. A pressure ulcer over a bony prominence may lead to extensive tissue necrosis of soft tissues including muscle and supporting structures with osteomyelitis of underlying bone. Loss of sensations in lower limbs can result in trophic ulcers in the foot and other bony prominences. In Indian subcontinent, Hansen's disease is an important pathology. Nonhealing ulcers developing over neoplastic lesions (Fig. 27.4) or squamous cell carcinoma developing over chronic draining sinus can be another indication for amputation.

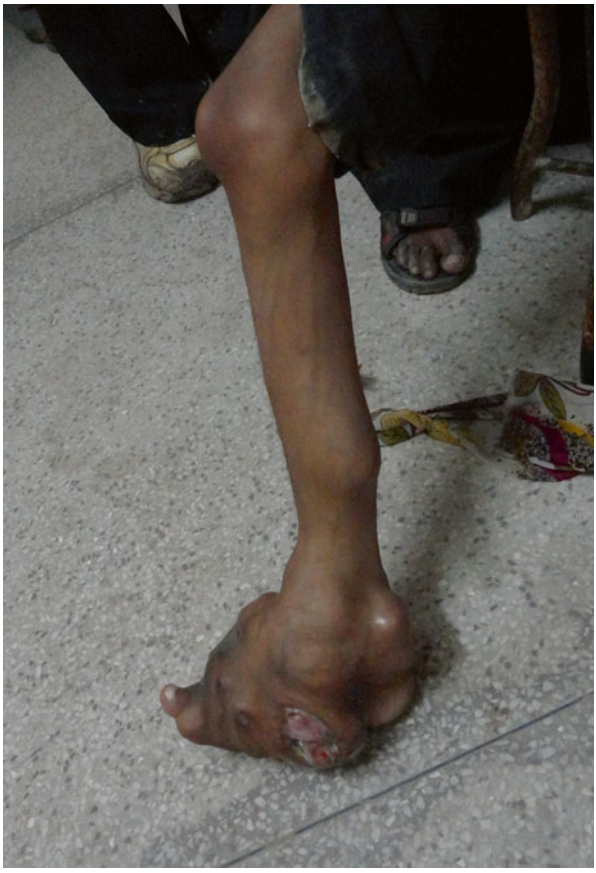

Fig. 27.4 Nonhealing ulcer over a case of neoplastic lesion of foot

Table 27.1 Wagner classification of diabetic foot

Grade 0	No ulceration, foot at risk
Grade 1	Localized superficial ulceration
Grade 2	Deep ulceration that penetrates tendon, bone, and joint
Grade 3	Osteomyelitis or deep abscess
Grade 4	Localized gangrene
Grade 5	Extensive gangrene requiring amputation

27.2.6 Diabetic Ulcers

Diabetic ulcers need special mention as they are one of the leading causes of nontraumatic lower extremity amputations (LEA) worldwide [5]. There are many classifications grading the diabetic foot ulcers (DFU). Wagner's classification [6] is more popular (Table 27.1). In this classification, in grade 4 and 5, amputation is often required. Edo et al. studied the risk factors, ulcer grade, and management outcome of diabetic foot ulcers in a tropical tertiary care hospital and concluded that spontaneous blisters, peripheral vascular disease, peripheral neuropathy, and visual impairment are common risk factors of DFUs [7]. 45.6 % patients presented with Wagner grade 4 and 5 ulcers with the resultant high rate of lower extremity amputations (LEAs). Early presentation and treatment of DFUs can reduce the amputation rates. The effective partial foot amputations in the high-risk diabetic population can minimize the need for major proximal lower limb amputations [8]. Monteiro et al. studied extensively the classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer and concluded that though there are numerous classification systems for DFU outcome prediction, but only few studies evaluated their reliability or external validity and reported accuracy measures [9]. Further studies assessing reliability and accuracy of the available systems and their composing variables are needed.

The various risk factors for lower extremity amputation in the diabetic foot are: (a) absence of protective sensation due to peripheral neuropathy, (b) arterial insufficiency, (c) foot deformity and callus formation resulting in focal areas of high pressure, and (d) autonomic neuropathy causing decreased sweating and dry, fissured skin.

27.3 Surgical Principles of Amputation

While deciding the level of amputation, one has to balance between conserving the limb as much as possible without compromising with the complication as a result of leaving behind the infected gangrenous part. In chronic ulcers with fulminate infection and vascular compromise, the decision is not easy.

(a) Screening tests for general health and immunological status is important as it may compromise with healing of wound.
(b) Skin flaps should be thick and muscles well stabilized with meticulous hemostasis before closure. Bone stumps left after amputation must be covered well with soft tissue padding.
(c) Postoperatively advice from physiotherapist, occupational therapist, and prosthetic expert should always be called for. In diabetic ulcers, it is important to keep sugar under control.
(d) Surgery should be carried out with meticulous details to avoid the postoperative complications like hematoma, infection, necrosis of the wound, phantom limb sensations, etc.

27.4 Types of Amputations in Ulcers of Foot (Fig. 27.5)

27.4.1 Toe Amputation

If toe is gangrenous (Fig. 27.6), amputation is recommended as it does not affect the functions significantly. Amputation of great toe can produce limp in running and walking as push off is affected. Whenever possible, planter flap should be made longer than dorsal flap.

27.4.2 Amputation Through Metatarsals

In diabetic ulcers, it is not uncommon to see involvement of metatarsophalangeal joint. In such conditions, amputation through one or multiple metatarsals may be required. Attempt should be made to conserve the metatarsals as much as possible to preserve the push-off phase of gait cycle and utilize the plantar skin as much as possible (Fig. 27.7). Prosthesis is usually not required.

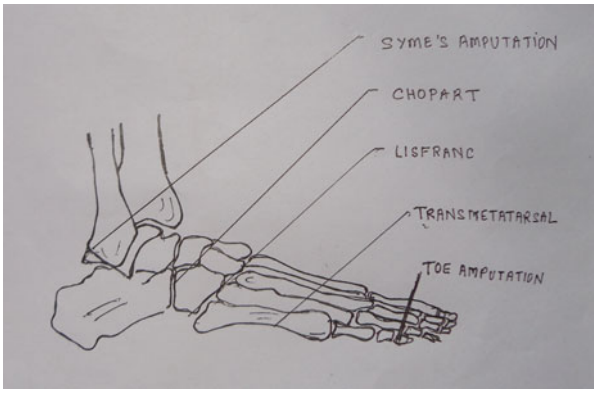

Fig. 27.5 Levels of foot amputations

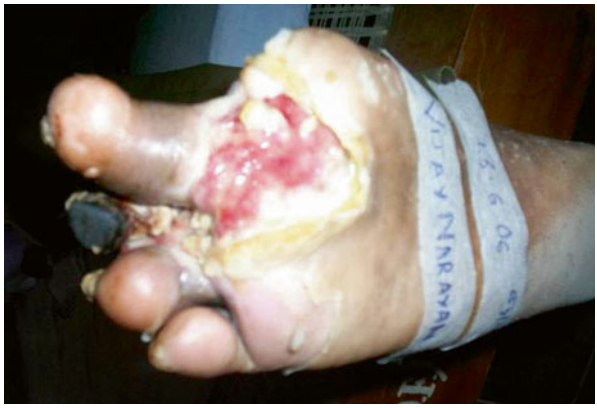

Fig. 27.6 Gangrene of third toe with impending gangrenous changes of second toe. First toe is already amputated

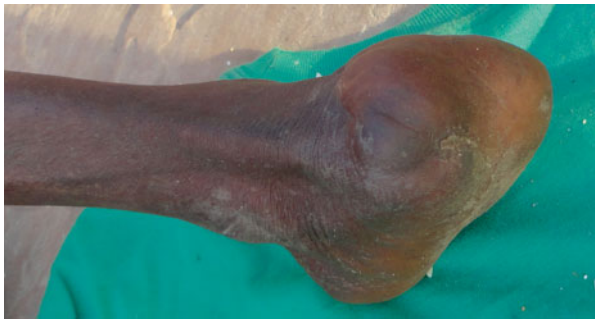

Fig. 27.7 Diabetic foot with extensive soft tissue necrosis and infection; preferred to manage with two-stage amputation

27.4.3 Amputation Through Mid Foot

Amputation through tarsometatarsal joint (Lisfranc) and through midtarsal joint (Chopart) is indicated when forefoot is badly involved due to ulcers complicated by infection and vascular compromise. This amputation affects the foot function significantly. Further as tendo achilles is intact and dorsiflexors are sacrificed, significant equinus deformity is resulted. To prevent the development of equinus deformity after midfoot amputation, Roach and Mcfarlene recommended to tenotomize the tendo achilles [10]. Tendon transfers of ankle dorsiflexors can also be done. Alternatively one can amputate the limb at higher level. Once the wound is healed, the patient can walk with partial foot prosthesis.

27.4.4 Amputation Through Hindfoot/Ankle

When ulcer in the foot is associated with osteomyelitis of tarsals and metatarsals not responding to nonoperative treatment, with dysfunctional unsalvageable foot, the amputations around the ankle can give acceptable results. The two common amputations in this region are Syme's amputation and Boyd's amputation.

27.4.5 Syme's Amputation

Syme's amputation is more acceptable to the patients. It provides end-bearing stump. The tibia and fibula are sectioned 0.6 cm. proximal to ankle joint covered by thick heel pad as weight-bearing surface. Prosthesis is usually not required after Syme's amputation; however, stump is cosmetically not very good and prosthesis can be used for cosmetic reasons.

In a diabetic foot with gangrenous changes and uncontrolled infection, Wagner recommended Syme's amputation to be carried out in two stages for better results [6]. In the first stage, ankle disarticulation is done with heel pad flap covering the wound along with antibiotic suction irrigation. The purpose is to control the infection. After around 6 weeks, when the infection is well controlled, second part of the procedure is done with transection of tibia and fibula at designated level with proper soft tissue coverage.

27.4.6 Leg Amputation (Fig. 27.8)

Transtibial amputation is required in ulcers of the foot where the foot is either unsalvageable (Fig. 27.9) or remaining stump in the foot is functionally and cosmetically not acceptable. Amputation technique depends on if the ulcer is in the ischemic or nonischemic limb. The knee joint should be preserved in either type. In nonischemic limb, amputation through middle third of leg provides better result. Ideal length of stump varies between 12.5 and 17 cm approx.

If amputation is done for ulcers on ischemic limb, the flap designing is important. Since the blood supply in the skin is better on the posterior and medial aspect of leg, the posterior flap is kept longer. The dissection along the tissue plane is kept at minimum to preserve the blood supply. The stump is kept relatively shorter as compared to nonischemic limb. Myodesis or osteomyoplasty procedures are not recommended. All attempts are made to preserve the blood supply to stump as much as possible. When a prosthesis is fitted, frequent observation of the stump is necessary to look for skin necrosis particularly if sensation of the stump is an issue. Disarticulation of knee and transfemoral amputations are not performed for ulcers of the lower limb as majority of ulcers are around the foot and ankle.

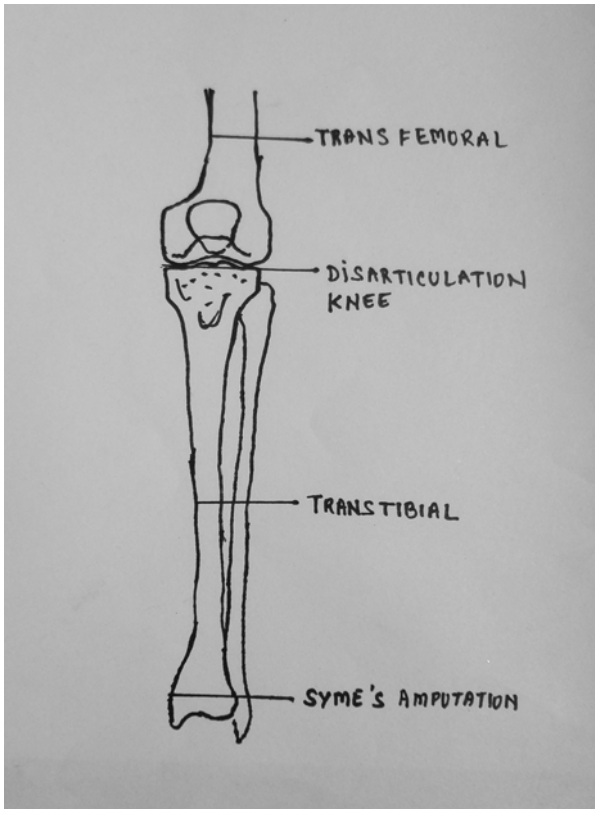

Fig. 27.8 Levels of amputation in leg

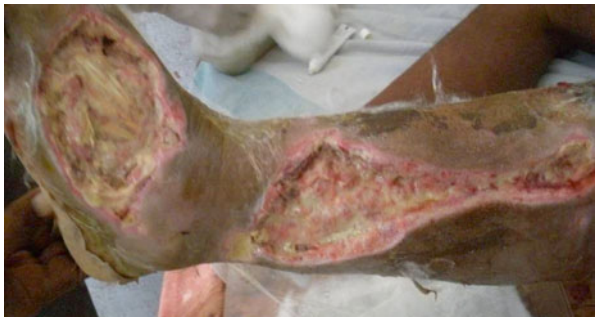

Fig. 27.9 Extensive tissue necrosis over the foot, ankle and leg; indicated for transtibial amputation

References

1. Kahle B, Hermanns HJ, Gallenkemper G. Evidence-based treatment of chronic Leg ulcers. Dtsch Arztebl Int. 2011;108:231–7.
2. Belatti DA, Phisitkul P. Declines in lower extremity amputation in the US Medicare population 2000–2010. Foot Ankle Int. 2013;34:923–31.
3. 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;29:566–70.
4. Yusmido YA, Hisamud-Din N, Mazlan M. Elective proximal lower limb amputation in spinal cord injury patients with chronic pressure ulcers. Eur J Phys Rehabil Med. 2014;50(5): 557–60.
5. Moses SE, Klein BE. The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med. 1992;152:610–6.
6. Wagner Jr FW. A classification and treatment program for diabetic, neuropathic and dysvascular foot problems. Instr Course Lect. 1979;28:143.
7. Edo AE, Edo GO, Ezeani IU. Risk factors, ulcer grade and management outcome of diabetic foot ulcers in a tropical tertiary care hospital. Niger Med J. 2013;54:59–63.
8. Boffeli TJ, Thompson JC. Partial foot amputations for salvage of the diabetic lower extremity. Clin Podiatr Med Surg. 2014;31:103–26.
9. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2014;30(7):610–22. doi:10.1002/dmrr.2535.
10. Roach JJ, Mcfarlane DS. Midfoot amputations: applications of pioneer procedures in a new age. Contemp Orthop. 1989;18:557.

Pain Management

28

V. Rastogi, Sandeep Khuba, and Anand Vishal

28.1 Introduction

Pain because of leg ulceration can influence the quality of life of patient and can have serious psychological and social effects. The most common leg ulcers are venous, ischemic, and neurotrophic. More than 95 % of chronic leg ulcers fit into one of the recognized categories [1]. The pain may be severe in all types of ulcer with the possible exception of diabetic sensory neuropathy. Pain causes the release of catecholamines via limbic system, increase levels of adrenaline and nor adrenaline and steroids, often decreases appetite, reduces mobility, and may lead to depression. Pain is a response to tissue damage and influences patients' compliance. The ulcers are quite painful. Nocturnal ischemic rest pain in the distal forefoot is typical of chronic leg ulcers.

28.2 Etiopathology and Pathophysiology of Leg Ulcer Pain

In addition to poor circulation and neuropathy, factors that contribute to chronic wounds include systemic illnesses, age, and repeated trauma. Comorbid ailments that may contribute to the formation of chronic ulcers include vasculitis, immune suppression, pyoderma gangrenosum, and diseases that cause ischemia [2]. Immune

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suppression can be caused by illnesses or medical drugs used over a long period, for example, steroids [2]. Emotional stress can also negatively affect the healing of a wound, possibly by raising blood pressure and levels of cortisol, which lowers immunity [3]. What appears to be a chronic wound may also be a malignancy; for example, cancerous tissue can grow until blood cannot reach the cells and the tissue becomes an ulcer [4]. Cancer, especially squamous cell carcinoma, may also form as the result of chronic wounds, probably due to repetitive tissue damage that stimulates rapid cell proliferation [4]. Another factor that may contribute to chronic wounds is old age [5]. The skin of older people is more easily damaged, and older cells do not proliferate as fast and may not have an adequate response to stress in terms of gene upregulation of stress-related proteins [5]. In older cells, stress response genes are overexpressed when the cell is not stressed, but when it is, the expression of these proteins is not upregulated by as much as in younger cells [5]. Comorbid factors that can lead to ischemia are especially likely to contribute to chronic wounds. Such factors include chronic fibrosis, atherosclerosis, anemia, sickle cell disease, and arterial insufficiency-related illnesses [2]. The complex neural connections involved in the processing of pain are difficult to understand.

In 1965, Melzak and Wall proposed a "gate control" mechanism of pain that occurs in the spinal cord [6]. Their theory asserted that a pain stimulus is first regulated in the peripheral nervous system and spine. The dorsal horn of the spinal cord receives nociceptive or pain stimuli from Aδ and C nerve fibers as well as non-nociceptive or sensory stimuli from large affixers. Aβ fibers transmit sensory input faster than both Aδ and C fibers. Melzak and Wall [6] summarized that when Aβ nerve fibers are simultaneously stimulated, the smaller pain fiber signals race ahead of the pain transmissions and, by synapsing with an inhibitory and projection neurons, "close the gate" for transmission of pain stimuli to the brain. This theory would explain why pain is lessened when an injured area is massaged. If only the small A δ and C nerve fibers are stimulated or if an abundance of smaller fibers are stimulated, they inactivate the inhibitory and projection neurons and "open the gate" to the brain [6]. Once nerve fibers have been stimulated, electrical signals are transmitted through the opening and closing of sodium and other ionic channels through the peripheral nerves and ascending pathways and through the spinal cord to the thalamus, hypothalamus, limbic system, and cerebral cortex. Pain transmission of a small Aδ nerve fiber is quickly relayed to the thalamus and cerebral cortex for an immediate response (withdrawal and pain relief) that occurs through descending pathways. The C nerve fiber travels the same ascending pathway through the spinal cord, only more slowly. In the brain, the signal takes a path through the hypothalamus, which releases certain hormones including those for stress, and the limbic system, which affects emotions. This might explain why chronic back pain often is associated with depression and anxiety. Descending pathways originating in the cortex inhibit the ascending pathways in the midbrain and spinal cord, "closing the gate" and diminishing pain perception. Natural opiate neurotransmitters (endorphins, dynorphins, and encephalin) also are released from the hypothalamus and work to alter pain perception [7]. The pain experience may be changed by anxiety, stress, emotions, and cognition [8]. High levels of anxiety and the release of stress hormones may inhibit descending pathways and "open the gate" causing pain perception to intensify. This

explains why individuals experience pain differently and why an individual may respond to the same type of pain differently each time it occurs. Pain thresholds are largely influenced by previous pain experiences. Once the type, intensity, location, and cause of pain have been assessed, the patient's physical and emotional well-being should be evaluated. Fears and expectations should be discussed openly. A consensus statement by the World Union of Wound Healing Societies proposed general guidelines for prevention of pain during dressing-related procedures that included awareness of the current status of the patient's pain, identification of pain triggers, and use of pain reducers and preventive analgesia whenever necessary [9].

There are two physiological types of pain: nociceptive and neuropathic. Nociceptive pain is defined as the normal physiological response to a painful stimulus [10]. Soft tissue injury associated with nociceptive pain causes inflammation and stimulation of peripheral nerve endings. The resulting hypersensitivity means that even minor stimulation can cause intense pain. Neuropathic pain is caused by a primary lesion or dysfunction in the nervous system and may be caused by nociceptive pain, ischemia, diabetes, or trauma that has damaged the peripheral nervous system and altered the pain response. An individual's experience of wound pain is complex and is influenced by a wide range of factors unique to them [11, 12]. Pain has a strong emotional dimension that is influenced by previous experience [10]. Therefore, it is no surprise that reduction of pain is frequently cited as the highest treatment priority from the patient's perspective [13]. The importance of adequate pain management associated with chronic wounds is now becoming recognized in clinical practice because it can significantly improve patient's quality of life. The patients experienced severe unrelenting persistent pain punctuated by acute episodes of intense pain. Ulcer pain and its effect dominated their descriptions of living with a leg ulcer at the start of the study. Recurring adjectives were used to describe the two elements of the ulcer pain. This persistent pain was described as "smoldering," "nagging," "creeping," and "tugging," emphasizing its insidious and dominant nature. Other descriptors such as "stabbing," "burning," "stinging," "shooting," "like lightning" and "electric shock" suggest that venous leg ulcer patients in this study also experienced intense periods of sudden pain more likely to be neuropathic in origin, in addition to nociceptive pain [10]. The coexistence of these different types of pain highlights the complexity of managing this type of chronic wound pain. One individual likened her leg ulcer pain to trigeminal neuralgia, describing the pain as like having "salt and chili on the wound surface."

28.3 Characteristics of Pain in Different Types of Ulcers

Patients with venous ulceration often describe their pain as an aching heaviness. Pain arising from arterial disease is often described as leg cramping or spasm with activity. As disease progresses, pain may occur at rest. In case of pressure, pain may be caused by inflammation and irritation from friction. Increase pain may indicate infection, improper dressing technique, or skin irritation. Patient with diabetic neuropathy ulcer may report burning type of pain associated with tingling and may be spontaneous, intermittent, or continuous.

Leg ulceration is a painful and sometimes a disabling complication of sickle cell disease that occurs in 5–10 % of adult patients. The most common site for the appearance of leg ulcer is on the inner side of the leg above the ankle and over the medial malleoli. Ulceration involves the skin and underlying tissues of the involved area. The deeper the more severe the leg ulcer pain is. Severe pain may necessitate the use of strong pain killers like opioids analgesics. Hayek et al. reported the successful use of synthetic heparin sulfate in the treatment of a sickle cell ulcer that had failed to respond to several other means of treatment [14]. Therapeutic success was assessed by complete wound coverage and vast improvement in pain score. This is the first study to report use of heparin sulfate in sickle cell ulcer.

28.4 Pain Intensity

The pain intensity can be measured by visual analogue scale. The intensity of venous leg ulcer pain experienced by patients (mean 85 mm) is greater than the mean score of 44 mm reported by Noonan and Burge in a similar client group [15]. The pain reduced significantly ($p = 0.003$) in eight out of ten patients during the treatment period. All but one participant reported a rapid decrease in pain between 30 min and a few hours after application of the first dressing. Most patients expressed a reluctance to withdraw from active treatment because they had experienced considerable pain reduction during the active phase of the study. The results showed that eight out of ten patients experienced increased pain when active treatment was discontinued. Patients with painful chronic venous leg ulceration (CVLU) feel their misery is never ending; Chase et al. coined the term "forever healing" to describe the extended time over which healing occurs [16]. The chronic illness experience of leg ulcer sufferers is dominated by persistent pain. Strauss et al. and Miller refer to this experience as the patient's illness trajectory which requires effective management of wound pain, thus further studies on the impact on quality of life of pain-relieving treatments are urgently needed [17, 18]. Nonadhesive foam dressing releasing ibuprofen consisting of a soft, hydrophilic, nonadhesive polyurethane foam containing ibuprofen (ibuprofen concentration: 0.5 mg/cm^2) has been successfully tried in management of leg ulcer pain of CVLU pain. Ibuprofen is released to the wound in the presence of wound exudates, and a study has shown that the dressing provides a continuous pain-relieving effect [19]. Ibuprofen is released to the wound in the presence of wound exudates, and a study has shown that the dressing provides a continuous pain-relieving effect [19]. In exudating wounds, ibuprofen will be released in therapeutic concentrations into the wound bed. A limited pain reduction effect could be due to many additional variables that affect the individual pain experience. No relationship was observed in this study between amount of wound exudates released and pain reduction. Disability and pain were assessed in patients with venous leg ulcers treated with split-thickness skin grafts to evaluate to what extent skin grafting improves functional status in this population. Patients with venous leg ulcers treated with split-thickness skin grafts showed improvement in functional status compared with controls.

28.5 Management of Pain in Chronic Leg Ulcer

Treatment of pain in chronic leg ulcer requires a multifacet approach controlling pain and emotional support. It is necessary to treat underlying pathology causing pain. Worsening or change in the intensity of pain may indicate a deteriorating condition or impending infection.

Controlling pain at every level of treatment will aid in wound healing. Pain triggers should be identified promptly and avoided. Analgesics, anesthetics, and other pain reduction modalities should be used to control pain during procedures. Patients should be encouraged to actively participate in their treatment. The primary etiology, size, depth, and extent of a wound help guide treatment. All contributing factors to chronic wounds should be identified and treated (e.g., ischemia, uncontrolled edema, or poor glycemic control). Control of infection and bacterial colonization is crucial. Principles of wound care should be followed, including appropriate debridement, dressing selection, and maintenance of moisture balance. Adjunctive therapies should be considered if appropriate conservative measures fail. The standard therapy for painful leg ulcer is shown in Table 28.1.

28.5.1 Topical

At present, there are few local options for the treatment of persistent pain, while managing the exudate levels present in many chronic wounds. Important properties of such local options are that they provide an optimal wound healing environment, while providing a constant local low-dose release of ibuprofen during weaning time. Various

Table 28.1 Standard of therapy in painful chronic cutaneous wound

Position change
Pressure relief
Improvement in nutritional status
Debridement
Topical antibiotics
Wound dressing
Vacuum-assisted closure
Platelet-rich plasma (PRP) rich in growth factor
Analgesics/anesthetics for pain relief
Diabetic ulcer:
Glycemic control/
Debridement
Clean, moist healing environment
Systemic antibiotics for cellulites
Miscellaneous:
TENS
Pulse radiofrequency
Ultrasound therapy

local topical drug-releasing regimes have shown to be effective in reducing the pain of chronic leg ulcerations. Use of ibuprofen slow-release foam dressings for persistent venous leg ulcer has shown improvement in terms of pain relief and quality of life. Ibuprofen gel when applied to chronic venous leg ulceration resulted in overall reduction of pain and improved mobility, sleep, and mood during the treatment, but the pain intensity increased in 1 week after discontinuing treatment. The release of ibuprofen is limited in a dry wound environment, and therefore the presence of dry necrotic tissue will impede any pain reduction [19]. Likewise, topical use of eutectic mixture of local anesthetics prilocaine-lignocaine (EMLA 5 %) has also shown improvement in pain scores and quality of life. Oral medications may be supplemented with topical aesthetic preparations [20] although they should be used with caution in open wounds because of increased absorption. Topical preparations used are eutectic mixture of local anesthetics applied 30–60 min before debridement under occlusion with a film dressing (not approved by the Food and Drug Administration for use in open wounds in the United States), 4 % lidocaine solution, 2 % lidocaine gel, 1 % lidocaine solution, 5 % lidocaine patch, topical diclofenac patch, and morphine topical gel [20].

28.5.2 Non-pharmacological Methods

The first line of pain treatment in patients with chronic wounds should be non-pharmacological. Changes in positioning, gentle wound cleansing, use of different types of dressing, and distraction or relaxation techniques have been shown to ease discomfort of cyclic pain during procedures. No pharmacological methods reduce anxiety and stress, thereby allowing the body to naturally readjust pain perception and raise tolerance to future treatment.

Transcutaneous electrical nerve stimulation (TENS) has been used as a noninvasive, non-pharmacologic adjuvant treatment modality for chronic ischemic pain [21–23]. Electrodes stimulate non-nociceptive fibers to decrease pain. A lasting reduction of pain with the use of low-frequency ultrasound has been shown in patients with recalcitrant venous leg ulcers [24]. Noncontact ultrasound has long been reported to decrease the mean healing time of chronic lower extremity wounds. Significant reduction in pain has been noted after using noncontact ultrasound for control of painful wounds [25–28]. Pulsed radiofrequency energy has been used as an adjuvant treatment in the healing of diabetic foot and pressure ulcers [29–32]. The mechanism by which pulsed radiofrequency energy alleviates pain is largely unknown. It has been demonstrated to increase the expression of cytokines (interleukin-related genes) and tumor necrosis factor-related genes that help to potentiate an initial inflammatory response production of anti-inflammatory cytokines (interleukin 10) as well as heme-oxygenase 1,2 (an off-switch for inflammation) which results in the release of potent antioxidants, antiapoptotic, and anti-inflammatory agents [33]. Pulsed radiofrequency energy (PRFE) treatment is done usually at home with an applicator pad placed directly over the wound dressing. The applicator pad delivers regulated, nonthermal radiofrequency energy at 27.12 MHz consisting of 42 μs pulses delivered 1000 times per second. Treatments last 30 min and are performed twice.

28.5.3 Systemic Agents

Chronic background pain should be controlled quickly using oral analgesics. Patients exhibit a general reluctance to take oral analgesia due to concerns about side effects and dependency and confusion about administration and dosages. The World Health Organization (WHO) provided guidelines for the treatment of cancer pain in titrating the type and dose of analgesia to the level of pain. These guidelines can be applied to wound pain. The recommended steps for control of wound pain include:

1. Nonsteroidal anti-inflammatory drugs and local anesthesia
2. Addition of a mild oral opioid (if not controlled at step 1)
3. Replacement of the mild opioid with a more potent opioid (if not controlled at step 2)

Ideally, analgesics should be fast acting, easily titrated to require changes, and have minimal side effects. Persistent chronic pain associated with nonhealing wounds is caused by tissue (nociceptive) or nerve (neuropathic) damage and is influenced by dressing changes and chronic inflammation. Anticonvulsants and sodium channel blockers have been shown to be effective in neuropathic as well as nociceptive pain. The use of gabapentin, a voltage-sensitive sodium and calcium channel blocker, also has been used as a co-analgesic to morphine in a patient with cancer wound dressing pain [33]. Oral medications may be supplemented with topical anesthetic preparations, although they should be used with caution in open wounds because of increased absorption.

28.6 Surgical Management

28.6.1 Split-Skin Grafting

The split-skin grafting can be used to treat pain of chronic venous leg ulceration [34]. It has been shown to be effective in improving pain relief and functional status of the patients. Salomé et al. used split-skin grafting in 50 patients, and they have shown significant improvement in disability index of the Health Assessment Questionnaire (HAQ-DI), visual analogue scale (VAS), and McGill Pain Questionnaire (MPQ) at 30, 90, and 180 days as compared to control group [35].

28.6.2 Lumbar Sympathectomy

Sympathectomy is proposed to act primarily via its vasodilator effects on the collateral circulation secondary to decreased sympathetic tone. This is supposed to improve tissue oxygenation and ulcer healing and it decreases tissue damage and pain. Pain is also deemed to be decreased by interrupting sympathetic–nociceptive

coupling and by direct neurolytic action on nociceptive fibers. The sympathectomy may be surgical, chemical, or by heat generation (radiofrequency lesion).

28.7 Chemical Lumbar Sympathectomy

Mashiah et al. performed phenol lumbar sympathectomy on 373 patients with painful leg ulcers, of whom 226 (60.6 %) were diabetic [36]. Over 24–120 months of follow-up, 219 patients (58.7 %) experienced total relief from pain and healing of gangrenous ulcers, although the treatment was unsuccessful in 154 patients. A favorable result was marked in diabetic patients who had rest pain and in nondiabetic patients who had digital gangrene or digital ulcers. Age and sex did not affect the results, but heavy smoking did affect. Phenol sympathectomy should be considered as an alternative to surgical sympathectomy [37]. Furthermore, the technique may be a precursor to and even an alternative to amputation in patients who have diabetes and advanced arteriosclerosis of the lower limb. Cross et al. noted pain relief in rest pain in two third (66.67 %) of patients of critical limb ischemia undergoing chemical sympathectomy in treatment group as compared to 23.5 % in control group at 6 months interval [38]. Although reduction in vascular peripheral resistance was shown, no difference in ankle–brachial pressure index or graft survival was demonstrated [39]. Fify and Quin (1975) in a randomized trial using phenol sympathectomy versus local anesthetic controls in patients with intermittent claudication found no subjective or objective difference between two groups at 1–3 months interval [40]. Alexander showed encouraging result (72 %) improvements in patients with peripheral vascular disease undergoing chemical sympathectomy with an amputation rate of 24 % [41].

28.8 RF (Radiofrequency) Lumbar Sympathectomy

Lumbar sympathectomy has been employed for over 75 years for the treatment of a variety of painful and circulatory conditions in the lower extremities. Chemical sympathectomy decreased the need for open surgical sympathectomy with less morbidity and mortality but still has risks and complications that can be catastrophic. The development of precise neurolysis with radiofrequency significantly decreased the risks of sympathectomy with results comparable to chemical and surgical neuroablation [42]. Radiofrequency sympathectomy also allows repeat procedures without the risk of distorting the original anatomy.

28.9 Surgical Sympathectomy

It has been frequently observed that the results of surgical sympathectomy are better than indicated by the diagnostic block. Also the beneficial effect of sympathectomy is progressive over a period of several weeks. Since a diagnostic block with most

agents lasts only for 2–3 h, this may not be of sufficient time to permit more than a token improvement in collateral circulation. A phenol sympathetic block, which persists for several weeks, seems to be a more rational approach to evaluating patient to be good candidate for surgery. In addition to pain reduction, lumbar sympathectomy has been used as a vasodilator to increase blood supply to the legs in patients with ischemic peripheral arterial disease. It has been noted to improve tissue oxygenation and ulcer healing and decrease pain by interrupting sympathetic–nociceptive pairing. Decrease in pain between 35 and 85 % has been noted 6 months after lumbar sympathectomy [43]. A recent study found that most physicians in the United Kingdom believe that lumbar sympathectomy is an effective, inexpensive, and safe procedure for the treatment of lower extremity ischemia [44]. Chemical lumbar sympathectomy has been shown to be an effective alternative to surgical sympathectomy [36].

Severe pain is an indication of severe disease and in general results of sympathectomy are poor [45]. A rise in temperature of 3 F or more or a good subjective response following sympathetic block shows good response. This operation was popular between 1930s and 1950s, as it was the only available procedure to save an ischemic limb. After that time, revascularization surgery has replaced sympathectomy and limits its indications [45]. It is agreed that sympathectomy will lead to increases in cutaneous blood flow, and altered pain transmission can be used to treat specific conditions such as causalgia, symptomatic vasospastic disorders, and hyperhidrosis in addition to inoperable distal arterial occlusive disease [46–50]. In inoperable arterial occlusive disease, sympathectomy has been proved by meta-analysis to be beneficial in ulcer healing, limit the progress of superficial gangrene, and relieve rest pain with nearly fixed expected results in selected indications [45, 51].

Thromboangitis obliterans (Buerger's disease) is an inflammatory disease of unknown etiology affecting medium-sized arteries, vein, and adjacent nerves. The symptoms as a result of arterial occlusion are pain, change in color, and ulceration. Sympathectomy is helpful in improving symptoms by increasing the collateral circulation. The characteristic changes described by Raynaud's are typical of the lesion. The white color results from ischemia due to arteriolar and capillary spasm. Anoxia causes relaxation of capillary wall allowing dilatation and retrograde venous dilatation and blue discoloration of skin. It seems that the removal or inhibition of controlling sympathetic system would relieve the symptoms. Sympathectomy may, therefore, produce complete or partial relief of symptoms. Fifty-two patients undergoing surgical sympathectomy showed good results as evidenced by complete or partial relief of pain for more than 1 year. Surgical lumbar sympathectomy results in relief of intermittent claudication in half (51 %) of patients and another two third of the patients reported warm extremities and one third of patients relieved of rest pain. Ulceration, with or without amputation of digits, was improved or healed in 60 % of extremities after sympathectomy. Seventy percent of patients had good results as evidenced by significant or complete relief of symptoms for more than 1 year [36]. Over a 5-year period, 132 operative lumbar sympathectomies were performed on 118 patients with severe peripheral vascular disease unsuitable for

vascular reconstruction. In 62 patients, local ulcer debridement or toe amputation was performed at the same time. There was a 45 % subsequent limb loss, which occurred predominantly in the first 6 months after sympathectomy. The risk of limb loss was independent of diabetes, hypertension, ischemic heart disease, cerebrovascular disease, or concomitant reconstructive surgery. Of the limbs that survived, rest pain had resolved in 86 % within 6 months and 64 % recovered from all trophic changes over a similar period. This series suggests that lumbar sympathectomy coupled with local tissue management remains a valuable treatment option for the severely ischemic limb not amenable to reconstructive surgery [52]. Surgical sympathectomy not only relieves resting pain but also healing of leg ulcer and decreasing the need for amputation [53].

28.9.1 Endoscopic Lumbar Sympathectomy

Recently, Sheriff Reffat et al. compared endoscopic versus open lumbar sympathectomy and reported that in 58 % patients, rest pain disappeared, ischemic ulcer healed in 62.5 % patients, and gangrene demarcation changed following endoscopic lumbar sympathectomy [54]. There was a significant decrease in pain killer (paracetamol) in endoscopic group as compared to open surgery. On third day onward, none of the patients undergoing endoscopic surgery needed pain killers. Endoscopic lumbar sympathectomies are less invasive, with minimal complications decreasing patients' hospital stay.

28.9.2 Other Surgical Interventions

Arteriosclerosis obliterans is one of the most common indications of ischemia of the lower extremities. The clinical picture includes claudication, color changes, ischemia, ulceration, and gangrene. Although arteriosclerosis is systemic disease, one segment of the arterial tree may be affected as a result of thrombus. When such occlusion is in distal aorta or iliac or femoral arteries, the recently developed surgical intervention like endarterectomy, resection, or bypass graft or endovascular procedures will give best results. When arteriogram shows a block with little or no distal filling or a patent artery with a marked narrowed lumen and an irregular outline, direct surgical interference has little to offer. In such a case in which arteriosclerosis is more generalized, the sympathectomy by improving collateral circulation is useful [36].

Conclusion

Pain is the most predominant presentation of an ulcer of the lower extremity. All possible measures should be taken to alleviate the pain and have pain-free life. Local control of tissue is one of most important factors in relieving pain. But majority of the patients will need some form of analgesia. Preferably, the analgesics should be non-opioid and topical analgesics may be of some use. Lumbar

sympathectomy carried out by any route is a good alternative in relieving pain. In localized arterial diseases, some form of open or endovascular procedures may help.

References

1. Lu YM, Zhao WJ, Zheng YH. Painful leg ulcers: a misdiagnosed case report with literature review. Wounds. 2007;19(5):124–7.
2. Krasner D. Painful venous ulcers: themes and stories about living with the pain and suffering. J Wound Steamy Continence Nurs. 1998;25(3):158–60.
3. Augustin M, Maier K. Psychosomatic aspects and quality of life in patients with chronic wounds. Dermatol Psychosom. 2003;4:5–13.
4. World Union of Wound Healing Societies. Principles of best practice: minimizing pain at wound dressing-related procedures. A consensus document. London: MEP Ltd; 2004. Available from URL: http://www.wuwhs.org.
5. Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of Metalloproteinase's MMP-2 and MMP-9. J Invest Dermatol. 1993;101(1):64–8.
6. Melzak R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
7. Woo KY, Sibbald RG. Chronic wound pain: a conceptual model. Adv Skin Wound Care. 2008;21(4):175–88.
8. McCaffery M, Pasero C. Pain: clinical manual for nursing practice. 2nd ed. St.Louis: Mosby; 1999.
9. World Union of Wound Healing Societies. Principles of best practice: minimising pain at wound dressing-related procedures. Wound Care. 2008;21(4):175–88. A consensus document. London: MEP Ltd; 2004.
10. Johnson L. The nursing role in recognizing and assessing neuropathic pain. Br J Nurs. 2004;13(18):1092–7.
11. Doyle D, Hanks G, MacDonald N, editors. Oxford textbook of palliative medicine. 2nd ed. Oxford: Oxford University Press; 1989.
12. McMullen M. The relationship between pain and leg ulcers: a critical review. Br J Nurs. 2004;13(19):S30–6.
13. Lindholm C, Bjellerup M, Christensen OB, Zederfeldt B. Quality of life in chronic leg ulcer patients. An assessment according to the Nottingham Health Profile. Acta Derm Venereol (Stockh). 1993;736:440–3.
14. Hayek S, Dibo S, Baroud J, Ibrahim A, Barritault D. Refractory sickle cell leg ulcer: is heparan sulphate a new hope? Int Wound J. 2014; doi: 10.1111/iwj.12217.
15. Noonan L, Burge SM. Venous leg ulcer: is pain a problem? Phlebology. 1998;13:14–9.
16. Chase SK, Melloni M, Savage A. A forever healing the lived experience of venous ulcer disease. J Vasc Nurs. 1997;15(2):73–8.
17. Strauss A, Corbin M, Fagerhaugh S, Glaser B, Maines D, Suzek B, et al. Chronic illness and the quality of life. St Louis: CV Mosby; 1984.
18. Miller JF. Coping with chronic illness. Overcoming powerlessness. 2nd ed. Philedelphia: FA Davis; 1992.
19. Jorgensen B, Firis GJ, Gottrup F. Pain and quality of life for patients with venous ulcer: concept of efficacy of Biatain –Ibu, a new pain reducing wound dressing. Wound Repair Regen. 2006;14:233–9.
20. Hafner HM, Thomas SR, Eisner M, Steins A, Junger M. The influence of EMLA cream on cutaneous microcirculation. Clin Hemorheol Microcirc. 2003;28:121–8.

21. Debreceni L, Gyulai M, Debreceni A, Szabo K. Results of transcutaneous electrical stimulation (TES) in cure of lower extremity arterial disease. Angiology. 1995;46(7):613–8.
22. Brown L, Tabasam G, BJoordal JM, Jhonson MI. An investigation into the effect of electrode placement of transcutaneous electrical stimulation (TENS) on experimentally induced ischemic pain in healthy human participants. Clin J Pain. 2007;23(9):735–43.
23. Jünger M, Arnold A, Zuder D, Stahl HW, Heising S. Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Derma pulse): a prospective, placebo controlled, double blind trial. Wound Repair Regen. 2008;16(4):480–48.
24. Kavros SJ, Schenck EC. Use of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis. J Am Podiatr Med Assoc. 2007;97:95–101.
25. Ennis WJ, Foremann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: result s of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage. 2005;51:24–39.
26. Ennis WJ, Valdes W, Gainer M, Meneses P. Evaluation of clinical effectiveness of ultrasound therapy on healing of chronic wounds. Adv Skin Wound Care. 2006;19:437–46.
27. Gehling ML, Samies JH. The effect of noncontact, low-intensity, low-frequency therapeutic ultrasound on lower-extremity chronic wound pain: a retrospective chart review. Ostomy Wound Manage. 2007;53:44–50.
28. Bell AI, Cavorsi J. Noncontact ultrasound therapy for adjunctive treatment of non healing wounds: retrospective analysis. Phys Ther. 2008;88(12):1517–24.
29. Porreca EG, Giordano-Jablon GM. Treatment of severe (stage III and IV) chronic pressure ulcers using pulsed radio frequency energy in a quadriplegic patient. Eplasty. 2008;8:49.
30. Larsen JA, Overstreet J. Pulsed radio frequency energy in the treatment of complex diabetic foot wounds. Two cases. J Wound Ostomy Continence Nurs. 2008;35(5):523–7.
31. Abejon D, Garcia-del-Valle S, Fuentes ML, Gomez-Arnau JI, Reig E, van Zundert J. Pulsed radiofrequency in lumbar radicular pain: clinical effects in various etiological groups. Pain Pract. 2007;7(1):21–6.
32. Martin DC, Willis ML, Mullinax LA, Clarke NL, Homburger JA, Berger IH. Pulsed radiofrequency application in the treatment of chronic pain. Pain Pract. 2007;7(1):31–5.
33. Alcaraz MJ, Fernandez P, Guillen MI. Anti-inflammatory actions of the hemeoxygenase-1 pathway. Curr Pharm Des. 2003;9(30):2541–51.
34. Devulder J, Lambert J. Gabapentin for pain control in cancer patients' wound dressing care. J Pain Symptom Manage. 2001;22(1):622–6.
35. Salomé GM, Ferreira LM. Impact of skin grafting of venous leg ulcers on functional status and pain. World J Surg. 2013;37(6):1438–45.
36. Mashiah A, Soroker D, Pasik S, Mashiah T. Phenol lumbar sympathetic block in diabetic lower limb ischemia. J Cardiovasc Risk. 1995;2(5):467–9.
37. Bhattarai BK, Rahman TR, Biswas BK, Sah BP, Agarwal B. Fluoroscopy guided chemical lumbar for lower limb ischemic ulcers. J Nepal Med Assoc. 2006;45(163):295–9.
38. Cross FW, Cotton LT. Chemical lumbar sympathectomy for ischemia rest pain: a randomised, prospective controlled clinical trial. Am J Surg. 1985;150:341–5.
39. Barnes RW, Baker WH, Shank G, Maixner W, Hayes AC, Lin R, Clarke W. Value of concomitant sympathectomy in aortoiliac reconstruction results of a prospective, randomised study. Arch Surg. 1977;112:1325–30.
40. Fify T, Quin RO. Phenol sympathectomy in the treatment of intermittent claudication: a controlled clinical trial. Br J Surg. 1975;62:68–71.
41. Alexander JP. Chemical lumbar sympathectomy in patient with severe lower limb ischemia. Ulster Med J. 1994;63:137–43.
42. Oliver S, Royo J, Perez C, Eshevaria J, Clemente M. Radiofrequency Lumbar Sympathectomy in the treatment of hypertensive leg ulcers. Eur J Pain Suppl. 2011;5(1):01–10.
43. Sunni A, Hamid A, Dunning J. Is sympathectomy of benefit in critical leg ischemia not amendable to revascularisation? Interact Cardio Vasc Thorac Surg. 2005;4:478–83.

44. Nesargikar P, Ajit MK, Eyers PS, Nichols BJ, Chester JF. Lumbar chemical sympathectomy in peripheral vascular disease: does it still have role? Int J Surg. 2009;7(2):145–9.
45. Flotte CT. Evaluation of lumbar sympathectomy. Am J Cardiol. 1959;4:644–8.
46. Abdurahman AF, Rutherford RB. Lumbar sympathectomy, indications and technique. In: Rutherford RB, editor. Vascular surgery. Philadelphia: Elsevier Saunders; 2005. p. 1223–35.
47. Mick S. Role of sympathetic nervous system in pain. Anaesthesia and intensive care medicine. 2005;6(2):52–5.
48. Olin JW. Thromboangiitis obliterans (Buerger's disease). In: Rutherford RB, editor. Vascular surgery. Philadelphia: Elsevier Saunders; 2005. p. 404–18.
49. Tseng MY, Tseng JH. Endoscopic extra peritoneal lumbar sympathectomy for plantar hyperhidrosis: case report. J Clin Neurosci. 2001;8:555–6.
50. Ates A, Yekeler I, Ceviz M, Pac M, Basoglu A, et al. One of the most frequent vascular diseases in north eastern of turkey: thromboangitis obliterans or Berger's disease (experience with 344 cases). Int J Cardiol. 2006;111:147–53.
51. Sanni A, Hamid A, Dunning J. Is sympathectomy of benefit in critical leg ischaemia not amenable to revascularisation? Interact Cardiovasc Thorac Surg. 2005;4:478–48.
52. Baker DM, Lamerton AJ. Operative lumbar sympathectomy for severe lower limb ischaemia: still a valuable option. Ann R Coll Surg Engl. 1994;76:50–3.
53. Perez-Burkhardt JL, Gonzalez-Fajardo JA, Martin JF, Carpintero Mediavlla LA, Mateo Gutierrez AM. Lumbar sympathectomy as isolated technique for the treatment of lower limb chronic ischemia. J Cardiovasc Surg. 1999;40:7–13.
54. Sherif R, Hatem H, Mohamed A, Mamdouh EM. Endoscopic versus open lumbar sympathectomy. Eur J Surg. 2009;28(1):13–20.

Documentation of Ulcer

29

Seema Khanna

29.1 Introduction

The prevalence of lower extremity ulceration is 0.18–2 % in the general population, and in patients over 65 years of age, it is up to 5 % [1]. Because of the chronic nature of ulceration in majority of patients and its associated morbidity, it is debilitating not only for the patients but it also puts a considerable strain on the economy of the individual and the society. The cause of lower limb ulceration could be varied, e.g., arterial, venous, lymphatic, diabetic, neuropathic, malignant, infectious, etc. Hence evaluation of the cause is essential. The evaluation of a chronic ulcer encompasses clinical assessment, documentation, investigations to arrive at a diagnosis, and then follow-up of the patients once the appropriate treatment is initiated.

29.2 Significance of Documentation

Documentation of an ulcer is important both to the patient and the clinician. Documentation is a piece of written, printed, or electronic material that provides information or evidence. Keeping a record is an integral part of the effective care of the patients. It is of critical importance to communicate to the patients the severity of illness and document that communication. Documentation remains the cornerstone of avoiding litigation.

It also saves the physician from medical malpractice litigation. The approach to record keeping that a court of law adopts is that "If anything has not been recorded, it has not been done." Good record keeping helps to improve accountability and shows how decisions related to patient care were made [2].

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Documentation forms an initial and continuous part of treatment. It is an objective form of assessment which aids in reevaluation and also monitors treatment efficacy. Documentation is also important for the researchers for comparing healing responses among different groups of patients. Several researchers have described the importance of regular wound measurement and reported that a percentage change in wound area over a 4-week period of 30 % or more reliably predicted wound healing [3, 4]. Thus, a certain method of wound area measurement has to be adopted which is reliable, repeatable, valid, accessible, and minimally time consuming.

The wounds of a leg are not on a planar surface but on a curved surface; hence the problems inherent in obtaining accurate wound measurement are, by definition of wound boundary, undermined or deep wounds and natural curvatures of the wounds [5].

29.3 Describing an Ulcer (Table 29.1)

Various parameters and techniques have been used to describe and document an ulcer on the lower extremities. Firstly, an ulcer anywhere in the body should be described under the following headings (Fig. 29.1).

1. *Document the location of the ulcer*
   For example, venous ulcers are more common in the gaiter area and pressure ulcer on pressure points like the sacrum, ischial tuberosity, and heel.
2. *Document the type of wound according to etiology*
   For example, arterial, pressure ulcer, venous, diabetic, or neuropathic

Table 29.1 Documentation of wound

Information to be documented
1. Date and time of assessment
2. Type of wound and underlying etiology
3. Factors that could delay wound healing
4. Location of wound
5. Duration of wound
6. Wound measurements
7. Depth of damage
8. Type and color of tissue in wound bed
9. Presence of infection
10. Exudate levels and type
11. Presence of odor
12. Presence of pain and its level
13. Wound margins
14. Dressing selection and regimen
Wound assessed at each dressing and measured at 4 weeks interval

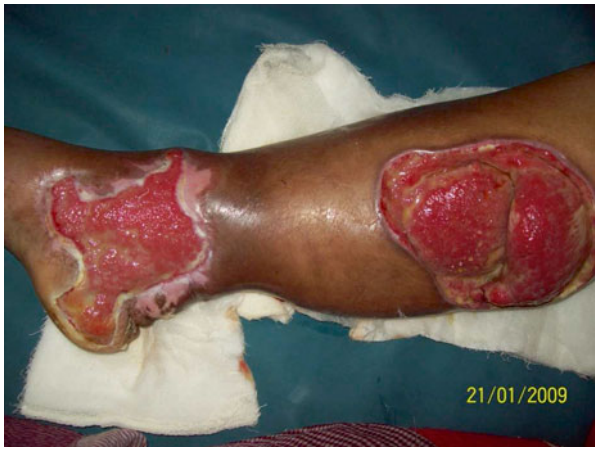

Fig. 29.1 Chronic diabetic ulcers of the lower extremity

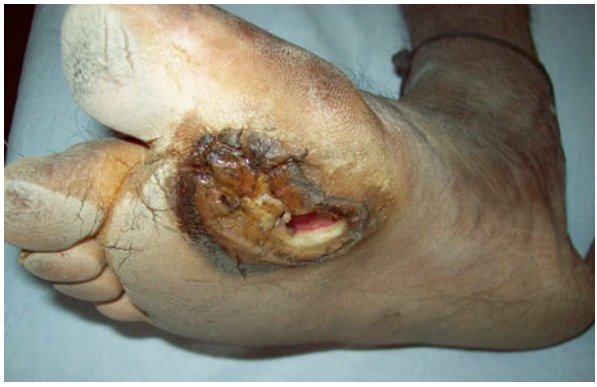

Fig. 29.2 A diabetic foot ulcer with undermined edges

3. *Document the size*
   It is measured in cm in three dimensions:
   - Length (maximum measurement in a head to toe direction)
   - Width (maximum measurement at right angle to above)
   - Depth (deepest part of the visible wound bed is measured)
4. *Document any sinus tract/undermining/tunneling*
   Undermining or tunneling is described as tissue destruction underneath the intact skin margins (Fig. 29.2). When this undermined area gets epithelialized, it forms a sinus tract.
5. *Document type/amount/odour of exudate:*
   Type – serous, serosanguinous, sanguinous, purulent
   Amount– none, scant, small, moderate, large
   Odour– absent or present
6. *Describe the presence or absence of necrotic tissue*
   It could be slough or eschar (Fig. 29.3).

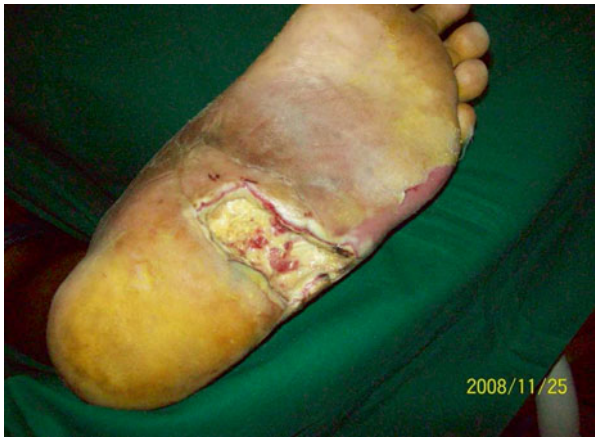

Fig. 29.3 Ulcer on plantar aspect of sole

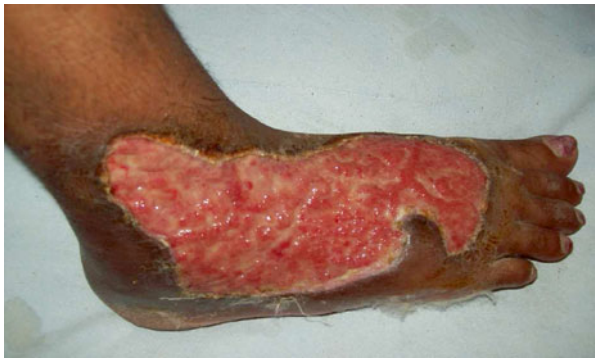

Fig. 29.4 Chronic ulcer showing granulation tissue on its floor

Describe the amount and color. Describe whether it is nonadherent, loosely adherent, or firmly adherent.

7. *Document about granulation tissue:*
   Whether it is pale or red, whether it is occupying whole of the floor or partial area of the ulcer floor, i.e., in islands or complete wound (Fig. 29.4).
8. *Define the wound edges:*
   Defined or undefined. Whether macerated, fibrotic, or callused.
9. *Describe the surrounding tissue:*

Whether the surrounding skin is normal, hyperpigmented, have evidence of lipodermatosclerosis, or have prominent veins.

29.4 Classification of Ulcers

Various systems are available to describe the various types of ulceration.

29.4.1 Wagner System [6]

Has six grades from Grade 0 to Grade 5

Grade 0 – Pre- or post-ulcerative site
Grade 1– superficial ulcer
Grade 2– ulcer penetrating to the tendon or joint capsule
Grade 3– lesion involving deeper tissue
Grade 4– forefoot gangrene
Grade 5– whole-foot gangrene involving more than 2/3rd of the foot

Another system has been described by the University of Texas:

29.4.2 University of Texas System

	Grade 0	Grade 1	Grade 2	Grade 3
	Pre or post ulceration site	Superficial wound not involving the tendon, capsule, or bone or joint	Wound penetrating to the tendon or capsule	Ulcer penetrating to the bone or joint
Lesions without infection or ischemia				
Infected/nonischemic lesions				
Noninfection/ischemic lesions				
Infected ischemic lesions				

Another system is SAD System.

29.4.3 S(AD) SAD System (Area, Depth, Sepsis, Arteriopathy, and Denervation) [7]

Grade	Area	Deep	Sepsis	Arteriopathy	Denervation
0	Skin intact	Skin intact	–	Pedal pulses present	Intact
1	Lesion <1 cm^2	Superficial (skin with SC tissue)	No infected lesions	Pedal pulses reduced or missing	Reduced
2	Lesion from 1 to 3 cm^2	Lesion penetrating to the tendon, periosteum, and joint capsules	Cellulite-associated lesion	Absence of both pedal pulses	Absent
3	Lesion >3 cm^2	Lesion in bones or joint space	Lesions with osteomyelitis	Gangrene	Charcot joint

29.5 Tools for Ulcer Measurement

Various systems have been devised to describe the severity of an ulcer. Any wound measurement tool should have following characteristics:

- Accuracy
- Repeatability
- Validity
- Reliability and interpreter reliability
- Usability

Various methods have been used to document an ulcer of the lower extremity. They can be broadly classified into:

(a) Contact methods
(b) Noncontact methods

(a) *Contact methods*
   1. Ruler method
   2. Graduated swab stick method
   3. Alginate cast
   4. Planimetry
   5. Kundin gauge
   6. Wound tracing

(b) *Noncontact methods*
   1. Clinical photography
   2. Stereophotogrammetry
   3. Structured light techniques
   4. Laser triangulation
   5. Alfred/medseed wound imaging system
   6. Video image analysis
   7. Magnetic resonance imaging

1. *Ruler method*

   This is a crude but commonly used measurement technique by which maximum perpendicular length and maximum perpendicular width are measured using a disposable scale (Figs. 29.5 and 29.6). Surface wound area is calculated by multiplying the two which is typically recorded in cm^2 [8].This method models the wound as a rectangle. The major flaw in this method is that it is subjective and normally overestimates the wound area by 25 % [9].
2. *Wound Tracing*

   Transparency tracing method is another low-cost technique frequently used. Two sterile transparent sheets are laid on the wound and the outline marked with

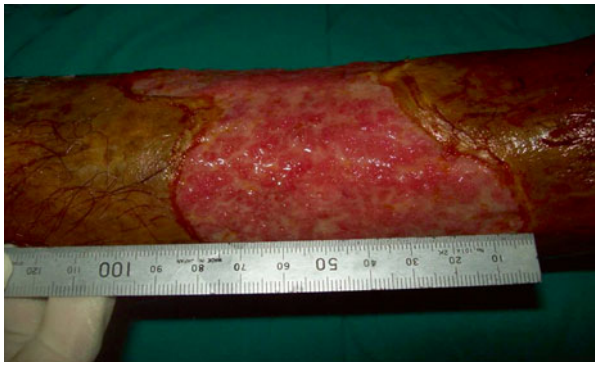

Fig. 29.5 Measurement by ruler method

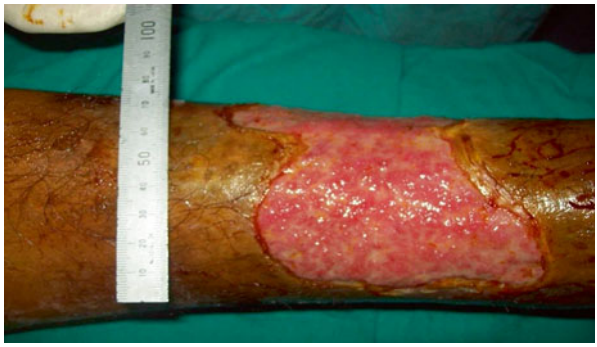

Fig. 29.6 Wound measurement by ruler method

a marker pen on the top sheet. The lower sheet is discarded and the upper sheet is placed over a grid and the areas calculated by the number of squares included [10, 11]. The advantage of the method is that it can be conveniently used on lower extremities and molded according to the curvature of the limb.

3. *Kundin Gauge*

   The Kundin wound gauge was developed and tested in 1985 [12]. It is an instrument that can measure area and volume. Kundin gauge is a ruler-based device using three disposable paper rulers set at orthogonal angles to measure length, breadth or width, and depth of the wound. This method models the wound as an ellipse with the area calculated as area = length*breath*0.785 [13]. The three rulers form four cross-arms and a vertical arm that can be placed over and into the wound. Four reference points are assessed and provide the radii for the calculation of the surface area. The vertical insert allows for volume calculation. Kundin provided the standard procedure and the formula used in the calculations [13]. The gauge is easily placed on the sterile dressing and assembled for either area or volume determinations.

4. *Acetate method* [14]

   The acetate method involves applying a two-layer transparent acetate over the wound and tracing the perimeter with a permanent pen. The contact layer is then discarded into clinical waste and the top layer stored with the patients notes.

Most acetates are provided preprinted with 1 cm^2 [15, 16]. Some acetates are preprinted in 1 mm^2 areas but these take too long to count and are not suited to routine practice. In addition to providing an area outline of the wound, the acetate can be used to identify areas of slough and epithelialization and can be dated and stored within patient's notes.

5. *Planimetry*

Planimetry is a measurement of the surface area. A freehand tracing of the outline of ulcer is digitized and the surface area of ulcer is calculated with the help of computer. The digital planimetry technique appears to improve the accuracy of surface area determination (error rate of ± 5.03 %) compared with direct tracing with the planimeter (error rate of ± 11.7 %) [17].

6. *Clinical Photography* (Table 29.2)

With digital cameras becoming easily available and affordable, clinical photography has become the easiest and most reliable way to document the course of an ulcer on the lower extremity. The clinical photograph can be used to document the ulcer and the disease process and progress. The photographic record depicts many details which can never be adequately described in words and certain findings may be brought to the notice of the surgeon in retrospect on examining the photograph. The clinical photograph provides the clinician with a multifaceted record for reference, record, and reflection and this perceived image becomes more important with time [18]. A 10.5 pixel digital camera is a handy and useful resource which can be carried in the operation theatre, outpatient department, and ward easily.

Attention to background of the photograph is an essential consideration to be kept in mind. The background must be of single solid color with no visible textural or interior design detail, wall switches, office or clinical equipment or articles, clothing, etc. These extraneous items are unacceptable and distracting. The common problems which are encountered in clinical photography include distor-

Table 29.2 Criteria for wound photography

1. Obtain written consent from patient
2. Photograph the wound on initial assessment and repeat every 4 weeks or more frequently if the wound condition changes rapidly
3. Photographs should be labeled with the patient's registration number, name, date of birth, date of photo, and wound position
4. Include a ruled measure with indication for direction
5. Upload the patient's record in chronological order
6. All photographs should be clean and well in focus
7. Privacy of patient, as covering the eye, should always be maintained
8. Always maintain the confidentiality of the patient
9. For publication, separate and specific consent must be maintained
10. Ideally photos should not be taken from mobile phones and should be deleted from digital camera once transferred to secure site
11. The camera should be cleaned after use to prevent cross infection

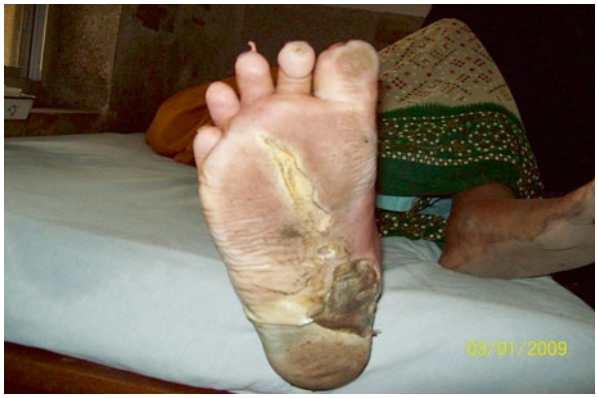

Fig. 29.7 Improperly taken photograph of ulcer foot with unnecessary background images

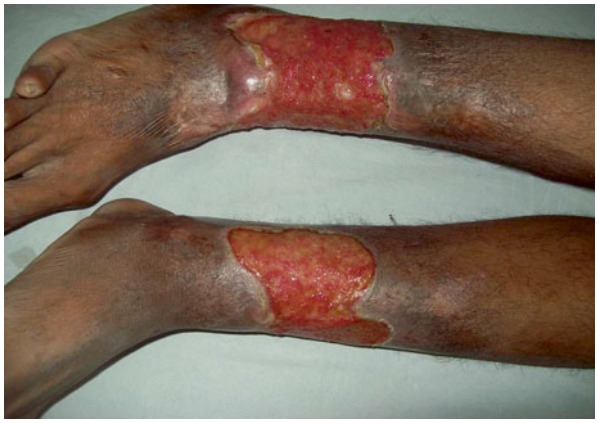

Fig. 29.8 Chronic venous ulcers of bilateral lower limbs

tion, over- or underexposure, shadowing, and variation in positioning, size, and framing (Figs. 29.7 and 29.8).

7. *Stereophotogrammetry*

   A portable stereo camera linked to a computer is used to take photographs in a clinical setting [18]. Stereophotogrammetry is >99 % accurate with a precision of <2 % between actual and measured surface areas of the ulcer modes. It is reported to be ten times more precise in the clinical settings. This technique consists of three sections: the camera apparatus, the plotting mechanism, and a computer to operate the required programs. The camera frame and two cameras take simultaneous overlapping positive color transparency. It is fixed focal length. The reprojection of the images from the same apparatus produces a full-scale three-dimensional image when moved through polarizing lenses. The plotting mechanism allows the operator to digitally record X, Y, and Z co-ordinates for computer analysis. The computer program calculates volume and surface area from the recorded co-ordinates using multiple cross sections of the ulcer and fitted triangles on the ulcer surface [19]. Stereophotogrametry is a valid and

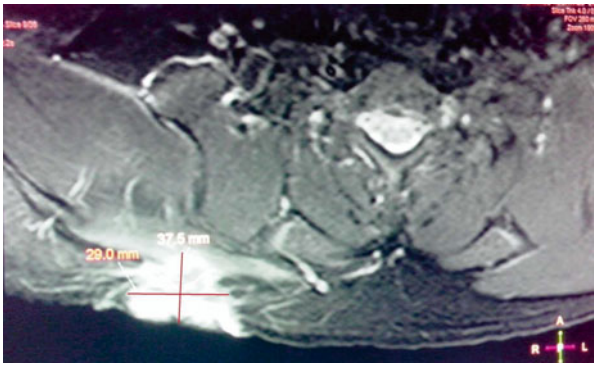

Fig. 29.9 Ulcer measurement and documentation by MRI

reliable method of volume and area measurement and has become the standard measure in comparison with other methods.

8. *Structured Lighting*

   Structured lighting is another vision-based technology used to measure wound areas. A specific light pattern is projected on the wound and it is photographed at a known angle. A computer is then used to calculate and volume based on this image [5, 20].

9. *Magnetic Resonance Imaging*

MRI has become an integral part of imaging arsenal with its ever expanding indications. The principle of MRI is that nuclei containing an odd number of protons or electrons have a characteristic motion in a magnetic field. In a uniform strong magnetic field like an MRI scanner, these nuclei align themselves with the main magnetic field and result in a net magnetic moment. A brief radiofrequency pulse is applied to alter the motion of the nuclei momentarily. The nuclei then realign themselves with the main magnetic field (relaxation) and in the process emit a radiofrequency signal that can be recorded, spatially encoded, and used to construct a grey-scale image [21, 22]. MRI is increasingly being used for wound assessment, extent evaluation, and measurement (Fig. 29.9).

Conclusion

In this era of evidence-based medicine, documentation is an essential component in the care and management of the patient. Any method of documentation of ulcers of the lower extremity which provides an objective assessment of the progress of the disease process and the results of therapeutic interventions is considered effective.

References

1. Spentzoris G, Labropoulos N. The evaluation of lower extremity ulcers. Semin Interv Radiol. 2009;26(4):286–95.
2. NMC. Record keeping – guidance for nurses and midwives. London: Nursing and Midwifery Council; 2009.

3. Gethin G. The importance of continuous wound monitoring. Wounds UK. 2006;2(2):60–7.
4. Papazoglou ES, Zubkov L, Neidrauer M, Rannou N, Weingarten MS. Image analysis of chronic wounds for determining surface area. Wound Repair Regen. 2010;18(4):349–58. Plassman P. Measuring wounds. J Wound Care. 1995;4(6):269–72.
5. Plassman P, Jones T. MAVIS: a non invasive instrument to measure area and volume of wound. Med Eng Phys. 1998;20(5):332–8.
6. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle Clin. 1981;2:64–122.
7. Parisi MCR, Zantut-Wittman DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. Eur J Endocrinol. 2008;159:417–22.
8. Falagan M. Wound management: can it help us to monitor progression to healing? J Wound Care. 2003;12(5):189–94.
9. Rodgers LC, Bevilacqua NJ, Armstrong DC, Andros G. Digital planimetry results in more accurate wound measurements: a comparison to standard ruler measurements. J Diabetes Sci Technol. 2010;4(40):799–802.
10. Langeno DK, Melland H, et al. Comparison of two wound volume measurement methods. Adv Skin Wound Care. 2001;14(4):190–6.
11. Maytovitz HN, Soontupe LB. Wound areas by computerized planimetry of digital images: accuracy and reliability. Adv Skin Wound Care. 2009;22(5):222–9.
12. Kundin JI. Designing and developing a new measurement tool. Perioper Nurs Q. 1985;1(4):40–5.
13. Kundin JI. A new way to size up wounds. Am J Nurs. 1989;89(2):206–7.
14. Geogina G. The importance of continuous wound measuring. Wounds. 2006;2(2):60–7.
15. Harding KG. Methods for assessing change in ulcer status. Adv Wound Care. 1995;8(4):528–42.
16. Melhuish JM, Plassman P, Harding K. Circumference, area and volume of healing wound. J Wound Care. 1994;3(8):380–4.
17. Bulstrode CJ, Goode AW, et al. Stereophotogrammetry for measuring rates of cutaneous healing: a comparison with conventional techniques. Clin Sci. 1986;71:437–43.
18. Nelson GD. The photography of patients. Clinical photography in plastic surgery. 1 ed. ISBN 0-316-60315-5. Little Brown and Company, USA. 1988.
19. Johnson M, Miller R. Measuring healing in leg ulcer: practice considerations. Appl Nurs Res. 1996;9(4):204–8.
20. Krouskop TA, Baker R, et al. A non contact wound measurement system. J Rehabil Res Dev. 2002;39(3):337–46.
21. Norman S Williams, Christopher JK, Bulstrode, P Ronan O' Connell Published by Hodder Arnold, an imprint of Hodder Education, an Hachette UK Company, 338 Euston Road, London NW1 3BH.
22. Gilman TH. Parameter for measurement of wound closure. Wounds. 1990;3:95–101.