Limb Salvage of the Diabetic Foot

An Interdisciplinary Approach

Michael E. Edmonds
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The use and dosages of medicines stated in the book are advisory and should be checked by the individual prescriber

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This book is dedicated to our families, for their unconditional love and support.

Preface

The prevalence of diabetes continues to increase worldwide and coincides with a progressive increase in the number of diabetic foot complications. A major amputation in a patient with diabetes takes place every 20 s throughout the world. It is said that 80% of amputations in diabetic patients are preventable. This book is devoted to limb salvage and is about saving the limbs and lives of diabetic foot patients.

After an introductory chapter on assessment, classification and approach to management, the book is divided into four sections, devoted to the four commonest presentations of the diabetic foot, namely, the neuropathic foot, the Charcot foot, the ischaemic foot and the infected foot. Each section has an introduction explaining the clinical approach to each of the presentations and is accompanied by an algorithm illustrating the limb salvage pathway and intervention steps for each of the four presentations. Each section contains clinical photographs illustrating the various presentations as well as the techniques of management.

This book emphasizes the need for an interdisciplinary team approach to the diabetic foot and should help individual members of the team to understand the differing roles of other members. The team is usually referred to as the interdisciplinary team, although in this book, the term multidisciplinary team is also used. There may be subtle differences in the meaning of these terms, but in this multi-author book, they are regarded as interchangeable.

This book is a collaboration between members of the interdisciplinary diabetic foot teams of King's College Hospital, London, and Yale University School of Medicine, New Haven. This collaboration started in October 2015 with a joint Yale-King's Vascular Symposium at King's College Hospital, which has been followed by two further symposia, at Yale and in Thailand, the latter in conjunction with the Thai Vascular Association. Contributors to these symposia, from Yale and King's, form the authorship of this book. We are grateful to them for agreeing to share their expertise in this book.

Finally, we wish to thank our developmental editors, Barbara Lopez-Lucio and Joni Fraser, for their excellent assistance and patience which have been much appreciated.

We hope this book will improve the outlook of the patient with diabetic foot problems and reduce the number of avoidable major amputations.

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Abbreviations

ABI	Ankle brachial index
ACC	American College of Cardiology
ADA	American Diabetes Association
AFO	Ankle foot orthosis
AFS	Amputation-free survival
AHA	American Heart Association
ALADIN III study	Alpha lipoic acid in diabetic neuropathy III study
AMWT	Advanced moist wound therapy
AOFAS	Academy of Foot and Ankle Surgeons
AP	Antero-posterior
ARI	Aldose reductase inhibitors
ATA	Anterior tibial artery
AVF	Arteriovenous fistula
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
BIS	Bispectral index
BMI	Body mass index
BMS	Bare-metal stent
BTA	Below the ankle
BTK	Below the knee
CAD	Computer-aided design
CAM	Computer-aided manufacture
CA-MRSA	Community-acquired methicillin-resistant Staphylococcus aureus
CAN	Cardiac autonomic neuropathy
CART	Controlled antegrade and retrograde subintimal tracking
CCO	Clostridial collagenase ointment
CE MRA	Contrast enhanced magnetic resonance angiography
CFA	Common femoral artery
CHF	Congestive heart failure
cFN	Cellular fibronectin
CGRP	Calcitonin gene-related peptide

CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CHF	Congestive heart failure
CKD	Chronic kidney disease
CLI	Critical limb ischaemia
CLTI	Chronic Limb Threatening Ischaemia
CN	Charcot neuroarthropathy
CoNS	Coagulase negative Staphylococci
CPA	Complete pedal arch
CPE	Carbapenamase-producing Enterobacteriaceae
CRE	Carbapenem-resistant Enterobacteriaceae
CROW	Charcot restraint orthotic walker
CRN	Contrast related nephrotoxicity
CRP	C-reactive protein
CT	Computed tomography
CTA	Computed tomography angiography
CTO	Chronic total occlusion
CWD	Continuous-wave Doppler
DAFNE	Dose Adjustment for Normal Eating
DAN	Diabetic autonomic neuropathy
DCB	Drug-coated balloons
DCCT	Diabetes Control and Complications Trial
DE-CTA	Dual Energy-CTA
DES	Drug- eluting stent
DFC	Diabetic Foot Clinic
DFI	Diabetic foot infection
DFO	Diabetic foot osteomyelitis
DFU	Diabetic foot ulcer
dHACM	dehydrated human amnion/chorion membrane
DIPJ	Distal interphalangeal joint
DN	Diabetic neuropathy
DP	Dorso-plantar
DPA	Dorsalis pedis artery
DPPN	Diabetic painful peripheral neuropathy
DR	Direct revascularization
DSA	Digital subtraction angiography
DSPN	Diabetic sensorimotor peripheral neuropathy
DUS	Duplex ultrasound
ECM	Extracellular matrix
EDB	Extensor digitorum brevis
eGFR	Estimated glomerular filtration rate
EPS	Extracellular polymeric substance
ES	Electrical stimulation
ESBL	Extended spectrum beta lactamase
ESR	Erythrocyte sedimentation rate

ESRD	End-stage renal disease
EURODIAB	European Diabetes Prospective Complications Study
EURODIALE	European Study Group On Diabetes and The Lower Extremity
EVT	Endovascular therapy
FDG PET/CT	Fluorodeoxyglucose positron emission tomography/ computed tomography
FDA	Food and drug administration
FSD	Flow-sensitive dephasing
GABA	Gamma-aminobutyric acid
GAS	Group A streptococci
GBCA	Gadolinium-based contrast agent
GI	Gastro-intestinal
GLASS	Global limb anatomic staging system
HA	Hydroxyapatite
HbA1c	Glycated haemoglobin
HBOT	Hyperbaric oxygen therapy
HFDS	Human fibroblast-derived dermal substitute
HFVA	Hybrid foot vein arterialization
HIV	Human immunodeficiency virus
HMPAO	Hexamethyl propylene amine oxime
HRQoL	Health-related quality of life
HSI	Hyperspectral imaging
ICGA	Indocyanine green angiography
IDDM	Insulin-dependent diabetes mellitus
IDSA	Infectious Diseases Society of America
IDT	Interdisciplinary team
IENFD	Intraepidermal nerve fibre density
IHD	Ischaemic heart disease
IL-1β	Interleukin-1β
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IM	Intramedullary
IPA	Incomplete pedal arch
IPOP	Immediate post-operative prosthesis
IR	Indirect revascularization
IV	Intravenous
IV-CCM	In-vivo corneal confocal microscopy
IWGDF	International Working Group on the Diabetic Foot
LDF	Laser Doppler flowmetry
LDI flare	Laser Doppler Imager flare
LDL-C	Low density lipoprotein cholesterol
LEA	Lower extremity amputation
LLLT	Low level laser therapy
LOPS	Loss of protective sensation

MAC	Medial arterial calcification
MALDI-ToF MS	Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry
MC&S	Microscopy, culture & sensitivity
MDFT	Multidisciplinary foot team
MDRO	Multi-drug resistant organisms
MDT	Maggot debridement therapy
MF	Monofilament
MI	Myocardial infarction
MIC	Minimum inhibitory concentration
MIP	Maximum- intensity projection
MMP	Matrix metalloproteinase
MNSI	Michigan Neuropathy Screening Instrument
MPR	Multi-planar
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-susceptible Staphylococcus aureus
MSC	Mesenchymal stem cell
MTPJ	Metatarsal phalangeal joint
NATHAN 1 Trial	Neurological assessment of thioctic acid in diabetic neuropathy 1 trial
NDS	Neuropathy Disability Score
NeuPSIG	Neuropathic Pain Special Interest Group
NICE	National Institute for Health and Clinical Excellence
NIDDM	Noninsulin-dependent diabetes mellitus
NIRS	Near- Infrared Spectroscopy
NIS-LL + 7	Neuropathy Impairment Score-Lower Limbs and seven neurophysiological tests composite score
NNH	Number needed to harm
NNT	Number needed to treat
NPA	No pedal arch
NPWT	Negative pressure wound therapy
NSF	Nephrogenic systemic fibrosis
NRS	Numeric rating scale
OM	Osteomyelitis
PA	Peroneal artery
PACS	Picture archiving computer system
PAD	Peripheral arterial disease
PCR	Polymerase chain reaction
PCT	Procalcitonin
PDGF-BB	Human platelet derived growth factor-BB
PHMB	Polyhexamethylene biguanide hydrochloride
PIPJ	Proximal interphalangeal joint

PMN	Polymorphonuclear
POP	Plaster of Paris
PRAFO	Pressure relief ankle-foot orthosis
PSM	Phenol soluble modulins
PSV	Peak systolic velocity
PTA	Posterior tibial artery
PTB	Probe to bone
PTT	Pulse transit time
PVI	Percutaneous vascular intervention
PVL	Panton-Valentine leucocidin
PVR	Pulse volume recording
PWV	Pulse wave velocity
QALYs	Quality-adjusted life years
QISS	Quiescent interval single shot
RANK	Receptor activator of nuclear factor kappa-β
RANKL	Receptor activator of nuclear factor kappa-β ligand
RCT	Randomised controlled trial
rRNA	Ribosomal ribonucleic acid
RF	Radiofrequency
SCF	Semi compressed felt
SCV	Small colony variants
SFA	Superficial femoral artery
SIRS	Systemic Inflammatory Response Syndrome
SFN	Small fibre neuropathy
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPECT/CT	Single-photon emission computed tomography/computed tomography
SPK	Simultaneous pancreas and kidney transplantation
SPP	Skin perfusion pressure
SSFP	Steady-state free precession
SSG	Split skin graft
STSG	Split thickness skin graft
SVR	Systemic vascular resistance
SVS	Society for Vascular Surgery
TAL	Tendo-achilles lengthening
TASC	Trans-Atlantic Inter-Society Consensus
TBI	Toe brachial index
TCC	Total contact cast
TCI	Total contact insole
Tc^{99m}MDP	Technetium^{99m}-labelled methylene diphosphonate
TCNS	Toronto clinical neuropathy score
TcPO2	Transcutaneous partial oxygen pressure
TGF-β1	Transforming growth factor-β1
TIMP	Tissue inhibitor of metalloproteinase
TIND	Treatment induced neuropathy of diabetes

TLR	Target lesion restenosis
Tmax	Time from onset to maximum intensity
TNF-α	Tumour necrosis factor alpha
TRPV1	Transient receptor potential cation channel subfamily V member 1
TSE	Turbo Spin Echo
US	Ultrasound
VAC	Vacuum assisted closure
VAS	Visual analogue scale
VGST	Vein Graft Surveillance Randomized Trial
Vr	Velocity ratio
VNA	Visiting Nurses Association
VPT	Vibration perception threshold
VR	Volume rendered
VRE	Vancomycin-resistant Enterococcus
WBC	White blood cell
WIfI	Wound, Ischemia, and foot Infection
XLPAD	Excellence in Peripheral Artery Disease

Chapter 1
Assessment, Classification, Staging and Intervention

Michael E. Edmonds and Bauer E. Sumpio

The diabetic foot is a major global public health problem. Health-care systems have failed the diabetic foot patient and a major amputation occurs every 20 secs. [1]. However, amputations are not inevitable and limb salvage can be achieved.

Three great pathologies come together in the diabetic foot: neuropathy, ischaemia and infection. Their united impact results in a rapid progression to tissue necrosis which is the fundamental pathway in the natural history of the diabetic foot. The pathway towards necrosis can be so swift and devastating that it has come to be considered as a "diabetic foot attack" akin to the heart and brain attacks of the coronary and cerebrovascular systems. A "diabetic foot attack" can quickly reach the point of no return, with devastating necrosis. Thus it is vital to diagnose it early and deliver rapid and intensive treatment. Furthermore, it is important to recognise the at-risk foot early so as to introduce prompt measures to prevent the onset of the "diabetic foot attack". This introductory chapter describes the initial approach to the diabetic foot, including assessment, classification and staging as a prelude to intervention in order to prevent limb loss.

1.1 Assessment of the Diabetic Foot

The initial approach to the diabetic foot starts with a simple assessment to enable the practitioner to make a basic classification and staging.

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The diabetic foot can be classified into two groups:

1. The neuropathic foot
2. The ischaemic foot

The neuropathic foot may be further divided into two clinical scenarios:

1. Foot with neuropathic ulceration
2. Charcot foot, which may be secondarily complicated by ulceration

The ischaemic foot may be divided into three clinical scenarios:

1. Neuroischaemic foot characterised by mild or moderate ischaemia and neuropathy and often complicated by ulcer
2. Severely ischaemic foot otherwise known as the critically ischaemic foot
3. Acutely ischaemic foot

(The Global Vascular Guidelines have recently proposed the term Chronic Limb Threatening Ischemia to include a broad group of patients with varying degrees of ischemia that can often delay wound healing and increase amputation risk. This will consist of both the neuroischaemic foot and the critically ischaemic foot.)

When the neuroischaemic foot and the critically ischaemic foot occur in patients with severe renal failure, then the presentation may be influenced by the underlying renal dysfunction and vascular disease, leading to an additional clinical presentation called the renal ischaemic foot which may complicate these two main presentations of the ischaemic foot.

Each of these five main clinical scenarios (two neuropathic and three ischaemic) are characterised by having specific stages in their natural history. These stages have been described in a Simple Staging System [2]. This system covers the whole spectrum of diabetic foot disease and describes six stages in the natural history of each of the five clinical scenarios and emphasises the relentless progression to end stage necrosis (Fig. 1.1). The Simple Staging System is based on clinical presentation. The stages are:

- Normal foot
- High risk foot
- Ulcerated foot
- Threatened foot
- Necrotic foot
- Unsalvageable foot

In Stage 4, the “threatened” foot indicates that the foot is in danger of its tissue being destroyed and losing its function.

- In the neuropathic foot, infection has developed and is the threat driving the foot towards tissue necrosis
- In the Charcot foot, it is again usually infection that is the threat but in some cases sheer mechanical instability threatens the integrity of the foot
- In the neuroischaemic foot, the threat is predominantly infection together with mild or moderate ischaemia
- In the critically ischaemic foot and the acutely ischaemia foot, it is ischaemia which is the threat, driving the foot towards necrosis.

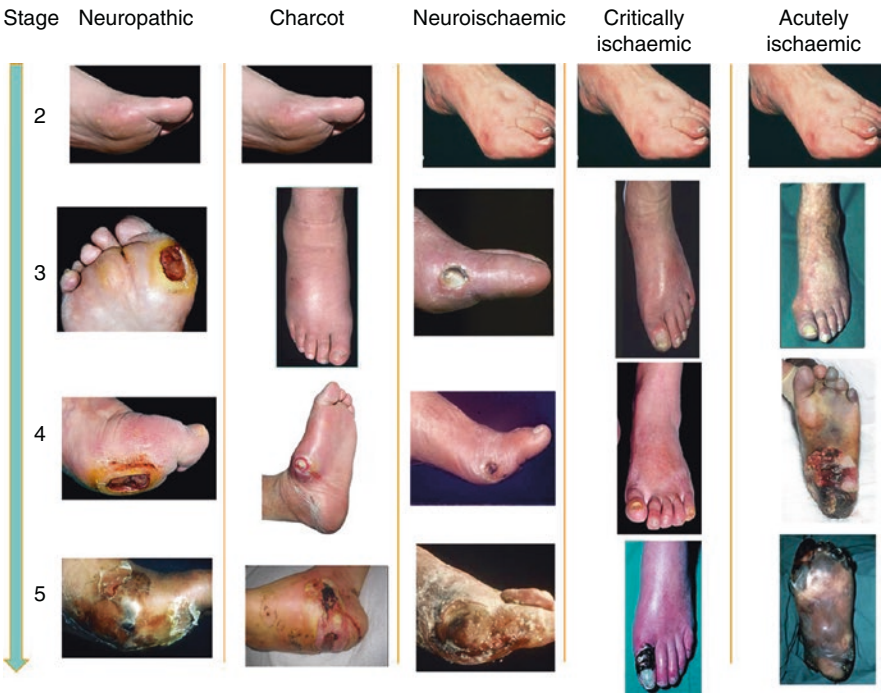

Fig. 1.1 Simple Staging System depicting the natural history of the diabetic foot

The Simple Staging System is useful in the day to day assessment in the clinic. A more detailed disease staging is needed when designing clinical trials and assessing comparative effectiveness of treatment and the Lower Extremity Threatened Limb Classification System of the Society for Vascular Surgery (SVS) is more suitable for these tasks [3]. In this classification, perfusion of the foot is considered in the context of wound characteristics and infection. Thus this system stratifies amputation risk according to wound extent, the degree of ischaemia, and the presence and severity of foot infection. The Lower Extremity Threatened Limb Classification System is known as the Wound, Ischemia, and foot Infection Classification System and is abbreviated as WIfI. It has been recently correlated with the probability of limb salvage and wound healing following revascularization [4].

In order to classify and stage the diabetic foot, a full history and examination should be carried out.

1.1.1 History

A careful history of presenting limb complaints should be documented and details of cardiovascular risk factors, drug history, and previous interventions should be recorded including vascular and endovascular revascularization procedures and amputations.

1.1.2 Examination

This should consist of three parts:

- Simple inspection
- Palpation
- Sensory testing

The examination should specifically include a search for the following major clinical features:

- Skin breakdown
- Necrosis
- Infection
- Ischaemia

A search should also be carried out for the following features that predispose to skin breakdown and ulceration:

- Neuropathy
- Deformity
- Callus
- Oedema

1.1.2.1 Skin Breakdown

An active search should be made for breaks in the skin or wounds over the entire surface of the foot and ankle, not forgetting the areas between the toes and at the back of the heel. Toes should be gently held apart for inspection (Fig. 1.2). The classical sign of tissue breakdown is the foot ulcer. However, fissures and bullae/blisters also represent breakdown of the skin.

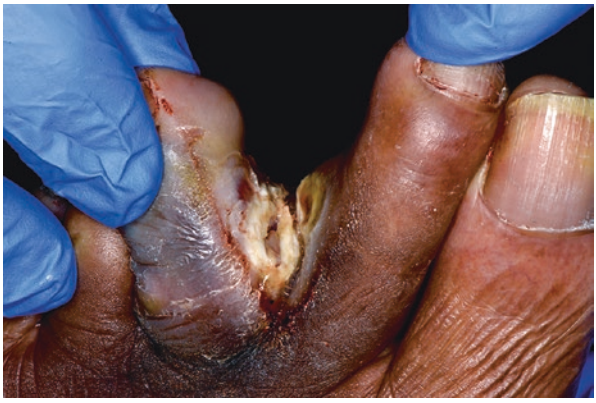

Fig. 1.2 Interdigital ulcer revealed by separating the toes

1.1.2.2 Infection

When skin breakdown develops, it may act as a portal of entry for infection which develops in 50% of ulcers. A close examination for signs of infection should be made. These include purulent discharge from the lesion and cellulitis as indicated by erythema, swelling and warmth of the toe or foot (Fig. 1.3) although in the presence of neuropathy these classical signs of infection may be diminished. Thus, it is important to look for subtle signs of infection including increased friability of granulation tissue, wound odour, wound breakdown and delayed healing.

1.1.2.3 Necrosis

Lesions of skin breakdown may progress to underlying necrosis which clinically can be either wet or dry necrosis.

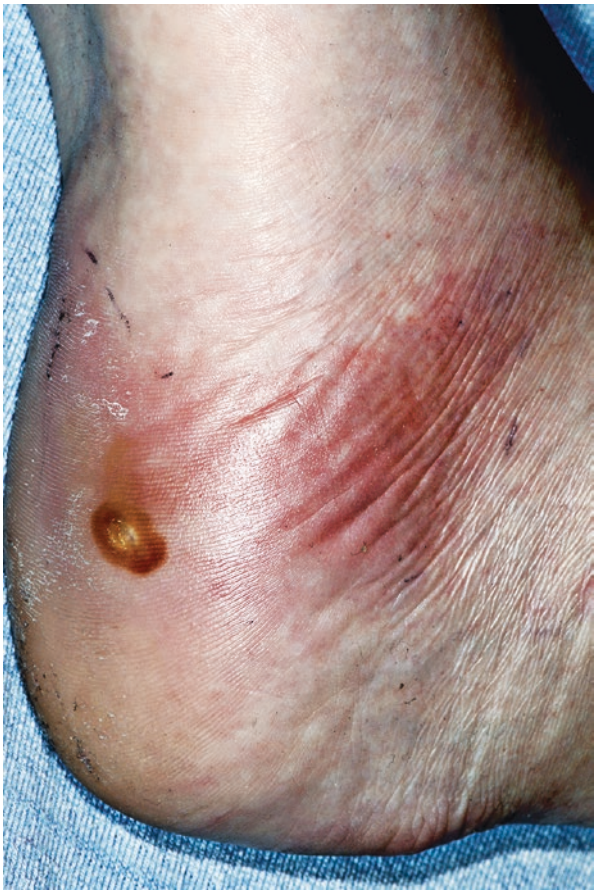

Fig. 1.3 Cellulitis complicating plantar ulcer

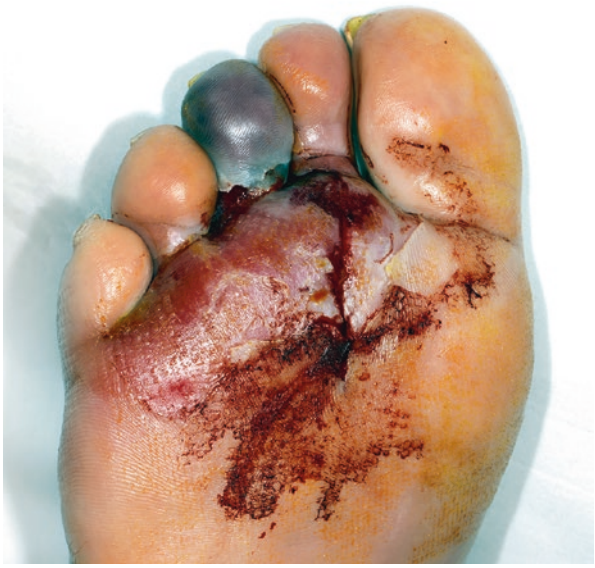

Fig. 1.4 Wet necrosis of the third toe in infected foot

Wet necrosis is secondary to a septic vasculitis accompanying severe soft-tissue infection and ulceration, and is the commonest cause of necrosis in the diabetic foot.

In the neuropathic foot, necrosis is usually wet, and is caused by infection complicating a digital, metatarsal or heel ulcer, and leading to a septic vasculitis of the digital and small arteries of the foot (Fig. 1.4). The walls of these arteries are infiltrated by polymorphs leading to occlusion of the lumen by septic thrombus. Wet necrosis is also prominent in the infected neuroischaemic foot and has a similar pathology of septic vasculitis. However, in the neuroischaemic foot reduced arterial perfusion to the foot resulting from occlusive disease of the leg and foot arteries is also an important predisposing factor.

Dry necrosis is hard, blackened, mummified tissue and there is usually a clean demarcation line between necrosis and viable tissue. It may be difficult to diagnose in the patient with a dark skin. Dry necrosis can be seen usually in three situations: in the ischaemic foot namely in critical ischaemia (Fig. 1.5) in acute ischaemia and in the renal ischaemic foot (Fig. 1.6). It can also result from emboli to the toes.

1.1.2.4 Ischaemia

Classical symptoms of ischaemia, namely claudication and rest pain are often absent because of a concomitant neuropathy. The most important manoeuvre to detect ischaemia is the palpation of foot pulses.

- The dorsalis pedis pulse is felt lateral to the extensor hallucis longus tendon on the dorsum of the foot
- The posterior tibial pulse is felt below and behind the medial malleolus

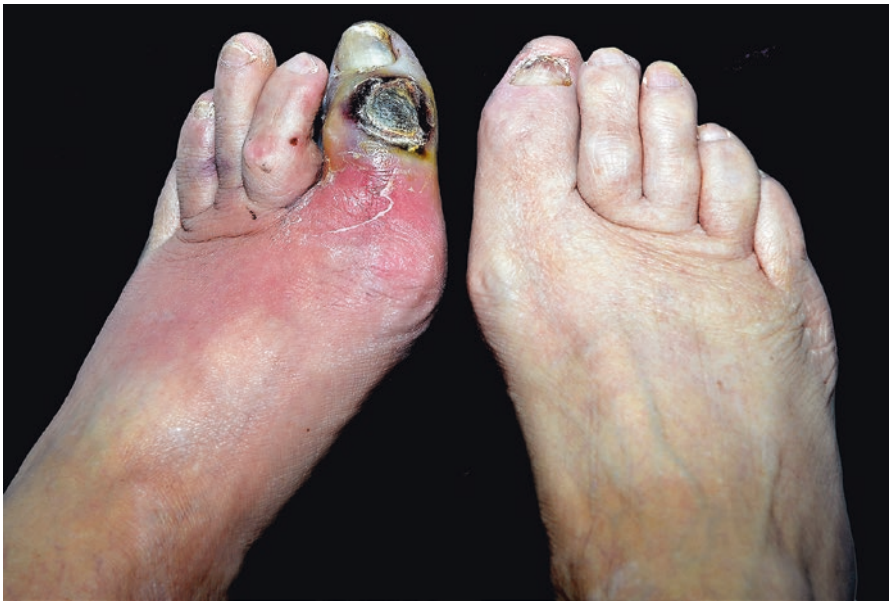

Fig. 1.5 Necrosis of toe in critically ischaemic left foot

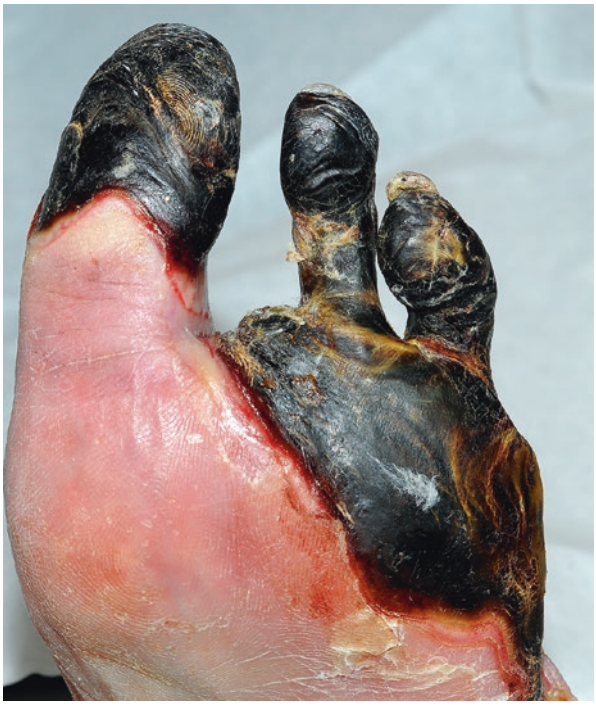

Fig. 1.6 Digital necrosis in renal ischaemic foot

If either of these foot pulses can be felt then it is unlikely that there is significant ischaemia. A small hand-held Doppler can be used to confirm the presence of pulses and to assess the vascular supply. Used together with a sphygmomanometer, the brachial systolic pressure and ankle systolic pressure can be measured, and the ankle brachial pressure index (ABI), which is the ratio of ankle systolic pressure to brachial systolic pressure, can be calculated. In normal subjects, the ABI is usually >1, but in the presence of ischaemia is <1. Thus, absence of pulses and an ABI of <1 confirms ischaemia. Conversely, the presence of pulses and an ABI of >1 rules out ischaemia. Arterial disease in diabetes is characterised by the distal anatomical localisation of the disease. The calf arteries typically show diffuse medial calcification which renders the vessel incompressible and can limit the utility of assessing the ABI [5]. If arteries are calcified, the ABI may be artifactually raised but the test is still important as long as one understands its interpretation.

Thus, if the ABI is 0.5, then it is low, and indicates severe ischaemia, whether the foot arteries are calcified or not. Indeed, if it is calcified, the true ABI may be lower. However it is important to assess the Doppler waveform which normally is pulsatile with a positive forward flow in systole followed by a short reverse flow and a further forward flow in diastole, but in the presence of arterial narrowing the waveform shows a reduced forward flow and is described as damped (See Chap. 19).

It is now accepted that ischaemia may occur very peripherally in the foot arteries and may not be detected by ABI. Thus it is advisable to include either the transcutaneous oxygen measurement on the dorsum of the foot or toe pressures. Recent studies suggest that toe pressure is more sensitive than ankle pressure in the diagnosis of limb threatening ischaemia, and is more predictive of amputation risk [6, 7].

There has been controversy regarding the impact of microvascular abnormalities at the level of the arteriole and capillary in the diabetic foot. The structural abnormalities such as capillary basement thickening are generally regarded as not significant. However, neuropathy leads to functional microvascular abnormalities such as reduced microvascular response to tissue injury. Abnormalities have also been described in resting blood flow, capillary flow, the vasoconstriction responses, the neurovascular flare response, hemoglobin oxygen saturation, and blood rheology [8].

1.1.2.5 Grading Regarding Wound, Ischaemia and foot Infection in WIfI

These major clinical features of the wound (including necrosis), infection and ischaemia determine the prognosis of the foot and are graded in the the WIfI classification as shown in Tables 1.1, 1.2 and 1.3 [9].

1.1.2.6 Neuropathy

Peripheral neuropathy is the most common complication of diabetes affecting 50% of all diabetic patients. Although neuropathy may present with tingling and a feeling of numbness, it is asymptomatic in the majority of patients and neuropathy

Table 1.1 Wound grading in WIfI

Grade	Wound
0	No ulcer or gangrene
1	Small, shallow ulcer on distal leg or foot; no exposed bone, unless limited to distal phalanx. No gangrene
2	Deeper ulcer with exposed bone, joint or tendon; generally, not involving the heel; shallow heel ulcer, without calcaneal involvement. Gangrenous changes limited to digits
3	Extensive, deep ulcer or gangrene involving forefoot and/or midfoot; deep, full thickness heel ulcer/necrosis ±calcaneal involvement

WIfI Wound, Ischemia, and foot Infection Classification System

Table 1.2 Ischaemia grading in WIfI

Grade	ABI	Ankle systolic pressure (mmHg)	TP, $TcPO_2$ (mmHg)
0	≥0.80	>100	≥60
1	0.6–0.79	70–100	40–59
2	0.4–0.59	50–70	30–39
3	≤0.39	<50	<30

WIfI Wound, Ischemia, and foot Infection Classification System

Table 1.3 Infection grading in WIfI

Grade 0	No infection
Grade 1	Mild Infection; two of following present. Erythema >0.5 to 2 cm around ulcer, local swelling or induration, local tenderness or pain, local warmth, purulent discharge
Grade 2	Moderate (deep) infection. Erythema > 2 cm, or abscess present or infection extends deep to joint or bone
Grade 3	Severe infection. Local infection with systemic inflammatory response syndrome (SIRS)

WIfI Wound, Ischemia, and foot Infection Classification System

will only be detected by clinical examination. Peripheral neuropathy can involve sensory, motor and autonomic nerves. Simple inspection will usually reveal signs of motor and autonomic neuropathy of the feet but sensory neuropathy must be detected by a simple sensory assessment.

Motor Neuropathy

The classical sign of a motor neuropathy is a high medial longitudinal arch, leading to prominent metatarsal heads and pressure points over the plantar forefoot. Complex assessment of motor power in the foot or leg is usually not necessary, but it is prudent to test the power of dorsiflexion of the foot to detect a foot drop secondary to a common peroneal nerve palsy. This is usually unilateral and will affect the patient's gait.

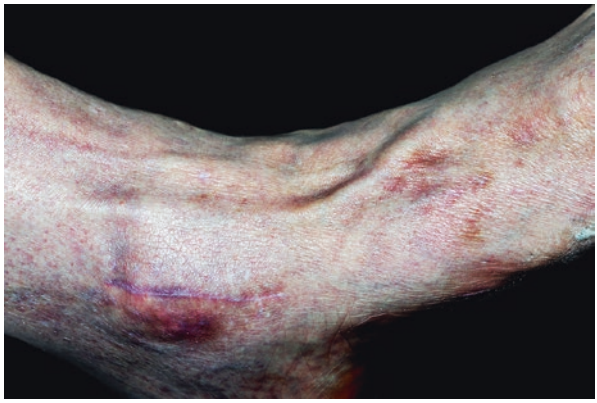

Fig. 1.7 Prominent vein over the dorsum of the foot due to arteriovenous shunting

Autonomic Neuropathy

The classical signs of peripheral autonomic neuropathy are:

- Dry skin which can lead to fissuring. The dry skin is secondary to decreased sweating. The sweating loss normally occurs in a stocking distribution, which can extend up to the knee.
- The veins over the dorsum of the foot and ankle are distended secondary to arteriovenous shunting (Fig. 1.7).

Sensory Neuropathy

Sensory neuropathy can be simply detected by:

- Clinical examination
- Monofilaments
- Neurothesiometry

Simple clinical examination consists of detecting sensation to light touch using a cotton wisp and vibration using a 128-Hz tuning fork, comparing a proximal site with a distal site to confirm a symmetrical stocking-like distribution of the neuropathy.

A simple technique for detecting neuropathy is to use a nylon monofilament, which, when applied perpendicular to the foot, buckles at a given force of 10 grams (Fig. 1.8). The filament should be pressed against several sites including the plantar aspects of the first toe, the first, third and fifth metatarsal heads, the plantar surface of the heel and the dorsum of the foot [10]. The filament should not be applied at any site until callus has been removed. If the patient cannot feel the filament at a tested area, then significant neuropathy is present and protective pain sensation is lost. After using a monofilament on ten consecutive patients, there should be a recovery time of 24 hours before further usage [11].

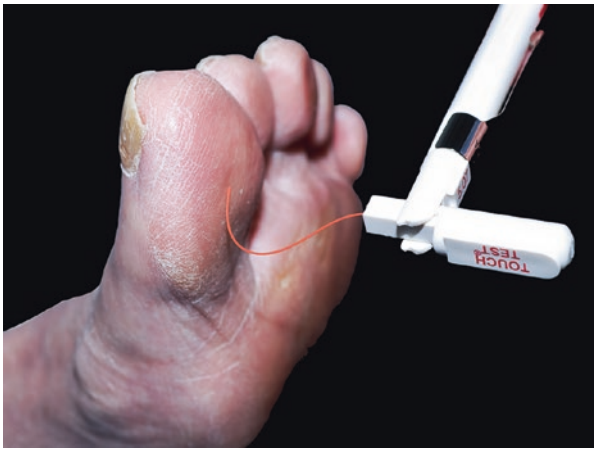

Fig. 1.8 Nylon monofilament buckles at a given force of 10 grams

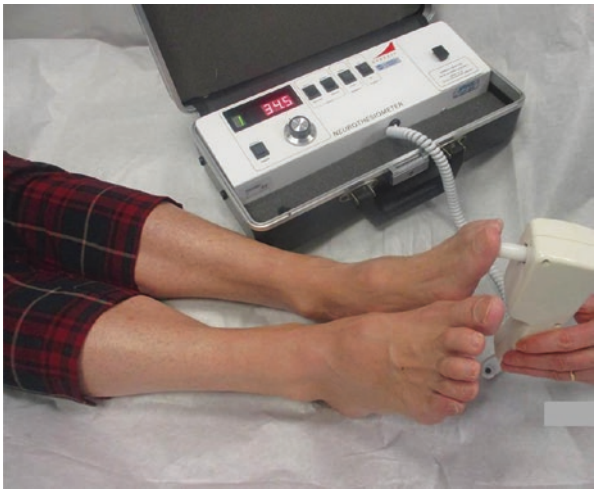

Fig. 1.9 Neurothesiometer which delivers a vibratory stimulus that increases as the voltage is raised until the patient notes the vibration sensation and this is deemed the vibration perception threshold

Neuropathy can be further quantified by the use of the neurothesiometer (Fig. 1.9). When applied to the foot, this device delivers a vibratory stimulus, which increases as the voltage is raised. The vibration threshold increases with age, but, for practical purposes, any patient unable to feel a vibratory stimulus of 25 volts has a significant peripheral neuropathy. Assessment with monofilaments or neurothesiometry detects patients who have lost protective pain sensation and are therefore susceptible to foot ulceration.

1.1.2.7 Deformity

Deformity often leads to bony prominences, which are associated with high mechanical pressures on the overlying skin (Fig. 1.10). This results in ulceration, particularly in the absence of protective pain sensation and when shoes are unsuitable.

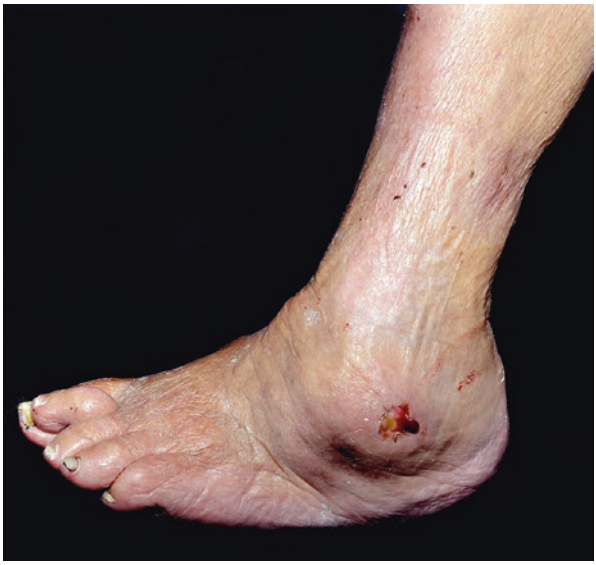

Fig. 1.10 Deformity from Charcot ankle with skin breakdown over lateral malleolus

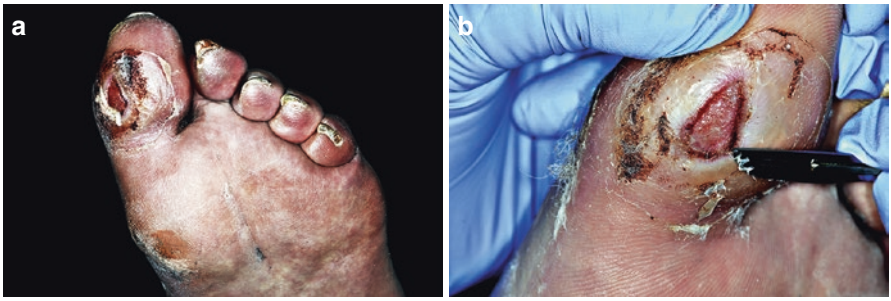

Fig. 1.11 (**a**) Ulcer underneath callus of first toe; (**b**) Ulcer is revealed after callus is removed

Ideally, the deformity should be identified early and either accommodated in properly fitting shoes before ulceration occurs or corrected surgically.

1.1.2.8 Callus

This is a thickened area of epidermis which develops at sites of pressure, shear and friction. It should not be allowed to become excessive as callus is a common precursor of ulceration in the presence of neuropathy (Fig. 1.11).

1.1.2.9 Oedema

Oedema of the tissues of the foot is a major factor predisposing to ulceration, and often exacerbates a tight fit inside poorly fitting shoes. It also impedes healing of established ulcers. Oedema may be unilateral or bilateral.

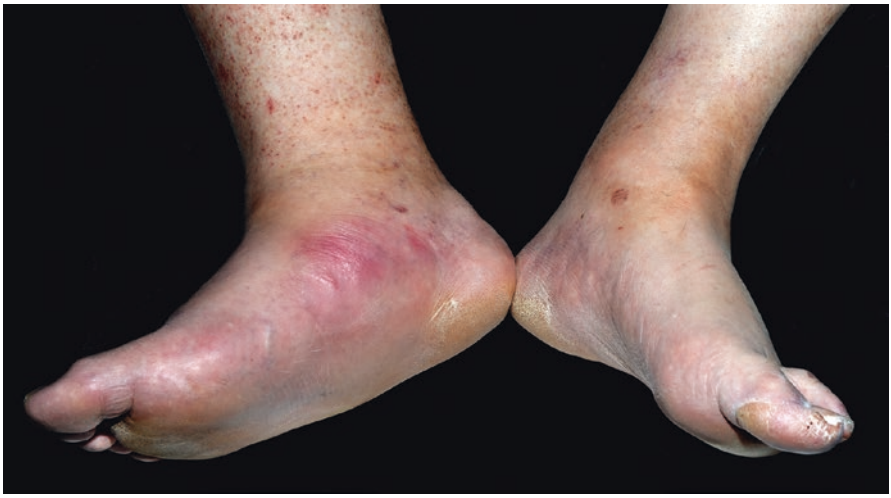

Fig. 1.12 Hot, red, swollen right foot of Charcot neuroarthropathy

Unilateral Oedema

This is usually associated with local pathology in the foot or leg.

Causes are:

- Infection, when it is usually associated with erythema and skin breakdown
- Charcot foot (a unilateral hot, red, swollen foot is often the first sign and the oedema can extend to the knee) (Fig. 1.12)
- Gout, which may also present as a hot, red, swollen foot
- Trauma, sprain or fracture
- Deep vein thrombosis
- Venous insufficiency
- Lymphoedema caused by lymphatic obstruction secondary to malignancy
- Venous obstruction by a pelvic mass, malignancy or ovarian cyst
- Localized collection of blood or pus which may present as a fluctuant swelling.

Bilateral Oedema

This is usually secondary to:

- Cardiac failure
- Hypoalbuminaemia
- Renal failure
- Venous insufficiency (sometimes unilateral)
- Inferior vena caval obstruction
- Lymphoedema
- Diabetic neuropathy when it is related to increased arterial blood flow and arteriovenous shunting and is known as neuropathic oedema

1.2 Classification of the Diabetic Foot

It is essential to differentiate between the neuropathic and the ischaemic foot as their management will differ. Infection is the most frequent complication in both the neuropathic and ischaemic foot and it is important to diagnose it early and intervene rapidly. It is responsible for considerable tissue necrosis in the diabetic foot and is the main reason for major amputation.

1.2.1 The Neuropathic Foot

- It is a warm, well perfused foot with bounding pulses. There is no clinically detectable ischaemia in the leg or foot. There is a normal ABI.
- The skin may be dry and prone to fissuring,
- Toes may be clawed and the foot arch raised
- Ulceration usually develops on the plantar surface of the foot or toes associated with neglected callus and high plantar pressures (Fig. 1.13).
- Despite the good circulation, necrosis can develop secondary to severe infection
- The neuropathic foot may have an abnormal response to minor traumatic injuries and this can lead to bone and joint problems (the Charcot foot)

1.2.2 The Ischaemic Foot

It is a cool, foot with reduced perfusion. It may also be complicated by oedema, often secondary to cardiac failure or renal failure. If it becomes infected, the ischaemic foot may be deceptively warm. The dorsalis pedis and posterior tibial are usually not palpable but in cases of very distal ischaemia, the foot pulses may still be palpable.

The subdivisions of the ischaemic foot will have characteristic appearances.

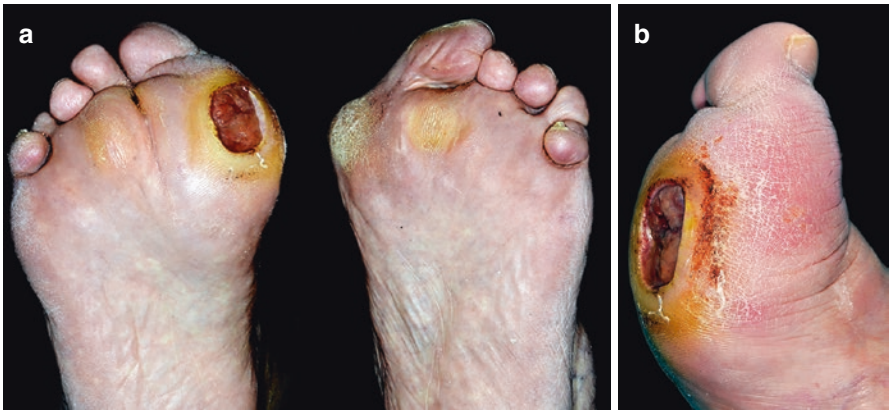

Fig. 1.13 (**a**) Plantar ulcer at high pressure area under first metatarsal head (**b**) side view shows complicating cellulitis

Fig. 1.14 Ulceration on the medial aspect of the first metatarsal-phalangeal joint

1.2.3 Neuroischaemic Foot

The neuroischaemic foot has mild to moderate ischaemia with neuropathy.

The presentation of the neuroischaemic foot is unique: it differs from the classical picture presented by the ischaemic patient without diabetes and without neuropathy, when there is usually a natural progression through claudication, rest pain, ulceration and necrosis. These early signs and symptoms reveal the problem in the non-diabetic patient. However, the signs and symptoms of ischaemia in diabetic patients with concurrent neuropathy are much more subtle. Claudication and rest pain may not be characteristic features and are often absent and patients may initially present with tissue loss from either ulceration or necrosis.

Diabetic patients with ulceration who have the ominous combination of neuropathy and ischaemia are, therefore, supremely fragile. It is the presence of neuropathy together with ischaemia that confuses the picture not only in the foot but also in the rest of the diabetic foot patient, where even myocardial infarctions can be symptomless. Thus the most frequent presentation is that of ulceration, commonly seen on the margins of the foot, including the tips of the toes and the areas around the back of the heel (Fig. 1.14). Ulceration is usually caused by minor trauma or by wearing unsuitable shoes. Even if neuropathy is present and plantar pressures are high, plantar ulceration is not as frequently present compared with the classical neuropathic foot, probably because the foot does not develop heavy plantar callus, which requires good blood flow.

1.2.4 Critically Ischaemic Foot

This presents as a pink often painful foot with pallor on elevation of the foot and rubor on dependency (Fig. 1.15). The colour of the critically ischaemic foot can be a deceptively pink or red. Pain may be present in the foot although this depends on the

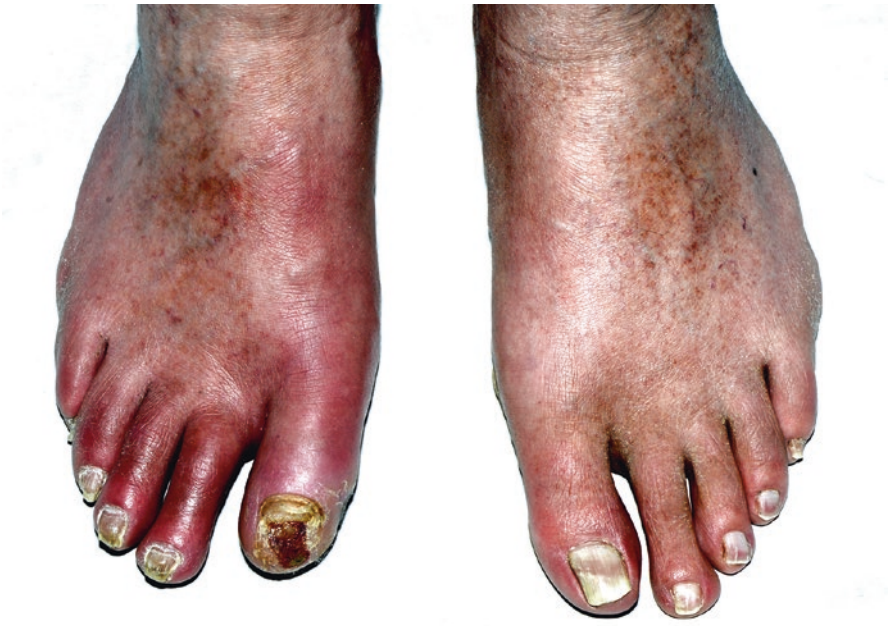

Fig. 1.15 Right foot of patient (to the left of the Figure) showing rubor on dependency and subungual ulcer

degree of ischaemia and neuropathy. This pain is relieved by hanging the foot over side of bed. The skin is taut and shiny. As blood flow diminishes, there is a critical reduction in perfusion leading to ulceration and dry necrosis.

1.2.5 Acutely Ischaemic Foot

This presents initially with sudden pallor. The foot is extremely cold and becomes mottled. There is paresthesiae, numbness and eventually paralysis.

In late presentations, there will be extensive necrosis (Fig. 1.16). The severity of pain will depend on the degree of neuropathy.

A fuller description and commentary of these presentations of ischaemia are described in Chap. 18.

1.3 Staging of the Diabetic Foot

The natural history of the diabetic foot can be divided into six stages.

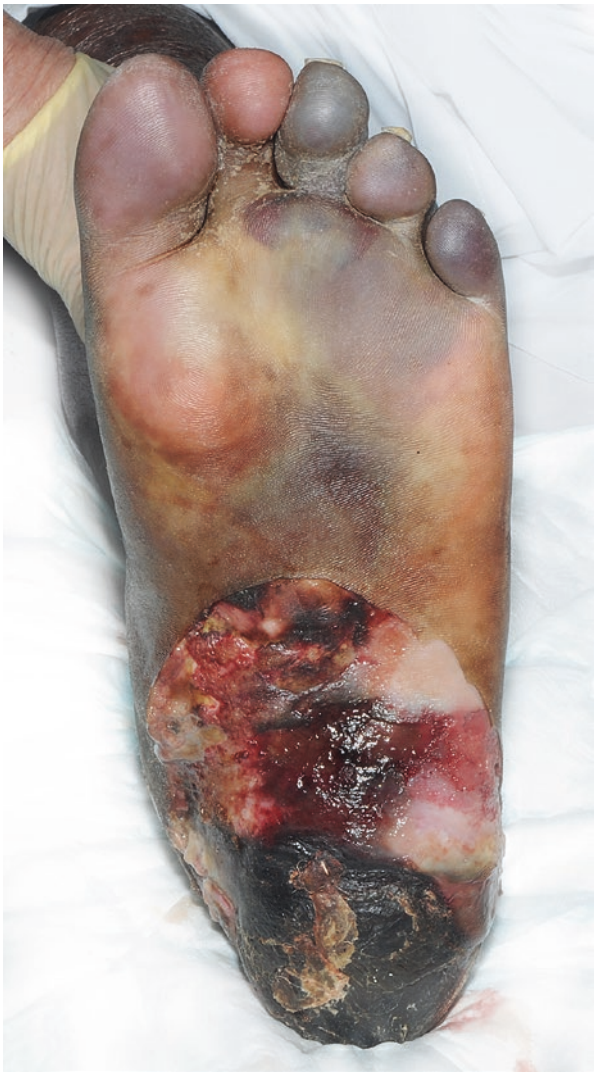

Fig. 1.16 Extensive necrosis of acute ischaemia

1.3.1 Stage 1

The foot is not at risk. The patient does not have the risk factors of neuropathy, ischaemia, deformity, callus and oedema and is not vulnerable to foot ulcers.

1.3.2 Stage 2

The patient has developed one or more of the risk factors for ulceration and the foot may be divided into the neuropathic foot and the ischaemic foot.

1.3.3 Stage 3

The neuropathic and the ischaemic foot have developed a skin breakdown. This is usually an ulcer, but because some minor injuries such as blisters, splits or grazes have a propensity to become ulcers, they are included in Stage 3. Ulceration is usually on the plantar surface in the neuropathic foot and usually on the margin in the ischaemic foot but can occur on the plantar surface in mild distal ischaemia.

1.3.4 Stage 4

The foot has become threatened and is in danger of its tissue being destroyed and losing its function.

- In the neuropathic foot, infection has developed and is the threat driving the foot towards tissue necrosis
- In the Charcot foot, it is usually infection that is the threat but in some cases mechanical instability threatens the integrity of the foot
- In the neuroischaemic foot, the threat is predominantly infection together with mild or moderate ischaemia
- In the critically ischaemic foot and the acutely ischaemic foot, ischaemia is the threat, driving the foot towards necrosis.

1.3.5 Stage 5

Necrosis has supervened. In the neuropathic foot, infection is usually the cause. In the ischaemic foot, infection is still the most common reason for tissue destruction although ischaemia contributes.

1.3.6 Stage 6

The foot has become unsalvageable with overwhelming necrosis, or has intractable pain or gross instability and cannot be saved and will need a major amputation.

The staging system was developed to emphasise the significance of ulceration in the neuropathic foot and the neuroischaemic foot, stressing the development of the ulcer as a pivotal stage in the natural history of the diabetic foot and the rapid progression through infection to necrosis.

However, staging can be helpful for the three less common scenarios, namely the Charcot foot, the critically ischaemic foot, and the acutely ischaemic foot. The natural history of these feet, together with that of the neuropathic and neuroischaemic foot, has been demonstrated in Fig. 1.1.

1.4 Intervention

There have been two crucial significant advances in diabetic foot care and limb salvage to improve the outlook of diabetic patients. First, there has been the recognition that diabetic foot patients undergo repeated crises from the swift onset infection and need a special form of easily accessible care within an interdisciplinary diabetic foot service to provide prompt treatment of infection before it progresses to necrosis [12]. Secondly, within such a service, rapid diagnosis of ischaemia and urgent revascularisation has been established as an important aspect of management of infected diabetic ischaemic feet [13].

Successful management needs the expertise of an interdisciplinary team which provides integrated care focused in a diabetic foot clinic [14].

The diabetic foot clinic should provide fast access, early diagnosis and prompt help for patients with foot problems [15, 16]. Rapid assessment and management is a crucial part of an interdisciplinary approach as diabetic foot problems progress extremely quickly. Within the interdisciplinary diabetic foot service, aggressive treatment of infection in both the diabetic neuropathic and ischaemic foot is important. Emergency services can be run concurrently with routine clinics so that patients with new ulcers can be seen the same day. Rapid admission to hospital for the patient with foot infection and/or severe ischaemia can also be arranged through this emergency service. The crucial factor in saving limbs is making a rapid diagnosis of infection and ischaemia and administering the appropriate treatment early. Moreover, the patient's medical condition should be optimised. In this way prompt healing can be achieved and amputations can be prevented. Thus, there are three main reasons for early referral to a diabetic foot clinic:

- To make an accurate diagnosis of the type and cause of ulceration and institute appropriate treatment to promote healing of the ulcer.
- To assess for the presence of infection and if present, to start immediate antibiotics. Infection is responsible for considerable tissue necrosis in the diabetic foot and this is the main reason for major amputation.
- To perform an immediate vascular assessment, to evaluate the necessity of early revascularisation in the ischaemic foot.

In summary it is important to achieve:

- Wound control
- Microbiological control
- Vascular control
- Mechanical control
- Metabolic control
- Educational control

If microbiological control is not achieved, then infection can spread with alarming rapidity, and can cause extensive tissue necrosis. Metabolic control ensures that there is no systemic, metabolic or nutritional disturbance to hinder limb salvage efforts. Educational control makes sure that patients understand both the reasons for their foot problems and also the range of treatments necessary to heal them.

The Global Vascular Guidelines on the Management of Chronic Limb-threatening Ischemia have recently been published [17].

1.5 Conclusion

The diabetic foot can deteriorate with alarming rapidity. Delays of a few days, even a few hours, cannot be accepted. Any delays can lead to the loss of a leg which could have been saved or to the need for many months of treatment of ulcers and infection, or even the death of the patient. At each stage of the diabetic foot, it is necessary to intervene early and take control of the foot to prevent further progression and thus achieve limb salvage.

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Part I
Neuropathic Foot

Chapter 2
Introduction to the Neuropathic Foot: Limb Salvage Pathway and Algorithm

Nina L. Petrova, Bauer E. Sumpio, and Michael E. Edmonds

2.1 Introduction

It is important to understand the impact of neuropathy in order to treat the neuropathic foot efficiently. The peripheral nervous system is an early warning system both to detect external insults to the body and internal malfunctions within and it is programmed to direct appropriate protective responses to maintain the integrity of the body. As a result of neuropathy, the signs and symptoms of external physical insults and also of intercurrent disease may be minimal. The response to physical insults and bacterial invasion is impaired [1]. In the presence of infection, there may be absence of pain, fever and leucocytosis. Nevertheless, the pathology emanating from such insults and disease proceeds rapidly, without the body being aware of them, and the end stage of tissue death is quickly reached. Thus the window of opportunity for intervention is limited and is often missed. Thus Chap. 3 is devoted entirely to neuropathy and to increasing the understanding of the impact of neuropathy. Diabetic neuropathy has been identified as a key element in the causal pathway to neuropathic foot ulceration as described in Chap. 4. Figure 2.1 is an algorithm summarising the management of the neuropathic foot.

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2.2 Management of Neuropathic Ulceration

Two aspects of control are important in the treatment of neuropathic ulceration, firstly wound control comprising debridement and wound care including adjuncts such as negative pressure wound therapy (NPWT) and secondly, mechanical control comprising off loading and casting. For the purpose of this commentary, it is accepted that ischaemia and infection, which are discussed in later commentaries, are not present.

2.2.1 Step 1. Wound Control: Debridement and Standard Wound Care

Debridement together with associated adjunctive measures is the most important part of wound control (Fig. 2.1). It removes the cellular burden of dead and senescent cells and also eliminates biofilm, both of which slow the progression of normal wound healing [2]. Tissue loss may be divided into minor and major tissue loss, which determines the mode of debridement.

Classical neuropathic ulceration is usually associated with minor tissue loss as defined by WIfI wound grade 1 and can be optimally sharp debrided with scalpel in clinic or office followed by simple dressings as part of standard care. With greater tissue loss, equivalent to WIfI wound grade 2/3, operative surgical debridement will be necessary. Post debridement, the wound can be treated with standard dressings although after extensive debridement, negative pressure wound therapy (NPWT) can be used for deep cavity wounds [3].

2.2.2 Step 2. Mechanical Control: Offloading

Neuropathic feet do not respond appropriately to increased physical forces. In treating neuropathic foot ulceration, the overall aim is to redistribute plantar pressures (Fig. 2.1). The most efficient way to redistribute plantar pressure is by immediate application of some form of cast (Chap. 5). If casting techniques are not available, temporary ready-made shoes with a cushioning insole can be supplied (Chap. 6). These can take the form of dressing shoes or weight-relief shoes, and felt pads may also be used. General measures such as the use of crutches, wheelchairs and Zimmer frames may be necessary.

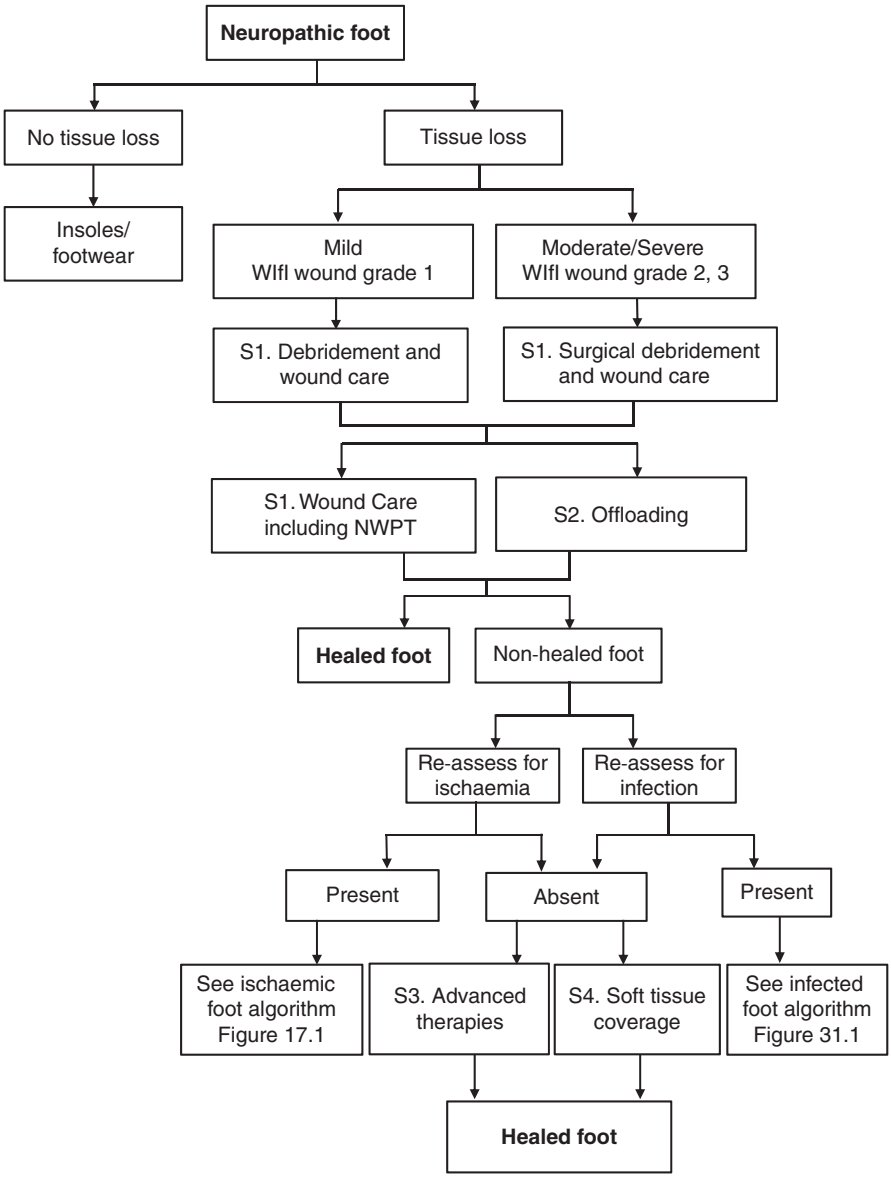

Fig. 2.1 Limb salvage pathway and algorithm for the neuropathic foot. The WIfI gradings of wound, ischaemia and infection are explained in Chap. 1. The prefixed numbers (S1–4) refer to the intervention steps described in the text

2.2.3 Step 3. Advanced Wound Therapy with Evidence-Based Adjunctive Therapies

In the course of initial treatment, the area of neuropathic ulceration or surgical post-operative wound should be measured every week. Typically, standard care is provided for a 4-week period and then the wound should be re-assessed. Wounds that do not reduce in size by more than 50% have a reduced likelihood of healing by 12 weeks [4]. At 4 weeks, it is important to check again (as at initial assessment) for infection or ischaemia. If present, then the ischaemic or infected algorithm should be followed (Chaps. 17 and 31).

In the absence of ischaemia and infection, but with a poor trajectory of healing, evidence-based adjunctive therapies may be then used and are described in Chap. 7. These include cell and tissue-based products such as bioengineered cell-based therapies, acellular matrices, placental-derived membranes, recombinant growth factors, platelet-rich plasma and matrix metalloproteinase inhibitors [5].

In addition, recent reports have shown that diabetic patients with chronic lower extremity ulcers who received weekly dehydrated human amnion/chorion membrane (dHACM) allograft in a prospective randomised, controlled multicentre clinical trial of 110 patients were significantly more likely to heal in 12 weeks compared with those not receiving dHACM (Intention To Treat (ITT)-70% versus 50%, $P = 0.0338$, per-protocol-81% versus 55%, $P = 0.0093$). A Kaplan-Meier analysis demonstrated that the time-to-healing performance with or without dHACM, showed a significantly improved time-to-healing with the use of allograft, log-rank $P < 0.0187$ [6].

Also, recently, a multicentre, international, observer-masked, randomised controlled trial of LeucoPatch in people with diabetes and hard-to-heal foot ulcers in neuropathic feet but also including ischaemic feet down to an ankle brachial index (ABI) of 0.5 was reported in 2018. Weekly application of LeucoPatch which provides autologous leucocytes, platelets, and fibrin, resulted in healing of 45 (34%) of 132 ulcers within 20 weeks versus 29 (22%) of 134 ulcers in the standard care group without LeucoPatch treatment (odds ratio 1.58, 95% CI 1.04–2.40; $p = 0.0235$) by intention-to-treat analysis. Time to healing was shorter in the LeucoPatch group ($p = 0.0246$) than in the standard care group [7].

2.2.4 Step 4. Soft Tissue Coverage

Operative soft tissue coverage can be utilised in conjunction with advanced wound therapy. Alternatively, it can be used instead of these therapies when they cannot be resourced, or when the tissue loss is extensive. The reconstructive ladder of tissue reconstruction as described in Chaps. 8 and 9, ranges primarily from healing by secondary intention, application of a split skin graft, soft tissue advancement, local rotational flaps to free tissue transfer.

2.3 Conclusion

A pathway of limb salvage of the neuropathic foot is presented, describing four important steps: debridement, offloading, advanced wound therapy and soft tissue coverage.

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Chapter 3
Diabetic Neuropathy

Prashanth R. J. Vas and M. Mahdi-Rogers

3.1 Introduction

In 2014, diabetes mellitus was thought to affect 422 million individuals globally, with worldwide prevalence rates reaching nearly 10% [1]. Amongst the 'triumvirate' of microvascular complications which include retinopathy and nephropathy, diabetic neuropathy (DN) is perhaps the most common, ultimately affecting more than 50% of those with diabetes. While acute forms exist, DN usually has an insidious onset with slow clinical progression to often debilitating complications. Although any part of the nervous system may be affected, the most classical presentation is the length dependent, sensory predominant distal symmetrical sensorimotor neuropathy (DSPN).

The consequences of DN are significant—it can cause considerable morbidity and is also recognised to confer an increased mortality risk [2, 3]. Development of DSPN in particular, may lead to neuropathic pain, Charcot neuroarthropathy, foot deformities and foot ulceration. Persistent ulceration in the diabetic foot is recognised to increase the risk of lower extremity amputation [4]. Furthermore, DN is now recognised as an important risk factor for depression with predictive ability for depression severity and increments in depression score [5]. The healthcare costs of DN and its associated complications are also quite significant. In 2003, it was estimated that the cost of managing DN in the UK was £252 million ($400 million) but a more recent estimate which has included the cost of managing diabetic foot

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disease has put the figure closer to £1.2 billion ($1.5 Billion) [6]. Another study from the USA, published in 2003, estimated that the cost was between 4.6 and 13.7 billion dollars [7].

3.2 Definitions of Diabetic Neuropathy

Diabetic neuropathy is defined as the "presence of a clinical state characterised by the presence of typical symptoms and/or signs of peripheral or autonomic nerve dysfunction in people with diabetes after the exclusion of other causes' [8]. In the Toronto Diabetic Neuropathy Expert Group consensus document, DSPN was defined as 'a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycaemia exposure and cardiovascular risk covariates' [9]. Diabetic painful peripheral neuropathy (DPPN), on the other hand, is defined as 'pain of a particular set of characteristics arising as a direct consequence of abnormalities in the peripheral nervous system in those with diabetes with symptoms that are symmetrical and which is often associated with nocturnal exacerbations' [9].

3.3 Type of Nerve Fibres

The nerve fibres in the human body can be divided into large and small nerve fibres. Large nerve fibres are fast conducting, and myelinated and mediate motor functions as well as sensory modalities of touch, vibration and proprioception. Small nerve fibres are mostly unmyelinated (C-fibres) or thinly myelinated (A-delta) and mediate pain, temperature and autonomic function.

3.4 Classification of Diabetic Neuropathy

Various classification systems have been proposed over the years to capture and categorise the different clinical and neurophysiological manifestations of diabetic neuropathy, many of which were an adaptation of the original classification by P K Thomas [8, 10]. In 2009, the Toronto Consensus on Diabetic Neuropathy was developed with the aim of ensuring that research studies utilised the same definition to characterise subjects as having diabetic neuropathy or not [9]. DN was categorised into two major divisions: Typical DN (to denote DSPN) and Atypical DN (to represent painful, autonomic and focal/multifocal nerve abnormalities) (Table 3.1). There was additional guidance on differentiating between possible, probable and confirmed DN. Increasingly, there is recognition that abnormalities of nerve conduction or small fibre measures may be present without any symptoms or clinical signs. The Toronto Consensus included a subdivision—Subclinical Neuropathy- to represent

Table 3.1 Classification systems for diabetic neuropathy

American Diabetes Association Classification of DN 2017 [11]	Toronto Consensus on Diabetic Neuropathy Classification [9]
A. Diffuse Neuropathy	**Typical Diabetic Neuropathy**
DSPN	Chronic Sensorimotor (DSPN)
Primarily Small Fibre or Primarily large fibre or Mixed type	**Atypical Diabetic Neuropathy**
Autonomic	Painful Diabetic Neuropathy Autonomic Diabetic Neuropathy Focal and Multifocal neuropathy with nerve morphological changes
Cardiac, Gastrointestinal, Urogenital, Hypoglycaemia unawareness, Sudomotor and Abnormal pupillary function	
B. Mononeuropathy (mononeuritis multiplex)	
Isolated cranial or peripheral nerve involvement or mononeuritis multiplex	**Subclinical Diabetic Neuropathy**
C. Radiculopathy or polyradiculopathy	
Radiculoplexus neuropathy and Thoracic radiculopathy	

such findings [9]. The 2017 American Diabetes Association position statement on Diabetic Neuropathy, classifies DN into a) Diffuse Neuropathy b) Mononeuropathy and C) Mono-Polyradiculopathy [11]. Diffuse Neuropathy is further categorised to include DSPN (and its subtypes) and the various autonomic neuropathies such as cardiovascular, gastrointestinal and urogenital [11].

3.5 Epidemiology

The true burden of DN remains unknown, although crossectional studies have reported prevalence figures between 10% and 85%, depending on the DN case definition used [11–14]. In the Rochester Diabetic Neuropathy Study 66% of insulin-dependent diabetes mellitus (IDDM) individuals and 59% of non-insulin-dependent diabetes mellitus (NIDDM) individuals had evidence of neuropathy [13]. In the Pittsburgh Epidemiology of Diabetes Complications Study, a prospective study of type 1 diabetes diagnosed between 1950 and 1980, the prevalence of neuropathy as assessed by signs, symptoms and abnormal tendon reflexes was 34% in those ages under 30 years, while it was 58% in those aged 30 years or greater [15]. In the Diabetes Control and Complications Trial (DCCT) trial, at study entry, the prevalence of confirmed DSPN and cardiac autonomic neuropathy was 6% and 4.5% respectively [14]. The North-West Diabetes Foot study set up to determine the incidence and prevalent risk factors for diabetic foot ulceration in the community, reported a 22% prevalence of moderate severity DSPN, determined by composite score assessment and a 21% insensitivity rate to the 10 g monofilament [16]. Another multicentre study from the United Kingdom representing randomly selected patients attending hospital diabetes clinics with a 8-year median duration of diabetes, put the prevalence of DSPN assessed with clinical examination and vibration testing at 29% [17]. The EURODIAB Prospective Complications Study, reported an 24% incidence of DN over the 7.3 year follow up period [18].

Pain is also commonly reported among those with diabetes. The prevalence of diabetic painful peripheral neuropathy (DPPN) reported in literature ranges from 10–20% of patients with diabetes and up to 50% in those with established DN [19]. It is important to note that many studies reporting on DPPN do not differentiate coexistent pain related to other aetiologies. Lack of prospective studies in DN has meant that precise incidence figures for DPPN are not available. However, both DPPN and non-specific painful symptoms are understood to be more prevalent in those with type 2 diabetes compared to those with type 1 diabetes [20]. Davies and colleagues reporting on a Welsh urban cohort, noted that that 64% of diabetes individuals surveyed reported pain. However, only 19% were thought to have pure DPPN [21]. An additional 7.4% were found to have pain of mixed aetiology, giving an overall prevalence rate of 26.4% [21]. Another study from Liverpool, UK reported a prevalence rate of 16.2% [22]. Worryingly, 12.5% had never reported their symptoms and 39.3% had never received any treatment for the pain [22]. Similarly, data from the Korean Diabetes Association Neuropathy Study Group indicates 14% of all type 2 diabetes patients may have DPPN [23]. In addition, atypical painful neuropathies have been recognized to impact those with prediabetes/impaired glucose tolerance [24–26].

3.6 Risk Factors for Diabetic Neuropathy

Studies have consistently shown, both in type 1 and type 2 diabetes, that poor glycaemic control, measured using HBA1c serially, is associated with a higher risk of developing microvascular complications, including DN [14, 27]. Intensive therapy during the Diabetes Control and Complications Trial (DCCT) significantly led to a risk reduction of 64% ($p < 0.01$) for the development of DSPN [14]. In addition to higher HbA1c, longer duration of diabetes may also confer a higher risk. There is some suggestion that glucose variability may contribute to the development of DN However the evidence is contradictory and limited [28]. Older age [29, 30], male gender [31, 32], height [32], hypertension [12], and certain ethnicities such as African-Americans have been noted to present an increased risk of DN development. In one small observational cohort from the UK, taller stature, higher quartiles of serum triglycerides and HbA1c were associated with neuropathy development at follow-up [33]. For neuropathic pain, one large community study based in the North-West of England has observed that type 2 diabetes, women and South Asian ethnicity also conferred additional increased risk over classical DN risk factors [20].

Improving glycaemic control, while reducing the risk of neuropathy does not eliminate it, especially in type 2 diabetes. In the EURODIAB study, after adjustment for age, hyperglycaemia and duration of diabetes, factors such as cigarette smoking, high-density lipoprotein cholesterol, elevated diastolic blood pressure, increased fasting triglycerides and presence of microalbuminuria were independently associated with DSPN development [34]. The concept that lipoproteins, especially tri-

Table 3.2 Risk factors for diabetic neuropathy (DN)

Risk factors for DN	Odds risk for DN
Duration of diabetes mellitus	1.40
HbA1c	1.48
HbA1c per unit increase (HbA1c%)	1.35 to 1.80
Total cholesterol	1.26
Triglyceride	1.35
Body mass index	1.4
Weight	1.3
Smoking	1.55
Hypertension	1.57–1.92
Any retinopathy	1.7
Any micro or macroalbuminuria	1.48
Any cardiovascular disease	2.74

Adapted from DCCT [14] and EURODIAB [12] data

glycerides, may have a role in DSPN development has been in evolution recently [35–37]. Genetic factors such as polymorphisms of the sodium channels [38] or apolioprotein E [39] may further predispose individuals to DN, especially those with shorter duration of disease or certain pain phenotypes. Important risk factors have been summarised in Table 3.2.

3.7 Pathogenesis of DN

The exact pathological basis for diabetic neuropathy remains unclear despite significant advances in research. While the earlier studies focused predominantly on mechanistic drivers related to hyperglycaemia, newer approaches, especially in type 2 diabetes, have investigated the role of other factors coupled with hyperglycaemia. Thus, multiple hypotheses have been proposed and these can be divided into hyperglycaemic, metabolic, vascular, immunologic and abnormal neuroregenerative mechanisms. Currently, it is difficult to identify which of the above mechanisms plays a predominant role or is the initial trigger for neural injury. The recognition that neuropathy may already exist at the time of diabetes diagnosis, and sometimes in prediabetes, prior to the development of significant hyperglycaemia or microvascular features, suggests that there are other factors, especially metabolic (insulin resistance or impaired signalling, c-peptide deficiency, dyslipidemia) and those related to nitrosative-oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress which are responsible for driving early neuropathic changes [40, 41]. A schematic representation of currently understood mechanisms of diabetic neuropathy is presented in Fig. 3.1. Atypical forms of DN may have an immunological basis. In those with proximal diabetic amyotrophy, examination of nerve biopsy specimens has shown evidence of perivasculitis, leucocytic infiltration with immune complex deposition and complement activation along the microvascular endothelium [42].

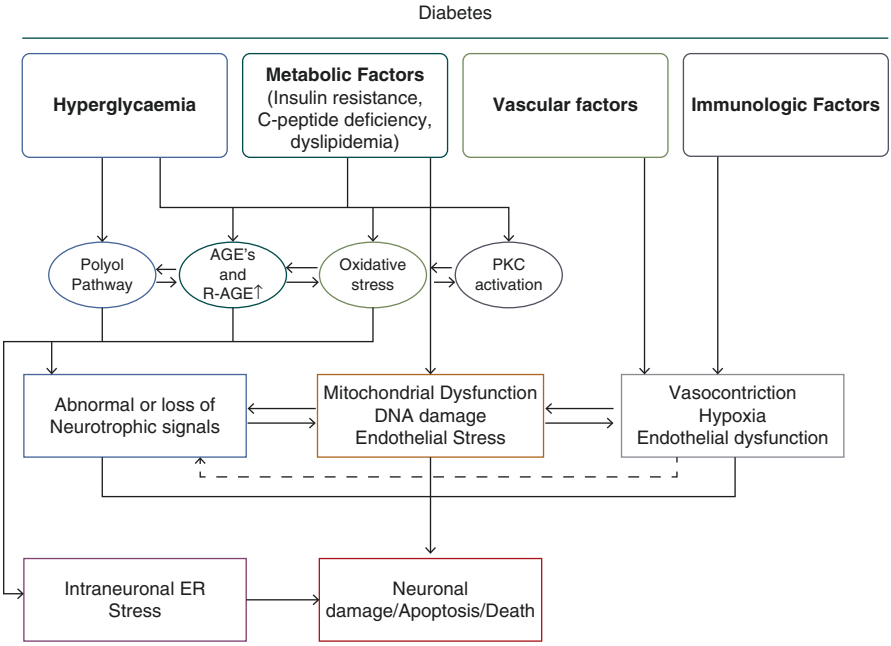

Fig. 3.1 Pathogenesis/Mechanisms of diabetic neuropathy. AGE advanced glycated end products, ER endoplasmic reticulum, R-AGE receptor for advanced glycated end products, PKC protein kinase-C

What comes earlier: Small fibre or large fibre damage? The development of sensitive techniques in the past three decades has resulted in the appreciation that small nerve fibres may be the earliest fibres to be impaired [4, 43, 44]. Impairment of large nerve fibres is understood to follow the small fibre change; however this remains unproven as other studies have demonstrated coexistent large fibre change [45, 46]. There is an unmet need for well conducted prospective studies evaluating the precise sequence of nerve fibre damage.

3.8 Clinical Features

3.8.1 Typical DN: Diabetic Sensorimotor Peripheral Neuropathy (DSPN)

The distal symmetrical length dependent, predominantly sensory polyneuropathy of diabetes is perhaps the most common form of DN, accounting for nearly 80% of the cases. Indeed, some use the terms DN and DSPN interchangeably. Typically, DSPN develops in the toes and distal leg, with proximal progression and in many instances may also affect the hands, in a 'glove and stocking' fashion. Negative sensory features such as numbness or hypoaesthesia may be the only initial symptoms.

Table 3.3 Typical sensory symptoms in diabetic neuropathy

Negative sensory symptoms	Positive sensory symptoms
Inability to feel tactile stimuli e.g. movement of hair	Burning pain
Decreased feeling of cooling or abnormal appreciation of warming	Hyperaesthesia
Numbness	Allodynia
Hypoaesthesia	Paraesthesia (tingling)
Analgesia/Hypoalgesia	Cramp type discomfort
Motor weakness	Fasciculations (rare)
Fatigue	

Positive sensory symptoms such as pain, hyperaesthesia, aches and cramps are also frequently reported [11]. However, there is poor correlation of these features with clinical or neurophysiological findings (Table 3.3). Motor symptoms such as gait disturbances, weakness and ataxia occur late into the condition and are less frequently reported [47].

Clinical examination may demonstrate abnormal sensation to pinprick assessment, impaired vibration perception, proprioceptive changes and abnormal/absent reflexes. Wasting of the small muscles of the feet and hands, deformities of the toes (claw or hammer toes) and callus on the plantar aspect may be contributory signs; however, muscle wasting or gross weakness of the major muscle groups is unusual. Concurrent cutaneous sudomotor neuropathy may result in dry skin and impairment of sweating. Established DSPN is a risk factor for development Charcot neuroarthropathy [48] and loss of protective sensation secondary to DSPN will increase the likelihood of developing neuropathic foot ulcerations [16, 49]. DSPN frequently coexists with other atypical neuropathies such as autonomic and painful [50]. Importantly, up to 50% of individuals with DSPN may be asymptomatic [11].

3.8.2 Atypical DN

3.8.2.1 Diabetic Painful Peripheral Neuropathy (DPPN)

Individuals with DPPN typically describe ‘burning’, ‘stabbing’ ‘tingling’ or ‘pins and needles’ but also ‘allodynia’ (non-painful sensations such as pulling the bed sheets over the feet are described as being intensely painful) and ‘hyperalgesia’ (painful stimuli are perceived with increased sensitivity). The symptoms are worse at night and many patients may report sleep disturbance [51]. This lack of sleep and constant pain could lead to pain amplification, personal distress, depression and a reduced quality of life leading to significant morbidity [51, 52]. While the feet are commonly involved in a symmetrical distribution, the hands may also be involved with significant additional functional burden to the patient. DPPN may be the predominant feature of acute painful generalised diabetic neuropathies such as treatment induced neuropathy of diabetes (TIND) or amyotrophy. DPPN may be the first presenting symptom of diabetes.

3.8.2.2 Focal or Multifocal Neuropathies

Diabetic focal and multifocal neuropathies often present dramatically, usually affecting those with longstanding diabetes or those older than 40 years. Diabetic lumbosacral radiculoplexus neuropathy (Diabetic amyotrophy) presents either acutely or subacutely and is characterised by severe pain in the lower limb/s, sensory loss, significant weight loss (often >10%) and weakness of thigh muscles. Cranial focal neuropathies are typically seen as III or VI nerve palsies but multiple simultaneous cranial neuropathies may occur. Affected individuals report pain, ptosis and diplopia which progresses over 24–48 h. Multifocal neuropathy may simultaneously involve the truncal and limb nerves and needs to be differentiated from chronic inflammatory demyelinating polyneuropathy (CIDP).

3.8.2.3 Diabetic Autonomic Neuropathy (DAN)

Neuropathy of the sympathetic and parasympathetic systems (or both) may lead to symptoms which could be specifically attributed to abnormalities of the cardiac, genitourinary, gastrointestinal, sudomotor systems (Table 3.4) [53]. Symptoms of cardiac autonomic neuropathy include palpitations, reduced exercise tolerance, dizziness and syncopal events [54]. Tachycardia, postural hypotension, minimal or no increase in heart rate and blood pressure during exercise and orthostatic hypotension are signs associated with cardiac autonomic neuropathy (CAN). Diabetic gastroparesis may be associated with nausea, increased satiety, recurrent abdominal pain and intractable vomiting [55]. Nocturnal diarrhoea and/or constipation may indicate lower bowel autonomic involvement. Genitourinary autonomic neuropathy is associated with erectile dysfunction, incomplete bladder emptying with increased post void residual urine and urine retention.

A high level of vigilance needs to be maintained while evaluating subjects with diabetic neuropathy as patients with DSPN may develop atypical features and vice versa. Furthermore, many individuals with DN do not necessarily complain of symptoms, even in advanced disease. Thus, the absence of symptoms should not be used to confirm the absence of neuropathy.

Table 3.4 Diabetic autonomic neuropathy

Salient features of diabetic autonomic neuropathy
Palpitations, reduced exercise tolerance, dizziness and syncopal events
Orthostatic hypotension
Nausea, vomiting, dull feeling in the stomach, constipation, diarrhoea
Dysuria, urinary retention or male and female sexual dysfunction
Non-symptomatic hypoglycaemia (hypoglycaemia unawareness)

3.9 Diagnosis

The diagnosis of DSPN is usually made on clinical grounds. The standard neurological examination may highlight impaired vibration perception (with a 128-Hz tuning fork or equivalent) or impaired or absent tendon reflexes. In addition, testing for light touch and pin prick sensation may allow determination of the proximal extent of the sensory loss. Nerve conduction studies, the gold standard investigation for DSPN confirmation are rarely required. Their primary role in the clinical diagnosis of DSPN is to exclude secondary causes when atypical features are present. However, they are still considered the gold standard surrogate endpoint in research trials [56]. The 2017 guidance from the American Diabetes Association (ADA) recommends using pinprick and temperature assessments for detecting small fibre function, while vibration perception, proprioception testing, 10-g monofilament sensitivity, and ankle reflexes can be used for large fibre function assessments [11]. Many clinical composite score are available, notably the Neuropathy Disability Score (NDS), Toronto clinical neuropathy score (TCNS) and the Michigan Neuropathy Screening Instrument (MNSI) [57]. These have been widely used both in research but also in clinical practice and possess good internal consistency and reliability for detecting DSPN [58]. The modified NDS is a ten point scale based on vibration, temperature, pin prick and ankle reflex assessments to grade the presence of DSPN [49, 57]. A score of two or lower has been shown to suggest the absence of clinical DSPN, while a score of three or higher is supportive for the presence of DSPN. A score of ≥ 6 has been shown to correlate with an increased risk for the development of foot ulceration (6.3% versus 1.1% when the score is ≤ 6) [16].

10 g monofilaments (10 gMF) allow assessment of light touch and are made of a single fibre nylon than can consistently generate a force 10 g when buckling under pressure (Fig. 3.2) The 10 gMF has been shown to have a sensitivity between 41%

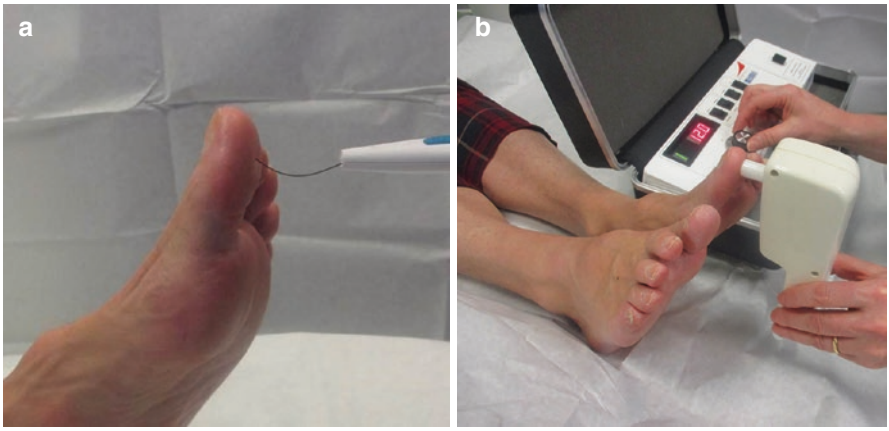

Fig. 3.2 Simple clinical tools for DSPN testing. (**a**) 10 g Monofilament, the filament is applied perpendicularly and when it buckles a standard load of 10 g is applied. (**b**) Neurothesiometer: The vibratory stimulus is gradually increased until the sensation of vibration is noted by the patient at what is called the vibration perception threshold

to 93%, and specificity between 68% to 100% for the detection of DSPN [59]. In addition, it allows for the detection of advanced neuropathy (loss of protective sensation) and the 'at-risk foot' for ulceration-insensitivity to 10 g MF has been shown to confer a 1.8 times to 7.7 times increased risk for diabetic foot ulceration [60]. However, users must be aware of an important difference in the testing methodology when the 10 gMF is used as a DSPN detection device [61] compared to when it is used to screening tool for the at-risk foot [62]. The neurothesiometer allows the quantitative assessment of vibration perception thresholds (VPT) as opposed to a tuning fork which only allows a qualitative approach (Fig. 3.2). The testing methodology is simple, with a reported sensitivity of 70% for the detection of mild DSPN [63]. In addition, a VPT of >25 volts has been shown to confer an eight times increased risk for developing neuropathic foot ulceration, compared to those with a VPT of <15 volts [64]. Vibratip™ is a relatively new, small electronic vibratory device, with an amplitude and frequency similar to a 128 Hz tuning fork. It has also been shown to be comparable to the MF and therefore could be considered as an alternative for DSPN screening, but its cost effectiveness is yet to be determined [65]. The Ipswich Touch test has been validated as a screening tool to detect at-risk insensate feet in those admitted to hospital with diabetes [66] but is finding broader application in DSPN assessment [67]. Importantly, for busy clinicians who want to conduct a quick foot-risk assessment during busy diabetes clinics, the 3-min foot exam has been proposed and received support from the American Diabetes Association [68].

Small fibre testing is indicated when clinical examination is negative despite the patient complaining of neuropathic symptoms such as pain. Nerve conduction studies primarily measure large fibres and are unable to detect small fibre neuropathy (SFN). The ADA recommends the use of bedside pinprick and temperature assessments as initial tests [11], but clinical examination can be notoriously subjective [69]. Skin biopsy with measurement of intraepidermal nerve fibre density (IENFD) allows for the assessment of small fibre structural abnormalities and is considered the gold standard test by some experts but is minimally invasive [70]. In-vivo corneal confocal microscopy (IV-CCM), can assess small fibre structure, non-invasively, by visualising the small nerves in the corneal subbasal plexus [71, 72]. The sensitivity and specificity of CCM for diagnosis of DSPN has been estimated to be 82% and 52% respectively [72]. Small fibre function may be evaluated using quantitative sensory tests of thermal and pain perception (QSTs for pain and temperature) [73], measuring the axon-reflex mediated microvascular flare response (LDIflare) [74] but also by assessing autonomic and sudomotor functions [57].

Quantification of pain can be done using the numeric rating scale (NRS, 0 representing "no pain" and 10 representing the other pain extreme (pain as bad as the patient can imagine), the visual analogue scale (VAS, "on a scale of 0 to 10, how bad is your pain at the moment?") or by utilising validated pain questionnaire instruments such as Brief Pain Inventory, the McGill Questionnaire or PainDetect questionnaire [75]. Diabetic autonomic neuropathy typically requires organ specific investigations for confirmation of diagnosis. The commonly used cardiovascular autonomic tests, include measurement of resting heart rate, heart rate variability to deep breathing, standing and/or Valsalva manoeuvre, lying and standing

blood pressure assessment and tilt table testing [76]. Radionucleotide gastric emptying studies are the mainstay of gastroparesis assessment [77] but complex tools that measure intraluminal pressure and stomach surface electrical profiles are also available in larger centres.

3.10 Differential Diagnosis

Individuals with diabetes may have an alternative or co-existent aetiology for their neuropathy (Table 3.5), and therefore, it is important to consider excluding non-diabetic causes of polyneuropathy, especially when atypical features such as short duration of symptoms, severe pain, focal motor defects, ataxia or significant proprioceptive abnormalities are present.

3.11 Management of Diabetic Neuropathy

The main treatment strategies for DN include good glucose control, cardiovascular risk modification and appropriate neuropathic pain management. Regretfully, there are no disease modifying agents approved by the Federal Drug Agency or licensed in the UK for the treatment of diabetic neuropathy.

3.11.1 Glycaemic Control

Good glucose control in type 1 diabetes has been shown to be very effective in reducing the incidence of diabetic neuropathy [14, 18, 78, 79]. In the DCCT study, those receiving intensive insulin therapy, had a 64% reduction in DSPN incidence and a 45% reduction in CAN incidence at study closeout [14]. In 32 newly diagnosed

Table 3.5 Differential diagnosis of diabetic neuropathy

Differential diagnosis in DN
Alcohol abuse or nutritional (e.g. post gastric-bypass)
Drug-induced
Chronic Kidney Disease
Vitamin B12/folate deficiency
Hereditary neuropathies
Inflammatory (CIDP—Chronic inflammatory demyelinating polyradiculoneuropathy)
Paraneoplastic (Malignancy or monoclonal gammopathy)
Thyroid Disease
Spinal canal Stenosis
Autoimmune (Vasculitis, Rheumatoid, Sjogrens, Sarcoid, etc.)
Infections (HIV, Hepatitis B and C, Syphilis, Lyme's disease)

individuals with type 1 diabetes who were followed up for 24 years with neuropathy assessments, near normal glycaemia, defined as a HbA1c consistently below 7% was associated with near complete prevention of a decline in DSPN and autonomic measures [78]. Improvement in small fibre indices, has been demonstrated post-pancreatic transplantation [80] and after starting insulin pump therapy [81]. The supportive literature in type 2 diabetes is more modest for the benefits of tight glycaemic control on development and prevention of DN [82, 83]. The UKPDS study, which enrolled subjects who were recently diagnosed, reported an improvement in vibration perception thresholds after 15 years follow up in those with enhanced control (0.60 (95% CI 0.39–0.94, $p < 0.05$). This modest benefit was not reproduced in the ACCORD study which recruited 5500 with ~8.5 years of type 2 diabetes duration and followed them for a median of 3.7 years [83]. In the study, there was a modest (5%) improvement of neuropathic symptom scores but no reduction in the development of incident neuropathy [83]. A Cochrane meta analysis concluded that although there was trend on annualised risk difference in type 2 diabetes, it did not reach statistical significance ($p = 0.06$) [79]. Importantly, and for both type1 and type 2 diabetes, the authors offered a cautionary point—with enhanced glucose control came a significantly increased risk of severe hypoglycaemia—which needs to be part of the risk/benefit consideration [79].

3.11.2 Management of Neuropathic Pain

Treatment of neuropathic pain can often be unpredictable and challenging. Sadly, there is no compelling supportive evidence for good glycaemic control in pain management. However, those with pain have been shown to have greater mean glucose as well as higher glucose excursions [84] and therefore good glycaemic control should be encouraged. Therefore DPPN management is based on using one or more of the pain agents to achieve a reduction in pain. Paracetamol or non-steroidal anti-inflammatory drugs such as ibuprofen are helpful in relieving mild to moderate pain, but are often underutilised. Early referral to a specialist pain service should be encouraged.

Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine), anticonvulsants (pregabalin, gabapentin) and the serotonin and norepinephrine reuptake inhibitor (SNRI) duloxetine are the current first line choices (Table 3.6). While the American Association Of Neurology recommends using pregabalin as the first line option [85], the Neuropathic Pain Special Interest Group (NeuPSIG) and National Institute for Health and Clinical Excellence (NICE) recommend clinicians to choose between duloxetine, amitriptyline and pregabalin for first line therapy [75, 86, 87]. The guidance on second line options is variable and suggestions include switching between the three first line drugs, use of topical lidocaine patches or anticonvul-

Table 3.6 Neuropathic pain drugs, mechanisms of action and NICE 2013 and NeuPSIG 2015 guidance

Drug	Action	NICE (UK) Guidance (2013) [87]	(NeuPSIG) Special Interest Group on Neuropathic Pain [86]
Tricyclic agents (amitriptyline, nortryptiline,imipranine)	Serotonin–norepinephrine reuptake inhibition, blockade of sodium channels, muscarinic receptor antagonism 25–150 mg, once a day or in two divided doses	First line choice. May be initiated in Primary Care	First line Higher doses (>75 mg/day) not recommended in those above 65 years or older
Pregabalin	α2δ Ca^{2+} channel inhibition 300–600 mg, in two divided doses	First line choice. May be initiated in Primary Care	First line
Duloxetine	Serotonin–norepinephrine reuptake inhibitor	First line choice. May be initiated in Primary Care	First Line
Gabapentin	α2δ Ca^{2+} channel inhibition 1200–3600 mg, in three divided doses	First line alternative, recommendation unclear	First line
Carbamazepine	Na^{+} channel blocker	Second or third line option. Refer to specialist service	Inconclusive recommendation for use
Valproate	Central pain inhibitor via inhibition GABA	Second or third line option. Refer to specialist service	Weak recommendation against use
Lamotrigine	Na^{+} channel antagonist, central inhibition of pain	Second or third line option. Refer to specialist service	Inconclusive recommendation to recommendation
Lidociane/Lignocaine 5% patch	Peripheral direct Na^{+} channel blockade	Needs referral to specialist service. May be an option to use in those preferring non-oral option	Second Line
Capsaicin Patch (8%)	Activation of transient receptor potential channel subfamily V member 1 (TRPV1)	Needs referral to specialist service	Second line but unclear if recommended in Diabetes

(continued)

Table 3.6 (continued)

Drug	Action	NICE (UK) Guidance (2013) [87]	(NeuPSIG) Special Interest Group on Neuropathic Pain [86]
Tramadol	Weak μ-opioid receptor agonist, Serotonin–norepinephrine reuptake inhibitor	Only for acute rescue therapy. Not as initial First line use	Second Line
Other opioids			Third Line; report says sustained release oxycodone and morphine have been the most studied opioids

sants such as valproate and carbamazepine, the SNRI venlaflaxine or introducing opioids such as tramadol. In difficult to control pain, combination therapy with pregabalin and duloxetine may be considered. In the COMBO-DPN study, the largest controlled trial looking into combination therapy, there was no difference in pain outcomes between combination therapy and high dose monotherapy [88]. These findings are in contrast to a smaller controlled study of 56 patients where a combination of gabapentin and nortriptyline was found superior to monotherapy with either gabapentin or nortriptyline [89].

Starting doses for duloxitene are 60 mg once daily (OD) (at night) which can be increased to 60 mg twice daily if tolerated. Hepatic dysfunction and an eGFR of less than 30 mL/min/1.73 m^2 are notable contraindications and a slight increase in HbA1c has been reported from pooled data (+0.52 versus +0.19 for placebo) [90]. Pregabalin is started at a dose of 150 mg daily in 2 or 3 divided doses and then increased (if necessary) to 600 mg daily in 2 or 3 divided doses. It has additional anxiolytic properties and may also improve sleep quality [91]. Cautions include the risks of precipitating encephalopathy and worsening congestive heart failure. In addition, and in contrast to gabapentin, it has linear pharmacokinetics and a much simpler regime for dose titration. One study showed that duloxetine was faster initially in achieving pain control. However, pregabalin ultimately was able to 'catch-up' over a period of time [88]. The numbers needed to treat range between 3 and 11 for the first line agents [11, 86]. Topical strategies and non-pharmacological approaches to DPPN have also been advocated because of the limitations of systemic agents. 5% Lidocaine medicated patches [92], Opsite® spray [93] and capsaicin cream 0.075% (not the 8% formulation which is unlicensed in DPPN) have all been shown to be of some benefit [94]. Extended release tapentadol has been shown to be effective in DPPN [95]. Non-pharmacological options, amongst many, include psychological support, acupuncture, transcutaneous spinal cord stimulation and exercise but lack randomised trial evidence. Complete resolution of neuropathic pain is unusual in real world practice. In clinical trials, a 30% pain reduction or 2 point reduction (out of 10) has been considered to be meaningful and adequate

outcome [48]. In addition, the quoted number need to treat and harm (NNT and NNH) in neuropathic pain are based on a particular drug achieving 30–50% pain relief [96]. Therefore, it is important to manage patient expectations around pain management.

3.11.3 Management of Autonomic Neuropathy

Treatment of orthostatic hypotension facilitates the reduction of postural symptoms, allows safe standing and improves functional outcomes. Avoiding or reducing medications than can cause inordinate vasodilatation, preventing volume depletion and safe postural changes (slow standing) are key strategies. The mineralocorticoid fludrocortisone has been shown to be of benefit [97], but oedema, hypernatremia, hypokalemia and supine hypertension may develop [76]. The alpha agonist midodrine has FDA approval for treatment of neurogenic orthostatic hypotension, but could also cause excessive supine hypertension [97]. Symptoms related to CAN will require referral to cardiology for specialist management. The prokinetic drugs, metaclopramide and domperidone have trial evidence in gastroparesis [55]. Antiemetic agents may help relieve nausea and vomiting but the effect is not usually sustained. Some specialist centres carry out implantation of gastric electrical stimulators (gastric pacemaker) [98]. Diabetic diarrhoea can often be managed by codeine phosphate but other anti-diarrhoeal preparations may be tried. Hypoglycaemia unawareness may benefit from patient education, close clinical surveillance, diabetes structured education such as DAFNE (Dose adjustment for Normal Eating) or consideration of subcutaneous insulin pump therapy with real time glucose monitoring [99, 100].

3.11.4 Control of Cardiovascular Risk Factors

Individuals with DN have an increased risk of cardiovascular events and increased mortality [2, 3, 101], it is important that CVD risk factors are addressed and optimised accordingly. Management of hypertension, lipids, smoking cessation advice and emphasising healthy lifestyle choices should all be a part of the treatment plan.

3.11.5 Disease Modifying Treatments

Prevention or arresting neuronal damage is the holy grail of DN management. Although numerous putative agents with potential to reverse neuropathy have emerged over the last three decades, there are no current licensed treatments. Aldose reductase inhibitors (ARI) have received the most attention [102], but have either struggled with tolerability issues (Zenerastat, Tolrestat), or have not met efficacy

endpoints despite showing moderate improvements in nerve conduction velocity (Ranirestat) [103]. The proposed role of oxidative stress in the development of DN, has led trials on the benefit of antioxidant therapy in DN. In the dose finding arm of the ALADIN III study, alpha-lipoic acid, an antioxidant and free-radical scavenger, infused at a dose of 600 mg/day over 3 weeks, improved pain, paraesthesia and numbness in type 2 diabetic polyneuropathy [104]. These encouraging results were not sustained in a RCT that followed, which included a 6 month oral continuation of alpha-lipoic acid at 600 mg three times daily after the initial 3 week intravenous regime [104]. The NATHAN I study which randomised 460 diabetic subjects with mild-modertae DSPN to alpha-lipoic acid or placebo for 4 years, also did not meet the primary endpoint which was improvement in the Neuropathy Impairment Score-Lower Limbs and seven neurophysiological tests composite score (NIS-LL + 7) ($p = 0.11$) [105]. Other agents, such as the protein kinase C inhibitor Ruboxistaurin, have had also promise in experimental neuropathy, but have been found wanting in human trials [106]. Nerve growth factors [107] and vascular endothelial growth factors and C-peptide [108] are among some of the newer agents in the process of being evaluated.

3.11.6 Diabetic Foot Risk Assessment

The development of foot ulceration is the most important consequence of DSPN. The lifetime risk for foot ulceration in those with diabetes is 15–25% [49]. Furthermore, individuals are also at risk for developing Charcot neuroarthropathy. The ADA suggests that all patients should be assessed for DSPN starting at diagnosis for type 2 diabetes and by 5 years of diagnosis for type 1 diabetes, followed by annual assessments [109]. The diabetes annual assessment should include a visual foot check, assessment for advanced neuropathy, palpation of foot pulses and categorisation of foot-risk [109, 110]. The risk then needs to be effectively communicated to the patient and those in moderate and high risk categories placed into a foot protection program. Any new ulceration or a red, hot, swollen foot should be referred urgently to the hospital or a specialist diabetes foot clinic for assessment.

3.12 Conclusions

Diabetic neuropathy may affect any part of the nervous system but the slowly progressive distal symmetrical variant (DSPN) is the most common presentation. The different forms of DN may coexist in the same individual and can cause significant morbidity and as well as pose a mortality risk, pathologies and cause significant morbidity. The aetiopathogenesis remains unclear and it is likely that multiple pathogenic factors are involved at the same time, and include factors in addition to hyperglycaemia. The diagnosis of DSPN can be made on clinical grounds in

those with obvious symptoms and signs. However, there is no single test available for diagnosis confirmation. Increasingly, small fibre damage is being recognised as representative of early diabetic neuropathy and can often be present at time of diagnosis or in prediabetes states. There is a paucity of effective disease modifying therapies and effective glucose control is the only proven treatment strategy. Long term clinical management includes annual reassessment of neuropathy status, pain management, effective patient communication and early referral to specialist teams when neuropathy related complications arise.

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Chapter 4
Neuropathic Diabetic Foot Ulceration

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4.1 Introduction

Among individuals with diabetes, ulceration of the foot is perhaps among the most serious and feared of the complications. It is estimated that the lifetime risk of developing a diabetic foot ulceration (DFU) is approximately 19–35% in individuals with diabetes [1]. Despite recent improvements in diabetic foot care and wound management, many individuals with DFU progress to lower extremity amputation(LEA). The rate of LEA continues to rise in many countries—in the United Kingdom, 135 of such procedures are conducted per week; while in the United States of America (USA), figures published by the Centers for Disease Control and Prevention, estimated the LEA rate in 2009 to be 3.2 per 1000 diabetic population adjusted for age. Development of DFU can lead to increased morbidity and significant disability [2–5]. In addition, there is an association with an increased mortality risk [5, 6]. The economic burden to health care systems is enormous: in England, for the year 2014–15, the estimated NHS cost in England was £972 million—£1.13 billion or £1 in every £140 spent on the National Health Service [7]. It is estimated that the future costs of diabetes foot care in UK by the year 2035 will rise to £2.1 billion, a 3.3 times rise in costs in only 25 years [8]. In the USA, the cost of diabetic foot management was estimated to be between $ 9–13 billion recently. DFU could add between $11,710-$16,833 incremental costs to a patient's annual healthcare costs, doubling the cost of delivering diabetes care [9]. There are substantial additional indirect costs, often invisible, such as the loss of individual earnings, burden to carers and effects of absenteeism on employers.

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4.2 Diabetic Foot Ulceration

Diabetic foot ulceration can be divided into two main groups: a) occurring in those with neuropathic feet without evidence of peripheral arterial disease (neuropathic DFU) and, b) those incurred in feet with neuropathy and coexistent arterial disease (neuroischaemic DFU). In this section, we focus on neuropathic DFU, and discuss the clinical features, management strategies and the future outlook.

4.3 Epidemiology and Risk Factors for Neuropathic DFU

The annual incidence of DFU is thought to be around 1.9% to 4.0% of the diabetes population, depending on the country surveyed [10–12]. However, among those with peripheral neuropathy, the incidence is higher, and estimated to be between 5.0%—7.5% [13]. In a large multicentre hospital based study from the UK, Abbott et al. noted that for each 1-volt increase in vibration perception thresholds, there was 5.6% increase in the risk of foot ulceration [14]. Prevalence rates for DFU range from 5% to 9%, depending on the cohort and the country studied [1]. Approximately 8% of Medicare beneficiaries with diabetes between the years 2006–2008 were reported to have a DFU [15].

4.3.1 Presence of Neuropathy in DFU

In the multicentre European EURODIALE study, a concerted effort aimed at understanding the characteristics and outcomes of patients presenting with DFU to 14 specialised foot units, peripheral neuropathy was present in 86%, while peripheral arterial disease (PAD) was present in 42% of the cohort at baseline [16]. In a combined analysis of DFU patients taken from hospital clinics from Manchester UK and Seattle USA, Reiber et al. noted that neuropathy as present in 78% of all patients, while the triad of neuropathy, minor foot trauma and foot deformity was present in > 63% of the ulceration causal pathways identified [17]. Nonetheless, the proportion of pure neuropathic DFU reported in literature varies between 40%-60%. In one study of 185 subjects, Moulik et al. reported that 45% were pure neuropathic, 24% were neuroischaemic and 16% were purely ischaemic in aetiology [5]. In another study from UK, 20 out of 42 (48%) DFU's were considered neuropathic, while 13 (30%) were neuroischaemic and 5 (11%) considered purely ischaemic [18]. From a well characterised, 5-year follow-up study from Nottingham UK the authors reported that 30% of the patients and 28% of ulcerations fulfilled the criteria for pure neuropathic DFU [19]. Likewise, from the baseline EURODIALE data it may be extrapolated that up to 58% of ulcerations were of pure neuropathic origin [16]. Another study from Brazil reported approximately 60% prevalence of neuropathic

DFU in their cohort [20]. In a group of 115 patients with Charcot neuroarthropathy followed up for 48 months, approximately 37% were noted to develop new ulceration over deformities [21].

4.3.2 Risk Factors for Development of Neuropathic DFU

Loss of protective sensation, or advanced neuropathy, has been a consistent risk predictor for foot ulceration. In the North-West Diabetes Foot Care study, insensitivity to the 10gm monofilament was associated with an increased risk of DFU development (relative risk RR 1.80, 95% CI 1.40–2.32) [11], while in the Seattle Diabetic Foot Study it was higher (RR 2.2 95% CI 1.5–3.1) [22]. Similarly, another study using vibration perception threshold (VPT) measurement noted that presence of VPT ≥25 Volts was associated with an odds risk of 7.99 for DFU development, compared to those with VPT ≤15 volts [23]. In addition to neuropathy, other factors contributing to the development of DFU include age [11], longer duration of diabetes [23, 24], poor glycaemic control [25], male gender [26], greater body mass [22], previous foot ulceration [11]. In the Seattle Diabetes Foot Study, presence of hammer/claw toe deformities and a history of laser photocoagulation of the eye were associated with a higher DFU risk [22]. External precipitants such as poorly fitting shoes/socks, acute mechanical trauma, shear stress and paronychia are also recognised as important triggers [27]. Medical comorbidities such as dialysis, previous cerebrovascular events and reduced mobility have been shown to confer additional risk [22, 28]. External precipitants such as poorly fitting shoes/socks, acute mechanical trauma, shear stress and paronychia are also recognised as important triggers [23]. Medical comorbidities such as dialysis, previous cerebrovascular events and reduced mobility have been shown to confer additional risk.

4.3.3 Risk Factors for Delayed Healing in Neuropathic DFU

Standard care arms in DFU healing studies have provided good insight into factors responsible for delayed healing. In a meta-analysis of 586 subjects with neuropathic DFU—all receiving good wound care, regular debridement and off-loading—Margolis et al., noted that 24% of patients healed within 12 weeks and 33% healed completely within the first 20 weeks of care [29]. Size of the ulcer (<2 cm^2) and a shorter duration of ulceration prior to entering the study were favourable towards healing [29]. Age, gender and baseline HbA1c were not associated with the probability of healing. In another study of 27,630 neuropathic DFUs the same group noted a healing percentage of 58% [30]. Important predictors of non-healing were a duration of ulceration ≥2 months, size >2cm^2 or a higher ulcer grade [30]. Indeed, there was a 0.81 likelihood of non-healing when these three factors were present [30]. Markuson did report that healing times were decreased in those individuals

who had lower HbA1c values [31] Presence of male gender [25, 32] and superadded infection [25] may be associated with an increased risk of non-healing at 12 weeks. While some have suggested that the ulcer site is not an independent predictor of outcomes [33], others have observed that hindfoot neuropathic DFUs take longer to heal [34, 35]. A history of smoking, deep vein thrombosis and previous cardiovascular events may contribute to delayed healing [36].

4.3.4 Risk Factors for Recurrence of Neuropathic DFU

DFUs are notorious for their recurrence. In a single centre follow up of the EURODIALE study (n=73), 58% of the patients developed a DFU recurrence over a 3-year period. Indeed, recurrence rates for the first, second and third year were 40%, 18% and 13% respectively (p=0.006 for trend) [37]. One limitation of the study was that it did not differentiate between neuropathic and non-neuropathic DFU. Risk factors for recurrence were plantar ulceration, previous osteomyelitis, HbA1c >7.5% and a CRP>5mg/l [37]. In a cohort of 253 subjects followed up for 18 months, of which 76% were neuropathic DFUs, there were 99 (43%) recurrences [32]. Presence of microvascular complications was the only variable associated with recurrence [32]. Another study from Netherlands which monitored recently healed neuropathic DFUs for 18 months as a part of a footwear trial reported that 71/171 (42%) of the patients developed a recurrence [38]. Presence of minor lesions (OR 9.06, 95% CI 2.98–27.57), daily variation in stride count (OR 0.93 95% CI 0.89–0.99), and cumulative duration of past foot ulcers (OR 1.03 95% CI 1.00 -1.06) were found to be independent predictors. For recurrent neuropathic DFUs secondary to unrecognised repetitive trauma, the independent predictors also included minor lesions (OR 10.95 95% CI 5.01–23.96), in-shoe peak pressure <200 kPa with footwear adherence >80% (OR 0.43 95% CI 0.20–0.94), and barefoot peak pressure (OR 1.11 95% CI 1.00–1.22) [38]. Another study of 101 patients with metatarsal head resection for confirmed osteomyelitis reported that 41% developed further ulceration over one or more of the remaining metatarsal heads within the following 13 months [39]. The risk was highest for 1st metatarsal head resection (69% transfer ulceration rate) and lowest for the 5th metatarsal head resection (19%) [39].

4.3.5 Risk Factors for Amputation in Neuropathic DFU

Diabetes confers a 12–20 times increased risk for lower extremity amputation (LEA, defined as the loss of any part of the lower extremity) [13]. Although the majority of those who develop a DFU eventually heal, it is estimated that between 5–25% may end up with a LEA [5, 40, 41]. In one study, the 5 year LEA rate was lower for neuropathic (11%) compared to neuroischaemic (25%) and ischaemic DFU (29%) [5]. Risk factors for amputation in those with an established DFU include male gender [20, 42], longer duration of diabetes [42, 43], higher HbA1c [43–45], dyslipidemia [45–47], current dialysis or chronic kidney disease [43, 44, 48], higher

grade wound classification/ulcer severity [32, 49], underlying osteomyelitis [50], severe necrotising infection [49], lower serum albumin [43, 49] and smoking [43]. In the EURODIALE study, decreased health-related quality of life (HRQoL) was a significant factor in major amputation [40]. Presence of vascular disease also significantly increases the risk of LEA [41, 43, 46], but is less relevant in the context of discussing neuropathic DFU. Patient compliance may additionally contribute; one study reported that the LEA rate was 26% higher in those deemed to be less compliant with treatment [51]. The contribution of the wider health-care system and its amputation preventative infrastructure is much harder to factor in studies; for example, in England there is a 2-fold variation between hospitals and a 10-fold variation between primary care boundaries for the incidence of amputation [52].

4.4 Pathway to Ulceration if Neuropathic DFU

Neuropathy, on its own, does not spontaneously drive ulceration. However, the sensory, motor and cutaneous autonomic changes brought on by neuropathy can lead to the development of foot deformities, drive alterations to the plantar pressure and increase the susceptibility of the plantar skin to damage. In addition, gait abnormalities secondary to proprioceptive abnormalities lead to abnormal load bearing and may cause further worsening of abnormal plantar pressures. When present, these factors will interact with external triggers, e.g. poor fitting footwear or trauma, leading to neuropathic DFU. This pathway, with its interactive complexity between the sensorimotor and autonomic neuropathic components, is described in Fig. 4.1 [53].

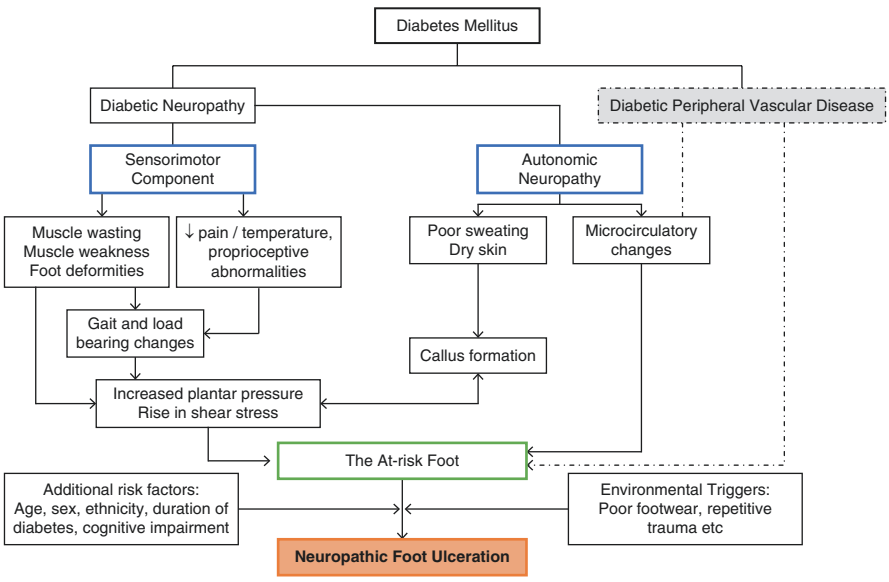

Fig. 4.1 The pathway to Neuropathic Foot Ulceration

4.5 Clinical Features

Neuropathic ulcers typically occur on the plantar aspect of the foot, especially under the metatarsal heads or on the plantar aspects of the toes. In a small group of neuropathic DFUs (n=77) specifically selected for lack of infection, 78% of the ulcers were located on the forefoot, 16% on the midfoot, and 6% on the heel [54]. However, in the EURODIALE study, which also included neuroischaemic DFUs, only 48% of the overall cohort had any plantar ulceration and the distinctive forefoot or midfoot plantar ulceration was present in only 22% [16].

The neuropathic foot is usually warm and well perfused and there may be signs of cutaneous neuropathic changes such as diminished sweating, dryness and fissuring. Repetitive mechanical forces during gait may lead to callus build-up [41, 55], the most important pre-ulcerative lesion on the path to neuropathic DFU [55]. If allowed to become too thick, the callus will press on the soft tissues underneath and cause ulceration. A layer of whitish, macerated, moist tissue found under the surface of the callus may indicate imminent ulceration. Other pre-ulcerative lesions include hammer or the claw toe deformity, ingrown or thickened toe nails, blisters, haemorrhage and fungal nail infection [56]. The neuropathic DFU typically develops in the plantar aspect, over a pressure area and is surrounded by thick rim of overgrown callus. Patients experience little or no pain and are often able to walk without a limp. In contrast, a neuroischaemic DFU typically has punched out edges with none or a rim of thin 'glassy' callus present over a non-pressure area. Furthermore, there may be features of ischaemia such as skin atrophy, loss of hair, cyanosis, tissue necrosis and the foot may feel cold. Moderate to severe pain may also be a feature of neuroischaemic ulceration (Fig. 4.2).

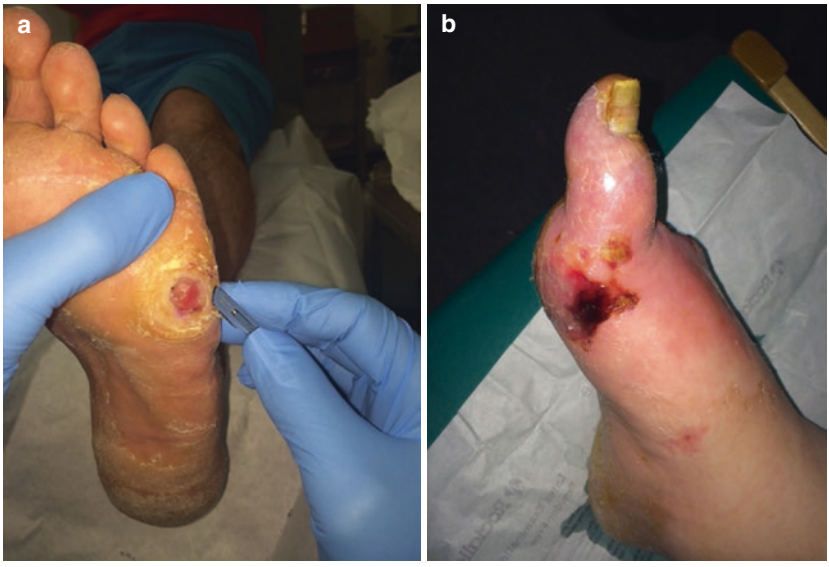

Fig. 4.2 Differences between neuropathic (panel **a**) and neuroischaemic (panel **b**) DFU. The neuropathic DFU typically is present over a pressure point with thick surrounding callus, while the neuroischaemic DFU may present at any site, including pressure points, with features elsewhere suggesting the presence of chronic ischaemia

4.6 Investigations and Assessments

All patients with a new DFU should be immediately referred to a specialist diabetic foot clinic, where facilities for multi-disciplinary care of the foot and the individual exist. This will allow for timely assessment and institution of therapies aimed at healing the DFU. Delay in referral has been shown to be associated with poor outcomes, including longer healing rates and higher risk of amputation [57, 58].

4.6.1 Confirmation of Neuropathy

If there is a foot ulcer and vascular disease has been excluded reliably (easily palpable pedal pulses or duplex waveforms of the pedal arteries excluding significant arterial involvement when pedal pulses are equivocal or not palpable), neuropathy is likely to be the major player. Detection of neuropathy in the context of DFU is most frequently undertaken to confirm the large-fibre nerve damage mediated loss of protective sensation (LOPS) [59]. The use of the Semmes-Weinstein monofilament (MF) device is ubiquitous. This is a nylon filament with ability to exert 10gm of force when applied to an area [60]. In one systematic review which used nerve conduction assessments as the reference standard, the sensitivity of the MF ranged from 41% to 93% while the specificity ranged from 68% to 100% for the detection of neuropathy [61]. Despite its widespread application, inter-operator variability and lack of a consensus on which anatomic testing sites are the most valid (commonly 8 or 10 are tested) remain concerns [61, 62]. However, it is widely agreed that the MF indeed is a valuable tool to screen for loss of protective sensation of the foot and is a part of both the American Diabetes Association [63] as well as National Institute for Health and Care Excellence (NICE) [64] recommendations for foot risk screening. Other modalities include the neurothesiometer [64], the 128Hz tuning fork [63] or a systematic neurological examination demonstrating unequivocally abnormal or absent reflexes [63, 65]. More recently, devices such as the Vibratip™ [64], an electronic vibratory device with a specified and consistent amplitude and frequency similar to that of a 128 HZ tuning fork, and the Ipswich Touch Test [66] have also been validated for detecting insensate at-risk feet. Of course, the final validation of LOPS is provided when a good debridement of the ulcer area is undertaken with the patient remaining unflinched.

Excluding peripheral vascular disease. We would like to emphasise that vascular insufficiency needs to be carefully excluded. Although palpation of pedal pulses is recommended in many guidelines, there is significant interobserver variability [67] and conflicting data on accuracy [67–69]. The International Working Group on the Diabetic Foot (IWGDF) recommends the use of bedside non-invasive tests to exclude PAD, including an ankle-brachial index (ABI) of >0.9, presence of triphasic pedal Doppler waveforms and a toe-brachial index (TBI) of ≥0.75 but without supporting one particular modality [70]. Measurement of toe systolic blood pressure and transcutaneous cutaneous oxygen tension ($TcPO_2$) may also provide valuable information, especially about the potential for healing without

revascularisation [70]. When faced with a slow-to-heal neuropathic ulcer despite the optimisation of all other factors, it may be important to revisit the presence of vascular disease, and if necessary, get an early vascular consult [67].

4.6.2 Identification of Infection

One of the most important but perhaps also the most challenging aspect is the identification of the presence of infection [55]. It is understood that between 50–90% of DFUs are infected by the time they present; these may range from mild (~30% of cases), moderate (30–60%) to severe cases (5–25%) as defined by the Infectious Diseases Society of America (IDSA) 2012 guidance [71], although inter-category distinction can be subjective and challenging [72]. In addition, one systematic review estimated that up to 20% all DFUs (not just neuropathic) may be associated with osteomyelitis [73]. However, up to 60% of all *severely* infected DFUs may harbour osteomyelitis [74, 75]. Other risk factors for osteomyelitis include longer duration of ulceration (>4 weeks), size larger than 2cm^2 and depth > 3mm [73, 76].

Typical features of infection include pain, increase in exudate, skin and soft tissue oedema and, cellulitis when there is spread of infection through the soft tissues. The latter is sometimes difficult to identify in darker coloured skin. The neuro-immunomodulation of diabetic neuropathy, however, while making the ulcer more susceptible infection, also may mask the typical symptoms and signs [77]. The presence of autonomic neuropathy may, at least theoretically, contribute by masking systemic features (such as fever, rising in heart rate) further distracting the physician. Thus, there is potential for an infection to proceed from a mild, easily treatable stage to more severe forms without detection [78]. Therefore, it is felt that up to half of infective episodes may not show typical signs of infection, even those that are limb-threatening [76, 79]. Some have advocated (albeit cautiously) the use of secondary surrogate findings, such as foul odour, friable or discoloured tissue or poor granulation as indicators of infection [80]. Microbiological samples should be sent when clinical infection is suspected [71, 81], preferably, soft tissue specimens [81]. In those with suspected osteomyelitis, attempts should be made to obtain a bone specimen. While, superficial swabs of DFUs are discouraged [81], a good deep wound swab, obtained after thorough cleansing and debridement *may* be valuable [82, 83]. Sadly, there is limited evidence available to determine the optimal sampling technique [84] and more research is urgently needed. Clinical features of limb-threatening infection include, but are not limited to, rapidly spreading cellulitis, blistering/necrosis of skin alongside systemic features such a temperature >38°C, tachycardia (heart rate >90 beats/min), tachypnoea (rate >20 breaths/min) and muscle aches [71, 81].

4.6.3 Imaging

Imaging the foot is important. Indeed, we believe it should be an extension of clinical examination. The aim of imaging in the neuropathic DFU is to evaluate underlying structural abnormalities, exclude soft tissue gas or presence of foreign body, provide supportive information to differentiate soft tissue infection from osteomyelitis and in the serial evaluation/monitoring of post-surgical changes. Plain radiography (X-ray) should usually be undertaken at the first visit or the earliest available opportunity in all DFUs; in addition, a repeat X-ray should be considered if there is further clinical change. For the detection of osteomyelitis, plain radiography may possess low sensitivity (40–60%) and specificity (60–90%) [85], especially in early bony infection as initial changes may take up to 2 weeks or longer to manifest. However, X rays are easily available, inexpensive and can be repeated multiple times when necessary. It is important to acquire weight-bearing lateral views of the foot in addition to standard views, and if possible, the contralateral non-ulcerated foot should also be imaged. The latter will provide important baseline information. In those with potentially limb-threatening infections, X-rays should be undertaken as a priority. Magnetic resonance imaging (MRI) is currently considered as the imaging gold standard for the detection of osteomyelitis and has a sensitivity reportedly reaching 100% in some series [86], while the reported specificity varies between40% to 100% [87, 88]. MRI is also useful for the detection of the extent of soft tissue infections or to ascertain if there are any deeper collections tracking from the DFU. Other modalities useful in the neuropathic DFU are ultrasound assessment (for detecting collections and in guiding aspiration for microbiological diagnosis) and occasionally, radionuclide imaging using radio-labelled white blood cell scans (for indolent infection).

4.6.4 Laboratory Blood Panel

Laboratory assessments provide valuable additional information, assisting in the diagnosis of infection but also help provide a metabolic overview of the individual. A rise in white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may occur in the setting of an acute infection or when osteomyelitis is present. Improvements in these parameters have been shown to be predictive of DFU healing and osteomyelitis remission, but worsening may indicate recurrence [89]. Renal and liver function tests give an indication of the general fitness and need to be monitored to ensure safe administration of antibiotics. Assessment of HbA1c (glycated haemoglobin) allows for the determination of recent diabetes control which may require optimisation. One recent study of 206 subjects noted higher serial HbA1c values in those with DFU compared those with type 2 diabetes without DFU ($p<0.0001$, $R2=0.0125$, $t=4.35$) [90]. Higher HbA1c values may contribute to slower healing [91].

The baseline laboratory investigations carried out at the King's Diabetes Foot Clinic are shown in Table 4.1.

Table 4.1 Investigations undertaken at the King's College Hospital Diabetes Foot Clinic for a DFU

Haematology	Biochemistry	Radiology	Vascular lab	Microbiology
Full blood count	Urea and electrolytes	X-ray foot with weight bearing views	Doppler waveforms	Tissue specimen or deep swab for culture (when tissue specimen is not possible)
Erythrocyte sedimentation rate	Liver function tests	MRI foot	Full arterial duplex if waveforms suggestive of arterial disease	Bone or pus for culture
	C-Reactive protein	Radionuclide scanning with SPECT/CT (white blood cell scans)	TcPO2 (in selected cases)	
	HbA1c (Glycated haemoglobin) and Lipid profile	Ultrasound imaging and diagnostic aspiration (where appropriate)		
	Vitamin B12, Folate, Iron profile (where appropriate)			

Those included in gray are undertaken during the first patient visit. Please note a valid test for neuropathy is also undertaken but has not been included in the above panel. All patients without easily palpable pulses will have Doppler waveforms assessed as standard. *MRI* magnetic resonance imaging, *SPECT/CT* single photo emission computed tomography/computed tomography, *TcPO2* transcutaneous oxygen tension measurement

4.6.5 Assessment of Foot Deformities and Abnormal Pressure

Abnormalities of foot pressure can be present early in the course of diabetic neuropathy [92, 93]. The risk of neuropathic DFU is increased in those with higher plantar pressure; one study noted that 35% of those with high foot pressures developed an ulcer over a 30-month follow-up, in contrast to none with normal plantar pressures [94]. Assessment of the foot shape and pressure points are critical when determining what off-loading technique to recommend. A detailed review of the patients' current and most recent footwear is also important.

4.6.6 Assessment of Comorbidities

As most neuropathic DFU patients are older or have had a significant duration of diabetes, they often have serious associated comorbidities. Studies have reported a 32%—76% rate for the presence of such serious comorbidities in DFU subjects

[16, 95]. In the EURODIALE study, 11% had heart failure or angina, 6% were on dialysis, 15% had severe visual impairment and 10% needed help to stand or walk. Another study which followed up those with a healed DFU for 2 years noted that up to 64% of the subjects reported a fall with an overall incidence of 1.25 falls/person-year (95% CI 1.17–1.33) [95]. Obstructive sleep apnoea frequently co-exists with diabetes and may impair wound healing [96]. Malnutrition [97], oedema of legs and anaemia [98] are also commonly associated with DFU. Therefore, a thorough systemic review should be undertaken at the first visit (or at the earliest possible visit) and a history of cardiovascular disease actively sought. Clinical depression [99] and cognitive impairment [100] are often present and may be associated with negative outcomes [32]. All of these will require early identification and management. Foot clinics are also seeing an increasing number of transplant recipients, especially those with renal and islet cell transplantation -their care will need to be coordinated with their specialist physicians.

4.7 Management of Neuropathic DFU

4.7.1 Wound Control

Careful attention to the ulcer bed is necessary to stimulate healing and to ensure that wound care strategies are effective. In the neuropathic DFU, the callus surrounding the ulcer should be removed by sharp debridement, using a scalpel, together with removing slough and non-viable tissue from the ulcer edge and base. Removal of callus may reveal an underlying ulcer (Fig. 4.2). This is also an opportune time to assess depth and determine if the ulcer tracks down to the bone [81]. In a suspected subungual ulcer, the nail should be cut back or pared away gently to expose and drain any stasis fluid that may have accumulated [79]. Dressings should be selected to maintain the right moisture on the wound bed, control exudate and to avoid maceration of the surrounding skin [101]. The recent guidelines from the American Podiatric Medical Association/Society for Vascular Medicine and from the IWGDF do not support the use of one particular single dressing product over another [101, 102]. Acute post-operative wounds, or those which have been aggressively debrided in clinic, may benefit from application of negative pressure wound therapy (NPWT) to enhance healing [102]. The use of NPWT has been shown to significantly improve wound healing time ($p=0.005$) [103] and the rate of secondary amputations may be lower ($p = 0.035$) [104]. Adjunctive therapies such as platelet concentrates, platelet-derived growth factors, extracellular matrix products, amniotic membrane products, epidermal growth factors, bioengineered skin, low-level laser and hyperbaric oxygen therapy have limited evidence of efficacy to justify adoption into routine practice [101, 102, 105]. However, there may be a role for them in recalcitrant, difficult to heal ulcerations [101]. In the United States, the recombinant human BB isoform of platelet-derived growth factor (Becaplermin) has Food and Drug Agency (FDA) approval for treatment in neuropathic DFU and is recommended for use in recalcitrant DFU [101]. In addition, larval debridement therapy may have a role in

challenging sloughy ulcerations where sharp debridement is not possible or very painful [106] with supportive controlled clinical efficacy data now available [107].

The percentage reduction in neuropathic DFU size may be a predictor of healing. It has been estimated that neuropathic DFUs with >50% size reduction at 4 weeks have an increased likelihood of healing within 12 weeks [108, 109]. Reassuringly, an improvement in the rate of healing has been noted over the past three decades. In 1991, only 34% of neuropathic DFUs had healed by 20 weeks; by 1999, the figure had risen to 51%. By the early 2000s, the healing rate in neuropathic DFUs had improved to 68% at 20 weeks in one large healthcare system [110]. While the data for smaller (<2 cm^2) and recent (<2 months old) neuropathic DFUs is encouraging, limited data is available on midfoot and hindfoot ulcerations that are increasingly observed in the specialist foot centres. Specialist units also utilise plastic surgical skills such as split skin grafting to achieve early closure of large defects [111].

4.7.2 Mechanical Control

In neuropathic DFU, redistribution of plantar pressure is very important. To facilitate this, the choices available include the total contact cast (TCC), a removable cast (bespoke or a prefabricated unit such as Aircast Diabetic Pneumatic Walker™) when a non-removable device is contraindicated or not acceptable to the patient, or a Scotchcast boot (Fig. 4.3). Among these, the TCC is the currently accepted 'gold standard' device [105, 112]. One recent systematic review determined, in comparison to removable devices, that non-removable off-loading was on average more effective at promoting the healing of neuropathic DFU (RRp=1.43; 95% CI 1.11, 1.84; I2=66.9%; p= 0.001; k=10) [113]. Using pedobarographic examination, it has been shown that the TCC provides a higher effective force reduction (75%)

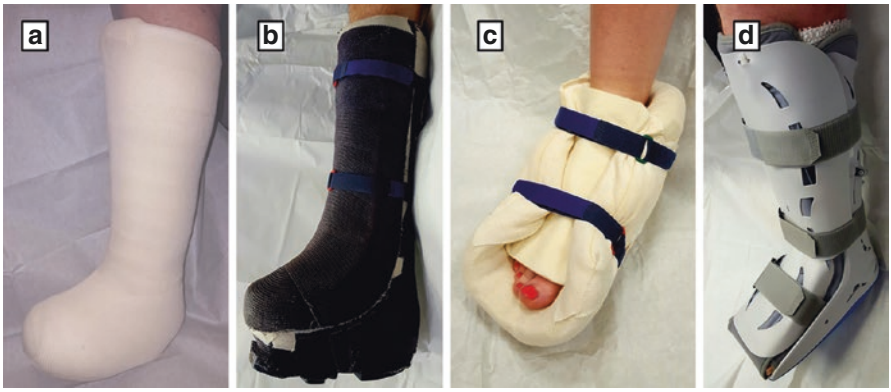

Fig. 4.3 Offloading Techniques in Neuropathic Diabetic Foot Ulceration. (**a**) Total Contact Cast (TCC), (**b**) Removable Contact Cast (Bi-valve cast), (**c**) Scotchcast boot and (**d**) Pre-fabricated removable walker

during ambulation when compared to the Aircast® Diabetic Pneumatic Walker™ (59%) or the VACO®Diaped (64%) devices [114]. If casting techniques or prefabricated devices are unavailable, temporary shoes with a cushioning insole or a wedge to provide forefoot or heel offloading should be supplied. The offloading device needs to be regularly changed (ideally 1 week for TCC) or closely monitored (other devices). Semi-compressed adhesive felt padding may be used to divert pressure, especially from small neuropathic DFUs. Occasionally, extra-deep, commercially available shoes with flat cushioning insoles may suffice in the absence of very high-pressure areas. The patient should be requested to limit unnecessary activities. However, it is unrealistic to immobilise the leg for the whole duration required to achieve healing [115]. When the neuropathic ulcer has healed, bespoke shoes with cradled insoles should be provided to reduce risk of recurrence. The foot shape and suitability of orthotics will require regular review. Pressure ulceration related to immobility usually involves the heel which can be offloaded using a pressure relief ankle-foot orthosis (PRAFO) or a pressure- relieving heel protector with pillow style cushioning.

Those feet with chronic or recurrent ulcerations resulting from high-pressure points secondary to deformities should be considered for surgical offloading [116]. An improvement in DFU healing rates, lower recurrence and relatively low incidence of post-operative complications has been reported for bony procedures such as metatarsal head osteotomies, hammer toe repairs, resection followed by arthroplasty of the small forefoot bone and joints [117], as well as for soft tissue procedures such as flexor tenotomies [118], tendon transfers and tendo-Achilles lengthening [119]. In those with significant midfoot and hind foot DFU related to deforming Charcot neuroarthropathy, surgical reconstruction with deformity correction has been shown to reduce the rate of recurrent ulceration as well as improve limb salvage [120, 121]. Although the majority of data in these emergent fields come from case series, with limited evidence from controlled studies, they are nonetheless, quite encouraging.

4.7.3 Microbiological Control

In the presence of an ulcer, there is a clear portal of entry for invading bacteria. Infection can range from mild, local infection to severe limb-threatening infection with necrosis and systemic features. In those with non-limb threatening infections, debridement of surrounding callus, removal of slough and necrotic tissue along with thorough cleansing will contribute to reducing the microbial bioburden. The choice of antibiotic depends on the patients' geographical location, previous infection status, past antibiotic exposure as well as the allergy status and comorbidities present. Gram-positive cocci, especially *Staphylococcus aureus*, are the most commonly isolated pathogens in acute new DFU infections in western countries [80]. In the warmer counties of Asia and Africa, it is not unusual to have gram-negative organisms, in particular *Pseudomonas spp*, predominating [122, 123]. In chronic DFUs, the milieu is typically polymicrobial, often including Gram-negative organisms and

anaerobes. When empirical oral antibiotic therapy is considered, it should definitely target Gram-positive organisms (*S.aureus* and *Streptococci*). Those with chronic DFUs or with antibiotic-resistant organisms may need to have bespoke antibiotic treatment from the outset. In our practice, Co-amoxiclav 625 mg, administered thrice daily is the primary empiric antibiotic of choice for mild infections in penicillin tolerant individuals. In many outpatient diabetic foot clinics, the emergence of antibiotic-resistant strains such as *Methicillin resistant Staphylococcus aureus* (MRSA), Vancomycin resistant enterococci (VRE) and multidrug-resistant gram-negative organisms are proving a significant challenge in determining antimicrobial therapy [124, 125].

Moderate and severe infections should be considered as potentially limb-threatening. These may require admission to hospital, intravenous antibiotics and possibly, surgical debridement. Indications for urgent surgical intervention, amongst others, include rapidly spreading necrosis, deep abscess with systemic features and gas in the soft tissues on X-ray examination [126]. Empirical broad-spectrum intravenous antibiotics are recommended until microbiology results allow for targeted therapy [127]; however, there is no international consensus on the best choice of agent or combination [128]. In our practice, Tazobactam-Piperacillin 4.5 grams, administered thrice daily along with Teicoplanin (in those with suspected or known MRSA infection), are the empirical intravenous agents of choice—Teicoplanin is discontinued if results for MRSA come back negative (approximately 48 hours). Use of other agents is influenced by microbiology results. Management of diabetic foot osteomyelitis includes surgical removal of sequestrum and targeted antibiotic therapy guided by bone culture. While there is some controlled evidence for managing osteomyelitis with primary antibiotic therapy, supporting literature is limited to forefoot predominant, stable (low-grade) osteomyelitis without evidence of necrotising infection [34, 129]. Duration of antibiotic therapy may range from 2 weeks for mild infection to more than 12 weeks in those with advanced hindfoot osteomyelitis. Optimal duration depends on the clinical picture; in addition, there is very little consensus on the optimal mode of antibiotic delivery [72, 81].

4.7.4 Metabolic Control and Management of Comorbidities

As neutrophil function and wound healing is impaired by hyperglycaemia, tight glycaemic control is recommended. Insulin initiation or consideration of newer anti-hyperglycaemic agents may be necessary. Furthermore, patients are likely to be less mobile whilst recuperating; focus on diet and lifestyle control may also be important. A recent systematic review of 9 randomised controlled trials observed that intensive control (HbA1c 6%-7.5%) was associated with a significant decrease in the risk of amputation (RR 0.65; 95% confidence interval [CI], 0.45–0.94; I^2 = 0%) and a slower decline in sensory vibration threshold (mean difference, −8.27; 95% CI, −9.75 to −6.79) [130]. As cardiovascular disease is common, optimising hypertension, hyperlipidaemia and antiplatelet therapy should be considered as

per local guidelines [131, 132]. Smokers should be advised to stop and referred to smoking cessation services. Those with leg oedema may benefit from compression bandaging and diuretic therapy—this will have additional benefits on wound moisture control. Other tenets of care to consider would be ensuring adequate nutritional support, optimising anti-cardiac failure therapies, monitoring renal failure, anaemia correction and where available, psychological and social support.

4.7.5 Education

Patient education in those who have already presented with a neuropathic DFU has two main streams—to allow healing and to maintain remission. Neuropathic DFU patients usually have a loss multiple sensory modalities and need advice on how to protect their feet from mechanical, thermal, and chemical trauma [79]. In addition, they will require instruction on the principles of ulcer care such as importance of rest, footwear, regular dressings, frequent observation for signs of infection and to ensure compliance with offloading devices. In practice, we find it useful to reinforce these principles at every clinic visit. The advice needs to be simple, memorable and in keeping with the individuals' emotional, educational and cultural sensibilities. In a large but non-controlled study from South India, among 1,259 patients with DFU, those who followed advice were 40% more likely to heal than those who did not adhere to advice [133]. Furthermore, ulcer recurrence rates were also lower (5% versus 26%) [133]. Malone noted a three times higher rate for ulcer incidence and amputation in a group randomised to receive no education when compared to the group receiving education [134]. Sadly, this encouraging observation from 1989 is yet to be reconfirmed [135]. In practice, ensuring effective education can be challenging and a recent Cochrane review concluded that there was insufficient robust evidence for patient education in achieving clinically relevant reductions in ulcer and amputation incidence [136]. Additionally, there is limited data on the content, ideal duration and cost-effectiveness of education programme. Moreover, the recognition that cognitive dysfunction is increasingly prevalent in diabetic foot disease adds further complexity [100]. Management algorithm for a non-limb theratening diabetic foot ulceration is detailed in Fig. 4.4.

4.8 Importance of an Integrated Approach

Evidence consistently highlights the benefits of multidisciplinary foot teams (MDFTs) in the outcomes of DFUs [137–140]. Over 11 years, one study found total amputations fell by 70% following improvements in foot care services, including multidisciplinary teamwork [138]. Similarly, a specialist foot team in Copenhagen noted no increase in amputation rates over a 6 year period, despite a 4-fold increase in referral rates, an outcome they ascribed to the benefits of MDFT working [140].

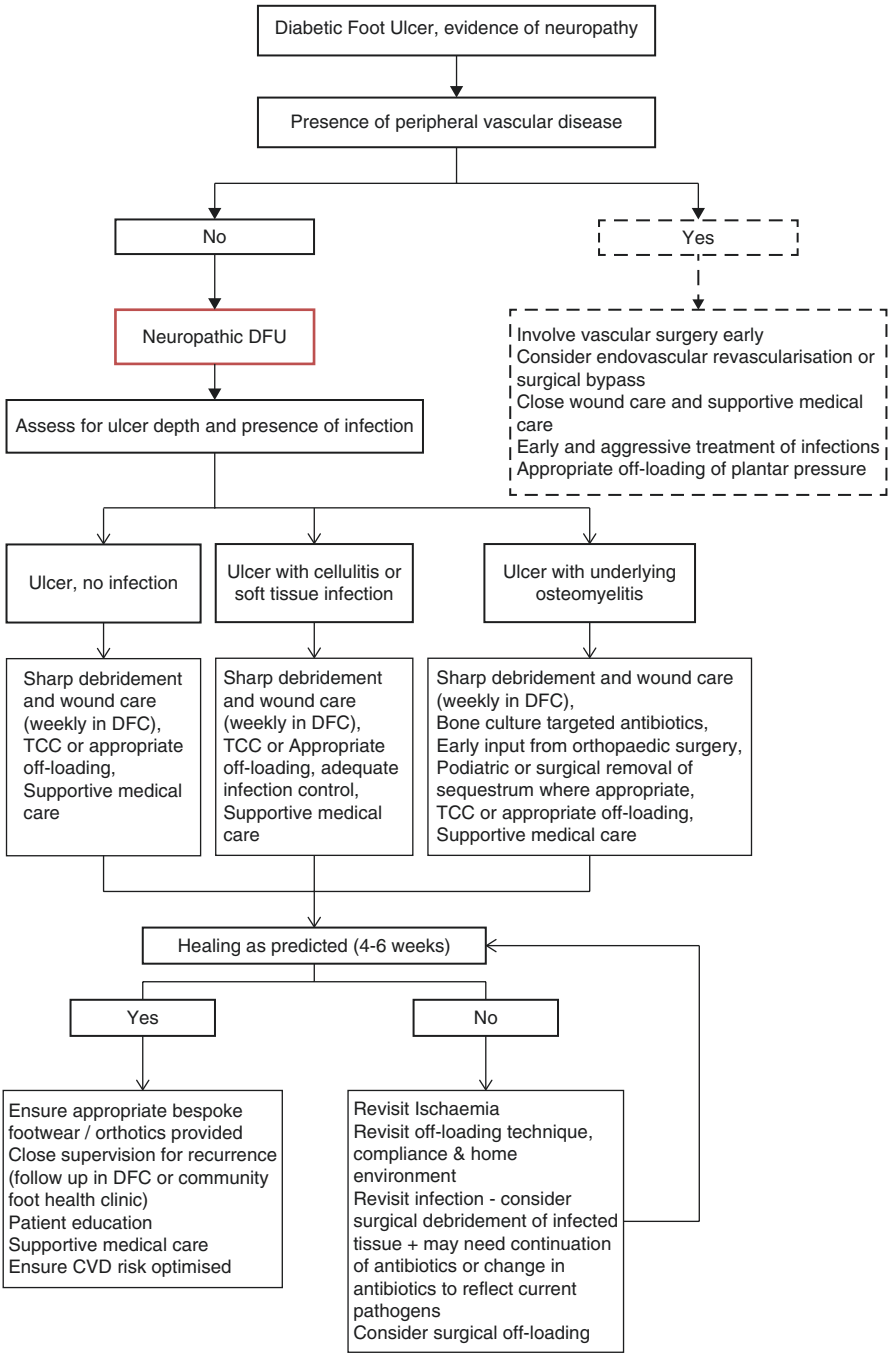

Fig. 4.4 Management of neuropathic diabetic foot ulceration (non-limb threatening). *DFC* Diabetic foot clinic, *TCC* Total contact cast, *CVD* Cardiovascular disease

We believe the importance of MDFT working cannot be underestimated, and ideally, all hospitals should have a MDFT present. Some countries such as United Kingdom [141] Netherlands [142] and Brazil [42] have been successful in achieving a national focus towards MDFT development but many countries, especially those with large diabetes populations such as China and India, have very limited or no access to such teams [143, 144].

4.9 Summary

Diabetic neuropathic foot ulceration requires a systematic approach of wound assessment, appropriate offloading, aggressive treatment of any infection along with optimisation of any co-morbidities present. This should be delivered within an experienced MDFT and early referral to such teams should be encouraged. While there are number of adjuvant wound care therapies available, many of them lack evidence and are not currently recommended. Close adherence to the established principles of wound care, ensuring the best possible offloading is offered and reinforcing foot protection principles at every visit remain key to achieving early healing and preventing recurrence.

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Chapter 5
Total Contact Casting

Maureen Bates, Timothy Jemmott, and Michael E. Edmonds

5.1 Introduction and History

The total contact cast (TCC) has been established as a useful treatment to offload neuropathic foot ulcers successfully, and thereby facilitate their healing [1, 2]. It should be carried out within the expertise of the multidisciplinary team, taking into account the risks and benefits of this procedure. The TCC was developed in India, in the 1930s by Joseph Khan, an Indian orthopaedic surgeon, to treat neuropathic foot ulcers as a result of Hanson's disease. His patients were unable to take time off work, mainly for financial reasons, and the TCC was applied to offload the ulcer but at the same time allow the patient to remain active.

This method of offloading was utilised by Dr. Paul Brand in India when he used the TCC to treat patients with diabetes and a neuropathic foot ulcer. As well as patients with Hansen's Disease. Dr. Brand then imported the technique to the USA, in 1965, when he moved to Carville, where he treated patients with both Hansen's disease and diabetes, to heal their foot ulcers. This technique was taught to Chief Podiatrist, Ali Foster of King's College Hospital, when she visited Carville. In addition to treating the neuropathic ulcer, the TCC is the optimal treatment for the acute Charcot foot (Chap. 13: *Conservative Management of Charcot Neuroarthropathy*).

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5.2 The Modern Approach

The classical TCC is applied with the patient lying in a supine position, using minimal undercast padding with added protection at the bony prominences followed by a top layer of Plaster of Paris (POP). Ali Foster then modified the technique such that the TCC can be applied by podiatrists to patients sitting in podiatry chairs in the diabetic foot clinic at King's College Hospital. It is a below knee cast which is made of a synthetic material. There are many types of casting material available including rigid and semi-rigid materials. Modern synthetic materials avoid the disadvantages of POP which include the elongated drying time of up to 72 hours, the tendency to drip over surfaces, and to block sinks.

5.3 The TCC Application

Before the application of the cast, all the materials required to complete the cast should be placed on a trolley beside the patient's couch and within easy reach (Fig. 5.1). The TCC is applied with the patient sitting on a treatment couch in an upright relaxed position. A triangular support is placed under the patient's knee to maintain the foot and leg in an elevated position. This is a good opportunity for the person applying the cast to provide a description of how the TCC works, and to advise patients how to check their cast, to warn them of possible problems, and to advise them to return to the clinic as soon as possible if they have had any difficulties with their cast.

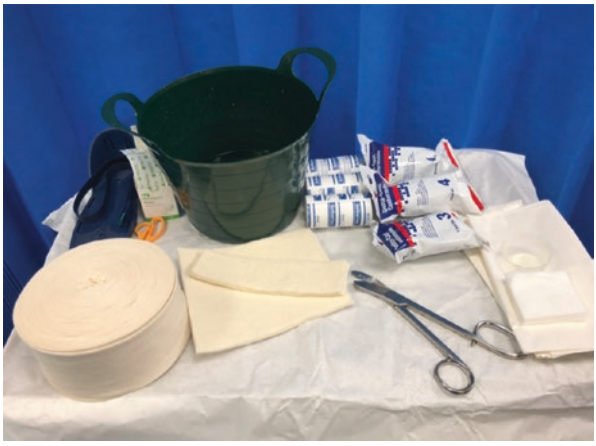

Fig. 5.1 Trolley containing all the materials required to complete the cast

5.3.1 Materials Required (Average Amounts)

- 3–4 Rolls of 10 cm soffban
- Stockinette (measured from to toes to the tibial tuberosity then doubled)
- 5 mm or 7 mm Semi Compressed Felt
- 3–4 Rolls of cast tape (In the King's diabetic foot clinic we use conformable tape, and different sizes of 7.5 cm, 10.0 cm and 12.5 cm according to practitioner's hand size and patient's limb size)
- 1 roll elastic plaster bandage 10 cm
- Cast shoes
- 3× Velcro straps 50 cm/rolls of Velcro,
- Sharp scissors
- Leg support

5.3.2 Technique

When applying a cast for the first time, it is always advisable to carry it out with a colleague. One person can apply the materials, whilst the other holds the leg and foot in the correct position. With experience the whole process can be carried out single handedly in as little as 10–15 minutes.

The technique is described in the following steps:

1. Stockinette (tubular bandage) is measured from the big toe to the tibial tuberosity. This measurement of stockinette is then doubled and the stockinette is applied from the toes to the knee, with the excess stockinette being gathered and left at the knee (Fig. 5.2).

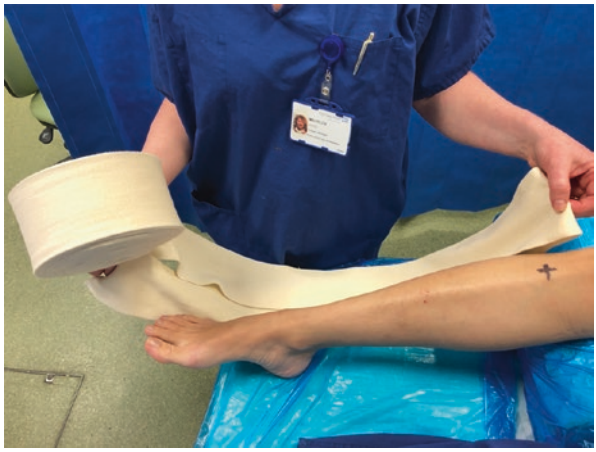

Fig. 5.2 Stockinette (tubular bandage) is measured from the big toe to the tibial tuberosity (marked by cross)

2. Cotton wool material (soffban) is applied between the patient's toes to prevent excessive maceration and to reduce the risk of toes rubbing on each other and thus prevent interdigital ulceration/lesions (Fig. 5.3). The toes are enclosed within the stockinette using tape.
3. The next step is to apply either 5 mm or 7 mm strips of adhesive Semi Compressed Felt (SCF) to the bony prominences of the foot and leg (Fig. 5.4). These

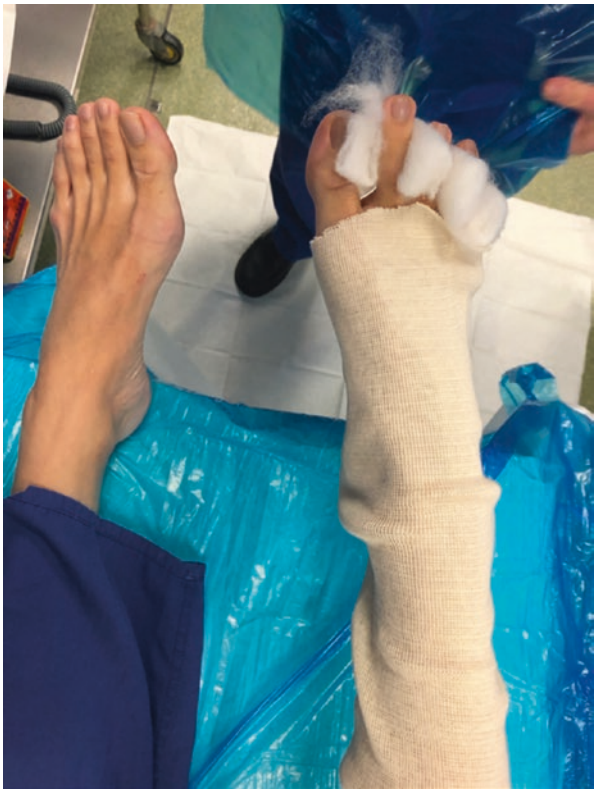

Fig. 5.3 Cotton wool material (soffban) is applied between the patient's toes to prevent excessive maceration

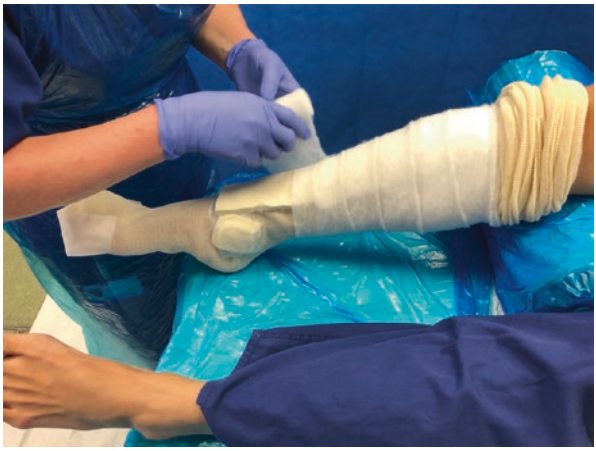

Fig. 5.4 Strips of adhesive Semi Compressed Felt (SCF) are applied to the bony prominences of the foot and leg; soffban is then applied to the leg as a bandage

include a long length of SCF applied to the tibial crest extending from the tibial tuberosity to the ankle. This is followed by disc shaped SCF pads to cover both the medial and lateral malleoli. These are the "standard" prominent areas which will benefit from extra padding. Other areas of the foot which have become prominent may also require additional SCF padding for protection, for example, the skin over the medial cuneiform, the navicular or the base of the fifth metatarsal.

4. The creases in the stockinette at the ankle are cut and the excess stockinette at the toes is smoothed of any wrinkles, and stuck down by tape.
5. The leg is then ready for the application of soffban (cotton wool bandage). Beginning from the tibial tuberosity, soffban is applied as one would apply any bandage, encircling the leg at the knee four times (Fig. 5.4). Then the rest of the leg is continued to be bandaged with the soffban overlapping the previous wrap by half, "in a half on half off way", working down the leg until the ankle is reached. At the ankle, soffban is encircled four times, ensuring all bony prominences are well padded including the back of the heel. (The ankle area is prone to movement within the cast and application of four layers around this area is wise to protect the ankle from cast rubs).
6. Soffban is then applied to the foot and the toes. When the toe area is reached, the soffban is applied from the plantar surface to the dorsal surface twice and then encircling the foot further, by once again wrapping the soffban around the toes.
7. At this stage, it is wise to palpate the whole foot and leg to ensure every area is well padded and that there are no "bald parts" most commonly occurring at the posterior aspect of the calcaneum. If necessary, more soffban can be applied to the "bald parts".
8. The next step is the application of the cast tape (Fig. 5.5). The cast tape is applied in precisely the same manner as the soffban with a few minor differences When starting at the knee, the cast tape is applied 3 cm closer to the ankle than with the soffban. This will ensure that around the top of the cast there are no sharp edges which rub against the skin at the knee, reducing risk of skin

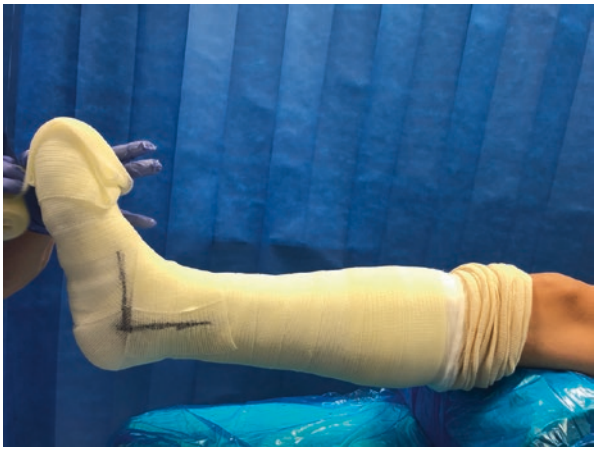

Fig. 5.5 The cast tape is applied to the leg in a similar manner to the soffban

abrasions. Also, by applying the cast tape 3 cm closer to the ankle, the risk of rubs on the upper leg will be reduced when the knee is flexed. Extra layers of cast tape are applied at the tibial tuberosity and at the ankle and this is important for cast strength.

9. When applying the cast tape, the position of the foot to the leg must be held at, or as close to a 90° angle as possible, allowing the foot and leg to be completely weight free. This is carried out by holding the plantar surface of the foot with the flat of one hand and by molding (massaging) the cast material from the knee to the toes with the other hand. The foot should be held in this position until the cast tape is dry and fixed. The time for this will vary according to different brands of cast material. If the foot is not held at the 90° angle to the leg, the foot may become plantar flexed with regard to the leg and this may increase the risk of tripping over the fore-foot, losing balance or falling over when walking. If this does happen, then the cast must be removed, reapplied correctly or a different mode of treatment should be considered. However, the problem can sometimes be overcome by building up the rear foot of the cast by either adding SCF to the plantar surface of the cast or by placing the SCF directly onto the rear foot of the cast shoe.
10. If the foot is at a dorsiflexed position to the leg, creases or dents can occur on the anterior aspect of the leg. Sometimes this happens due to the practitioner forcing the foot into this position or because the patient is trying to help the practitioner, by tensing the leg and holding the foot in what is considered to be the correct position. The patient should be asked to relax to allow the clinician to take the full weight of the leg and foot. It is a good idea to check that the quadriceps is relaxed, rather than tensed. The creases at the anterior of the leg can then be ironed out whilst continuing to mold the cast material.
11. It should be noted that the temperature of the water used for the casting will impact on cast drying time. (Warm water tends to have a quicker cast tape drying time than cold water. Therefore when applying a cast for the first time it is advisable to use cold water for more “working time”).
12. Another consideration whilst applying the cast tape to the leg and foot is the tension of the cast tape which should be neither too loose nor too tight.
13. After application of the cast, it can be covered by the excess stockinette. Alternatively, patients can cover the cast in a large sock (men) or opaque sock (women) of their chosen colour, to blend in with any particular outfit. This will reduce the risk of rubs on the contralateral limb especially when the patient is asleep in bed. The cast material may be rough and can be abrasive.
14. The cast shoe is then fitted. This should be worn when the patient leaves their home (Fig. 5.6). It will protect the cast from wear and tear. The patient is advised not to leave the clinic until the cast is completely dry. The drying time varies with different cast tapes.
15. Patients should be supervised when they take their first few steps in the dry cast to ensure that they are able to walk safely, comfortably and confidently. If it is the first cast application, then patients should be observed when walking, such that they feel safe and confident to walk. Crutches, a walking stick, or physiotherapy advice or assessment may be required.

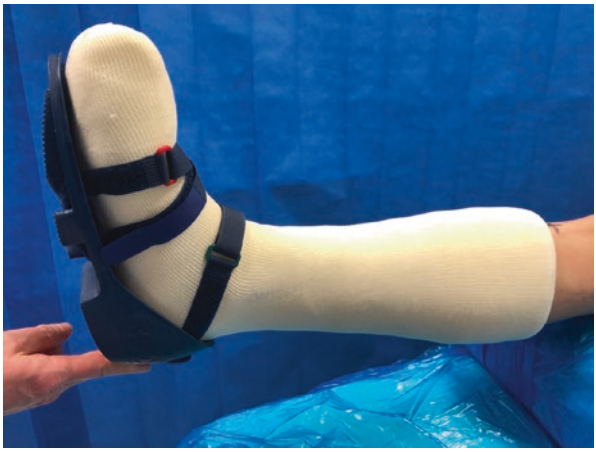

Fig. 5.6 The cast shoe is then fitted

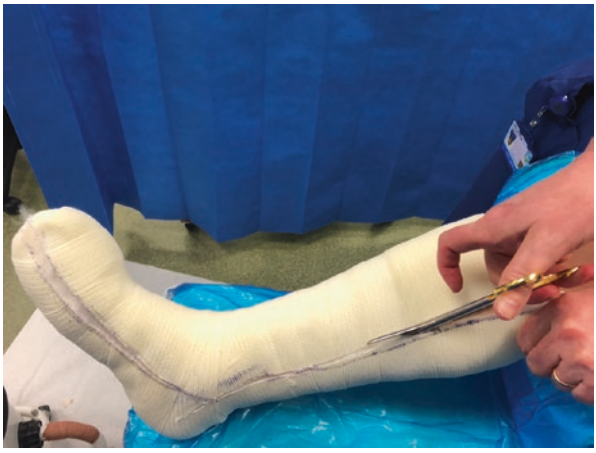

Fig. 5.7 To remove the cast, it is useful to mark the cast with a pen to guide the cast saw

16. To remove the cast, it may be helpful to mark the cast firstly with a pen to guide the cast saw (Fig. 5.7). The blade of the cast saw can get hot. Therefore, it is important to rotate it and to use the whole of the blade, whilst keeping the cast saw moving along the leg.
17. Once the cast tape is cut, the soffban and the stockinette can be cut using blunt ended sharp scissors. It is important when removing the cast, to advise the patient about what they may see, which can be unsightly.
18. The dressing and casting material may be saturated with ulcer exudate and blood, which can make patients anxious. The patients should be reassured that that this is a normal occurrence and as the ulcer heals the amount of exudate and malodour should reduce.
19. If possible, once the ulcer has been cleaned and debrided, the patient should be invited to look at their foot ulcer, using a mirror. It is also useful to take a photograph of the ulcer and show it to the patient. If possible, the size of the ulcer should be measured. If the patient can be shown that the ulcer has improved, it

is often enough for the most unwilling patient to agree to be recasted. If the cast is performing its function and the ulcer is healing, the patient is usually encouraged to continue with casting therapy. As the ulcer improves, the interval to the next cast change can be increased.

20. Should patients develop problems with their cast, they should be encouraged to telephone the clinic or attend the clinic sooner than their planned appointment [3]. Possible problems include staining under the cast, which is normal if it coincides with the position of the ulcer, but if it is in another area, it must be presumed that the cast has caused a rub and should be removed immediately. Patients should be advised to attend their local emergency departments if this occurs "out of hours "so that the cast can be removed and then attend the diabetic foot clinic as soon as possible for further cast application or change of management.
21. If any swelling occurs above the cast then the patient should return to the foot clinic and have the cast removed and the foot and leg should be examined for clinical signs of infection, or a deterioration of the ulcer. The leg should also be inspected for signs of a deep vein thrombosis such as pain on palpation especially in the calf area. If a thrombosis is suspected, a deep venous duplex scan should be carried out.
22. Patients are advised to check their blood glucose on a regular basis and if it is raised unexpectedly then they are advised to return to the foot clinic to determine if there are problems under the cast such as infection that is causing the blood glucose to be raised.
23. If patients have a history of deep vein thrombosis or pulmonary embolism, then the administration of prophylactic anticoagulants, according to local protocols is advised throughout the duration of casting.

5.4 How the TCC Works

The TCC is a semi-rigid boot that has cotton wool and Semi Compressed Felt applied within it, with the foot being cast at a 90° angle to the leg; the casting tape is applied from the tip of the toes to the tibial tuberosity. By covering a large surface area of the foot and leg with casting tape, the plantar pressure is evenly distributed through the sole of the foot and also transferred to the lower leg.

In a recent study, TCC decreased the average pressure by 32% under the fifth metatarsal head, by 63% under the fourth metatarsal head, by 69% under the first metatarsal head, by 65% under the great toe and by 45% under the heel [4]. Pressure is additionally transferred from the plantar surface to the rest of the lower leg with which the cast material is in contact [5]. The TCC reduces oedema in the lower leg and ankle. The TCC will also keep friction to a minimum, as the foot position with regard to the leg is held within a semi-rigid encasement, limiting any movements within the cast.

5.5 TCC for Neuropathic Ulcers

Neuropathic ulcers are commonly caused by repeated pressure over a particular area of the foot. The patient is unaware of the damage being caused by normal daily activities and the skin and soft tissues are unable to sustain this activity. The skin develops callous, followed by blistering under the callous. As pressure continues, an ulcer develops as the skin sustains further pressure from weight-bearing activities. Common areas for the development of neuropathic ulcers are on the apices of toes and the fore-foot. Foot ulcers are also often associated with rocker bottom or medial convexity deformities caused by a Charcot foot, or develop as large plantar calcaneal ulcers, none of which should be considered as a contraindication to applying a TCC. Indeed, the site of the neuropathic ulcer is not important when considering the application of the TCC. Several randomised controlled trials have shown that the TCC is more effective than removable devices, both in healing of foot ulcers and also in reducing time to healing [6–8]. The healing rate was significantly higher using a fibreglass casting boot compared with an offloading shoe [6]. Also, the TCC healed a higher proportion of ulcers in a shorter amount of time compared with two other widely used offloading modalities, the removable cast walker and the half-shoe [7]. A further study has shown a significant difference in the proportion of ulcers healed and the speed of the reduction of area of neuropathic plantar ulcers when treated with a fibreglass cast compared with a specialised cloth shoe [8].

However, a recent study suggests that a walking boot was as effective and safe as TCC in offloading the neuropathic diabetic foot ulcers, irrespective of removability [9]. Nevertheless, the TCC remains the most important indication for the treatment of the neuropathic foot ulcer.

5.5.1 Large Deep Neuropathic Ulcers

Although large deep neuropathic ulcers often have considerable amounts of discharge and exudate, the TCC is still a useful treatment. The exudate first leaks into the dressing and then into the material of the cast. In the first few days after having the cast applied, this is manageable by the patient and their family. However, as the ulcer exudate continues to moisten the cast, the dressings and the foot, the cast will become malodorous. It is important that patients understand that this is to be expected and such an explanation is often helpful to them and their family. If the cast is not changed frequently enough to prevent this, it can be disturbing to the patient and their family or friends. For any cast treatment to be successful, problems that may discourage the patient from continuing with this treatment, such as malodour, must be avoided. The practical difficulty for both the patient and the clinic is the problem of achieving the necessary frequency of cast changes with limited resources.

If the full cast cannot be tolerated because of the malodour, then a cast with a window cut out of it should be considered. This allows the patient to see the ulcer

regularly, and allows it to be monitored, cleansed and redressed by nursing staff or by family. This reduces unbearable odours caused by ulcer exudate soaking the dressings and the cast and it will encourage the patient to continue with cast therapy. Herniation of skin and soft tissue through the window can be avoided by applying a close fitting cast cover. The ulcer is dressed and the cast cover is made by applying stockinette over the TCC from the toes to the ankle, followed by a thin layer of cast material. When the cast material is set, it can be cut along the dorsal surface of the cast to separate it from the TCC. It is important not to cut into the TCC and damage its integrity. The cast cover can be stretched over the TCC but this may be a tight fit. Therefore a cast material with some elasticity is advisable for this purpose. Large deep ulcers can be thus successfully treated with casting but will obviously take longer to heal than smaller more superficial neuropathic ulcers.

One of the many advantages of the cast is that it is bespoke and therefore will fit all shapes and sizes of the lower limb unlike the "off the shelf'' counterparts. These are, however, good alternatives when a casting service is unavailable. Removable cast walkers have been demonstrated to be as effective as TCCs to reduce foot pressure at ulcer sites [10]. Furthermore, modification of a standard removable cast walker by using cast tape to make it irremovable, increases patient's adherence and may increase both the proportion of ulcers that heal as well as their healing rate [11].

5.5.2 Small Superficial Ulcers

Applying a TCC may seem extreme for the treatment of small ulcers. However, neuropathic ulcers which often occur on the apices of the toes, and can be as small as 0.5 cm^2, may benefit from casting just as much as their large counterparts. As these are pressure areas, then a TCC is a very good option if other offloading techniques have not worked. Successful healing takes place more quickly on the apices of the toes after casting rather than after standard therapy in bespoke footwear/insoles.

5.6 How to Overcome Patient's Unwillingness to Undergo Treatment with TCC

When a patient attends the foot clinic with a neuropathic ulcer, it is important to explain all treatment options. Despite the advantages of casting treatment, getting the patient to agree to a period of casting can be difficult. However, to fully understand this, it must be appreciated why patients are unwilling to undergo or continue to undergo cast treatment. Patients who have worn casts state:

- They may be uncomfortable at night and cause disturbed sleep,
- Patients cannot check their feet, which they will have been advised to do so on a regular basis,

- They cannot wash their feet on a daily basis and are concerned about developing an infection.
- Walking speed is slowed down by the cast.

It is essential to take time to understand the concerns of each patient, and their understanding of the TCC. It is important to explain to the patients why the TCC is required to be applied, and how it will heal their foot ulcer. However, the TCC may restrict their independence by curbing their mobility and their ability to go to work, to go shopping, to do cooking and housework, to get on and off buses and to walk up and down stairs. Whilst discussing these disadvantages, it is important to point out the advantages of casting. Treatment with TCC will protect the foot and the ulcer and promote ulcer healing. The TCC can enable patients to remain at work, carrying out their normal day to day activities in certain occupations, instead of being forced to stay at home. Patients may more readily take on board this cumbersome treatment if the prospect of faster ulcer healing in a cast is appreciated.

5.7 Conclusion

The TCC is an established treatment to offload neuropathic foot ulcers. Whilst it may have disadvantages that limit its use from fear of iatrogenic complications, when applied by experienced operators in an interdisciplinary environment, it can be an effective and safe treatment of neuropathic ulcers.

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Chapter 6
The Role of an Orthotist Within the Diabetes Foot Interdisciplinary Team

Christian Pankhurst and Chris Cody

In the UK, orthotists are autonomous, state registered healthcare professionals who are extensively trained in engineering, biomechanics and material science along with anatomy, physiology and pathophysiology. With this knowledge, an orthotist is able to provide gait analysis and engineering solutions to patients with problems of the neuro-muscular and skeletal systems and are responsible for recommending, assessing and fitting orthoses which will best achieve the objectives determined during a consultation. Their qualifications make them competent to design and provide orthoses that modify the structural or functional characteristics of the patients' neuro-muscular and skeletal systems which can reduce pain, prevent falls, facilitate healing of/reduce the risk of ulceration and can enable patients to mobilise through the elimination of gait deviations [1].

An orthosis can encompass any part of the body although the majority of work undertaken is concerned with the lower limbs. Orthoses have a variety of functions, some of which are highlighted below:

- Provision of control to unstable and/or painful joints
- Reduction of pain
- Compensation of weak or absent muscles
- Control against abnormal muscle tone
- Maintenance of function and alignment
- Reducing the risk of deformity
- Limitation of movement in order to protect healing body structures
- Redistribution of weight within a limb
- The provision of compression to aid lymph or venous return

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Whilst often working as autonomous practitioners, orthotists increasingly form part of interdisciplinary teams (IDTs), such as the interdisciplinary diabetes foot team or neuro-rehabilitation team, of which the collective responsibility is to effect and optimise the care and rehabilitation of the patient. The team will ideally include all parties who have a direct input to the needs of the patient, which will vary from patient to patient. As shown in Fig. 6.1, an ideal IDT would consist of (or have access to) many different members of various health care disciplines, including the patient themselves at the core of all treatment planning and decision making [2–6].

An orthotist compliments the Diabetes Foot IDT through extensive knowledge of the underlying biomechanics of the gait cycle with its inherent peak pressures, through thoughtful engineering of solutions, and their understanding of material science and design. This knowledge is utilised to protect the limb from detrimental and deleterious biomechanical stresses and forces that could lead to delayed ulcer healing, further ulceration, dislocation, subluxation or fracture. The functional and

Fig. 6.1 The members of the interdisciplinary team

mechanical role of the foot and leg as a stable base of support for standing and gait, along with its relationship to the rest of the body needs to be recognised. Coupled with this, the maintenance of skin integrity remains at the forefront of the mind of a practitioner in a high risk foot clinic. The orthotist may also have access to technology to measure plantar pressures of the foot during weight-bearing along with the knowledge and experience to interpret the information obtained. It is upon this knowledge that an orthotist formulates prescriptions that serve to provide offloading of a vulnerable foot at key instances during gait, where any deformity present can affect the degree of variability and intensity of these forces on the foot and the ensuing pathomechanics. Moreover, due to the wide variety of commercial products and materials that are available, an orthotist must keep an up-to-date knowledge of these products, remain current with the evidence available and be able to critically appraise the studies surrounding their use. The orthotist will therefore know when a pre-made or a bespoke item is warranted, along with the design and material choice required.

Orthotics services play an essential role in enabling quality of life for people with long term conditions, disabilities and limb loss. Being able to access the right orthotics equipment in a timely fashion and with appropriate support within an integrated interdisciplinary service is of paramount importance.

The correct supply and fitting of orthoses can help improve quality of life by reducing pain, keeping people mobile and independent and preventing more invasive and expensive interventions like surgery, amputation or the need for social care. Previous studies have estimated that for every £1 spent on improving orthotics services, the National Health Service in the UK could potentially save as much as £4 [7]. For the population with a diagnosis of diabetes, the provision of orthoses can have a beneficial impact by prevention and reduction of ulceration rates and amputation, relief of pain, increase in mobility, protection of tissues and promotion of healing along with a whole host of other benefits, including improved independence and self-image.

When considering a person with diabetes-related foot problems, it is always important to assess them holistically and as an individual. A full medical history and lower limb assessment is required in order to determine important factors:

- Age, gender, weight and socioeconomic status of the individual
- Degree of protective sensation present
- Rate and quality of blood flow to the foot
- Are there any clinical signs of infection present?
- Can the patient recall any history of trauma to their foot?
- Is there a history of ulceration?
- Does the patient complain of any pain?
- Is the anatomically normal role and range of movement of the foot/ankle complex present?
- Are there any deformities present?
- Is there any rigidity or areas of increased flexibility about the foot/ankle complex?

- Are there any musculoskeletal issues present?
- Are there any neurological issues present?
- Are there any dermatological concerns to note?
- Does the individual have any coexisting diagnoses?
- Are there any psychological concerns to consider?

Studies have shown that elevated plantar pressures are a causative factor of many plantar foot ulcerations in people with diabetes [8]. Therefore it is important for the orthotist to discover what led to the breakdown. The position, size and severity of the breakdown are important factors to consider when determining the most appropriate management for healing to occur and to reduce the risk of recurrence when presented with an active or healed diabetes-related foot ulceration.

When considering load redistribution (offloading) as with footwear/total contact insoles (TCIs) or an ankle foot orthosis (AFO) prescription as common examples, the biomechanical aims are to arrest any destructive forces, maintain the mechanical alignment and protect joint structures in all planes of motion. Elevated levels of mechanical loading can contribute to the development of foot ulceration when there is a reduction or loss of protective sensation, especially when associated with foot deformities and structural changes (such as if Charcot changes are present). Contact pressure on the plantar surface of feet with structural deformities can also generate local internal forces that can give rise to distortion of the subsurface tissues and the formation of localized tissue damage. Further to plantar pressure and number of load cycles an additional factor, namely the pressure-time integral, should be taken into account which is the time spent on a particular area during gait. The consideration therefore of accurate anatomical profiling of any external supporting surface and appropriate material choice/cushioning characteristics is imperative.

The International Working Group on the Diabetic Foot (IWGDF) states that "once an ulcer has formed, healing may be chronically delayed if the area is not effectively offloaded" [9]. The ultimate goal when offloading is to reduce tissue motion, accommodate osseous deformities and provide maximum shock absorption through a combination of clinical knowledge and a strong understanding of material science and product. It is important to remember that every patient is an individual—what is suitable for one person may not be indicated for another. Treatment therefore needs to be individualised to a patient's unique needs and expectations in order to create and provide an opportune environment for healing and reduce the risk of re-ulceration/re-activation of an acute episode [10–12].

When providing any form of orthotic offloading prescription, the orthotist will need to consider multiple factors, all of which will have an effect on the clinical outcome and concordance with orthotic therapy:

- What are the patient's expectations (foot shape, exercise, daily activities, work/home situation and driving)?
- What are the levels of cognition and health literacy of the patient?

- Are there any mental health issues which may be present?
- The functional/mechanical role of the foot and ankle complex (i.e. to provide a stable base of support for efficient standing and gait)
- Mechanical alignment and protection (i.e. to reduce 'trigger' forces and prevent deforming forces which could lead to subluxation and dislocation) and to accommodate any deformity present
- Acknowledgment of the biomechanical changes which occur in the foot in diabetes over time and after an ulceration
- Maintenance of skin integrity through redistribution of pressure and protection from shear and peak forces. This also involves knowledge of the large spectrum of materials available
- The change in biomechanical forces on the contra-lateral limb and the implications of immobilising the affected foot and ankle on the rest of the body and overall skeletal alignment
- Other considerations include ease of application and durability, cosmesis and comfort. (These may seem obvious but this is where many prescriptions can be weak but yet they are crucial to a successful outcome.)

It is important to understand the integration of mental and physical healthcare when providing any form of treatment or management due to the effect that this can have on the clinical outcome. The association between diabetes and depression is seen in the literature [13], with high levels of non-compliance to recommendations made by healthcare professionals and a significant association of depression with complications [14, 15], poor outcomes, impaired health-related quality of life [16] and increased mortality [13, 17]. There is a recognised link of depression with the development of foot ulceration [18, 19] and its recurrence [20]. The development of Charcot changes is also understood to increase the prevalence of depression and anxiety [21].

Other associations with diabetes include cognitive impairment [22], with poor physical functioning associated with increased depression symptom severity [23]. If any mental health concerns are noted, appropriate and timely referrals need to be made in order to address any psychological concerns.

With changes happening to a patient's soft tissues, blood vessels, neuropathy status and muscular/articular biomechanics over time as a result of aging with diabetes [24], continuing orthotic review, reassessment and on-going patient education will need to occur. For this vulnerable, high risk patient group, life-long foot protection is required with the aim of reducing the risk of tissue breakdown, infection and lower limb amputation, ultimately improving quality of life.

The provision of education is a very important aspect of an orthotist's role, just as it is from all other members of the IDT. Every effort needs to be made to optimise understanding, concordance, compliance and adherence through education and open discussions with all members of the IDT, especially the patient, at an appropriate level which can be understood during every contact.

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Chapter 7
Advanced Wound Healing: Neuropathic Foot

Amber R. Morra, Michael I. Gazes, and Peter A. Blume

7.1 Introduction

Approximately 415 million people worldwide have been diagnosed with diabetes. Twenty-five percent of people within this population will potentially develop diabetic foot ulcerations (DFUs). Diabetic neuropathy is the largest precursor to DFUs and increases risk of amputation fifteenfold; which results in approximately 70,000 annual diabetic amputations in the USA [1]. To minimize the risks associated with diabetes and DFUs, multidisciplinary limb salvage teams are necessary to promptly assess and treat patients to improve overall outcomes. Advanced wound healing is a crucial component of the treatment modality. Numerous advanced wound healing therapies exist, ranging from complex biologic dressings, split thickness skin grafts and flaps, stem cells, laser treatments, hyperbaric oxygen therapies, and negative pressure wound therapies (NPWT) [2, 3].

Wound healing consists of three phases: acute inflammatory, proliferative, and maturation. The acute inflammatory phase includes vasoconstriction of arterioles and capillaries, platelet aggregation, and the inflammatory cell cascade. The proliferative phase comprises fibroblastic activity, extracellular matrix reorganization, and angiogenesis [2–4]. Finally, the maturation phase involves the formation of scar tissue in addition to the synthesis and breakdown of collagen. Diabetic wound healing differs from traditional wound healing as DFUs often linger in the inflammatory phase. This delay, along with neuropathy, vasculopathy, infection, and hyperglycemic states seen in DFUs, leads to basement membrane thickening, endothelial proliferation, decreased vessel permeability, and altered cell migration [5]. This further leads to cellular senescence and induces protease enzymes, leading to an

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imbalance of matrix metalloproteinases (MMPs) to tissue inhibitors of metalloproteinases (TIMPs) [6–10]. As a result of this process, DFUs can take significantly longer periods of time to heal and often require specialized treatment options.

7.2 Collagen Modalities

One of the most popular and effective advanced treatment options for DFUs used today are collagen-based modalities. Collagen is the major protein in the extracellular matrix. Sustainable extracellular scaffolds are compromised in DFUs. Treatment with collagen based modalities provide a structural scaffold matrix to support extracellular components, increases fibroblast proliferation, mediates cell migration and organization, and inhibits excessive MMPs [10–12].

Apligraf (Organogenesis), is one of the most popular collagen based products, that is indicated for "care for the treatment of full-thickness neuropathic DFUs of greater than 3 weeks' duration, which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure." [13] The bioengineered living bilayer is derived from neonatal foreskin and placed in a type I bovine collagen matrix, composed of both an epidermal keratinocyte layer and a dermal fibroblast layer [3, 10]. The dermoinductive product functions by delivering the growth factors and matrix that are flawed in DFUs. Kirsner et al. evaluated Apligraf on 163 DFUs from 155 patients with an average wound area of 6.0 ± 5.5 cm^2 and wound duration of 4.4 ± 2.6 months. The study reported 70% improvement in wound closure in 12 weeks and found DFUs treated with Apligraf increased the probability of healing by 97% in comparison to dehydrated amniotic membranes [14].

Another bioengineered dermoinductive product for DFUs is Dermagraft (Organogenesis), a cryopreserved human fibroblast-derived dermal substitute. The combination of fibroblasts, extracellular collagen matrix and a bioabsorbable polyglactin mesh scaffold function to stimulate epithelialization. Dermagraft differs from Apligraf in that it is approved for full thickness DFUs present for over 6 weeks, which extend through the dermis but do not involve tendon, muscle, joint capsule or bone [10, 13, 15–17]. Marston et al. examined Dermagraft versus conventional therapy (wet to dry dressing) in 245 patients with chronic DFUs. They concluded that treatment with Dermagraft produced a significantly greater proportion (30%) of fully healed ulcers in comparison to the control group (18%). The Dermagraft group also had median percent wound closure of 91% by week 12 in comparison to 78% in the control group [18].

Integra Bilayer Wound Matrix (Integra LifeSciences) is a dermoconductive collagen-based modality for DFU. The epidermal layer is composed of a semipermeable thin silicone layer and the dermal layer is composed of cross-linked bovine type I collagen with glycosaminoglycan and shark chondroitin-6-sulfate. The composition of Integra is unique in that it allows the epidermal layer to

regulate moisture, while maintaining graft flexibility and resisting infection. The dermal layer thus functions to provide a scaffold for cellular invasion and growth [10, 17, 19, 20].

Omnigraft Dermal Regeneration Matrix (Integra LifeSciences), also known as Integra Dermal Regeneration Template, is FDA approved to treat "diabetic foot ulcers that exist for longer than 6 weeks and do not involve exposure of the joint capsule, tendon or bone, when used in conjunction with standard diabetic ulcer care" [21]. Driver et al. evaluated Integra Dermal Regeneration Template for DFUs with a two-phase study consisting of 307 patients with a minimum of one DFU. The first phase of the study was a 14-day period with patients receiving 0.9% sodium chloride gel with a secondary dressing and standard offloading. After the initial 14 days, the patients with less than 30% re-epithelialization entered into the second phase, which was randomized with a control group treated with 0.9% sodium chloride gel and a treatment group treated with Integra bilayer graft. The study concluded that after the 16-week follow-up, patients who received the Integra graft had a significantly greater complete closure rate (51%) versus the control group (32%). The mean time to closure in the treatment group was 43 days versus 78 days for the control group and weekly wound reduction size was 7.2% for the treatment group versus 4.8% for the control group [22].

Graftjacket Regenerative Tissue Matrix (Wright Medical) is another dermoconductive option composed of cadaveric collagen-based fenestrated allograft [3]. The acellular dermal scaffold is comprised of collagen, elastin, hyaluronan, fibronectin and blood vessel channels. Graftjacket Xpress (Wright Medical), functions similarly to Graftjacket Regenerative Tissue Matrix; however, it differs as it is an injectable soft tissue scaffold, suitable for use in wounds that have undermining, tunneling, or irregular shapes [10, 20, 23].

Protease inhibitor dressings are also useful advanced treatment options for DFUs. Promogran (Systagenix) is a hexagonal graft that is 55% collagen and 45% oxidized regenerated cellulose. The product binds and inactivates MMPs and elastases within the wound bed in addition to helping release positive growth factors. Promogran Prisma (Systagenix) is a version of Promogran that reduces bacterial growth with the addition of 1% silver [10, 24, 25]. Lobmann et al. studied the effects of Promogran on 33 patients with DFUs. After an 8-day treatment period, three separate tissue biopsies were obtained to analyze protease levels. The study demonstrated that Promogran treatment provided greater reduction in wound diameter in comparison to the control group (16%) and a significant decrease in the MMP-9/TIMP-2 ratio, likely due to MMPs binding to collagen matrix [26].

In addition to collagen-based dressings, other products add alginate to increase wound healing potential by absorbing excessive wound moisture and exudates. Fibracol Plus (Systagenix) which is composed of 90% collagen and 10% alginate functions as an autolytic debridement to achieve formation of granulation tissue [3, 10]. Donaghue et al. performed a randomized control study comparing Fibracol to saline-moistened gauze in 75 patients with DFUs.

The study concluded that the mean percent reduction in wound area was 80.6% in the Fibracol cohort (48% with complete healing) and 61.1% (36% with complete healing) in the control group [27].

Collagen dressings derived from human amniotic membrane are also effective ways to treat DFUs. PuraPly (Organogenesis) is a purified collagen matrix with a polyhexamethylene biguanide hydrochloride (PHMB) antimicrobial agent. PHMB is an added feature that provides broad antimicrobial coverage and reduction of bacterial loads within the wound with high tissue compatibility [28]. Preclinical studies using Puraply on methicillin- resistant *Staphyloccis aures* (MRSA) inoculated wounds revealed a statistically significant reduction in MRSA levels, 47%, at 72 h when compared to other current wound treatments utilizing silver technology [29].

Autogenous split thickness skin grafting for wound coverage has been an effective surgical option and treatment modality for decades. Theraskin (Soluble Systems) is an advanced wound care product that is similar to split thickness skin grafts (STSG) without the donor site risks. TheraSkin is a split-thickness human collagen allograft containing both epidermis and dermis, which is harvested within 24 h post-mortem and cryopreserved to sustain living cellular components. The graft contains 12 growth factors, 16 key cytokines, and 14 types of collagen (primarily I, III, IV). A study by DiDomenico et al. compared 12 wounds treated with TheraSkin to 17 wounds treated by Apligraf, resulting in a higher closure rate with the TheraSkin treatment group. The study also concluded that Theraskin had at least twice the amount of type I, III and IV collagen per unit area when compared to Apligraf and Dermagraft [30].

7.3 Hyperbaric Oxygen Therapy

Grafting has proven effective in overall wound treatments. Nonetheless, other treatment styles exist for DFUs. Hyperbaric oxygen therapy (HBOT) is one such therapy utilized for decades and well documented for advanced treatment of DFUs. HBOT works by exposing the patient to 100% oxygen at two to three times the normal atmospheric pressure, which increases the saturation of oxygen in the blood (up to 20 fold) to promote wound healing. More specifically, this process decreases hypoxia and edema to improve tissue perfusion, which promotes fibroblast and collagen proliferation and angiogenesis [31]. These features allow HBOT to promote an "ideal" wound healing environment, even in the uncontrolled diabetic population. Current randomized double blind study by Löndahl et al. revealed 52% (25/48) of diabetics with chronic (>3 months) Wagner grade 2, 3 or 4 ulcers had complete healing at 1 year follow-up when treated with HBOT for 85 min 5 days a week for 8 weeks, when compared to 29% healing in a placebo group [32].

7.4 Low Level Laser Therapy

Low level laser therapy (LLLT) as a therapeutic tool in the medical field has demonstrated numerous benefits, including its treatment with DFUs. While the exact mechanism of how LLLT works is still under investigation, it is widely believed that it functions to stimulate cell activation and enhance wound healing by increasing the proliferation and synthesis of collagen via activation of fibroblasts and keratinocyte motility [33, 34]. Although the power, duration, and frequency of treatment depends on wound characteristics, most DFUs are treated with 2–10 J/cm^2 at 50–60 mW daily, for upwards of 20 weeks. A recent study by Kajagar et al. looked at the use of LLLT for DFU in 68 patients for 15 days at 60 mW, and concluded that the cohort of wounds treated with LLLT contracted significantly more than the wounds in the non-treatment group (40.24% versus 11.87%); concluding that LLLT may be an effective option or adjunct in the treatment of DFU [35].

7.5 Ultrasonic Debridement

Advanced wound debridement techniques are another form of enhancing wound healing. Low frequency ultrasonic debridement instruments can be used in both the clinical and surgical setting. By precisely delivering sterile saline at frequencies between 20 and 40 kHz, these systems, such as MIST Ultrasound Healing Therapy (Alliqua BioMedical), Misonix, and Versajet (Smith & Nephew) all function to help remove necrosis, debris, biofilm, reduce MMPs, and increase angiogenesis while preserving healthy and vital structures [36–38]. More specifically, these devices do so using acoustic streaming, or mechanical force via saline, to revert chronic wounds into acute wounds via the theory of cavitation and dynamic reciprocity [39]. After the enhanced debridement modality is utilized, an advanced collagen based product, STSG, or biological dressing is often applied to the DFU to increase wound healing potential (Fig. 7.1).

7.6 Electrical Stimulation

Another advanced wound healing treatment that accelerates wound healing is electrical stimulation (ES). ES can be delivered to wounds in the form of direct current, alternating current, or pulsed current. ES emulates the natural electrical current that occurs when skin is naturally injured. This process promotes the proliferative stage of wound healing by decreasing the doubling time of fibroblast and endothelial cells, while increasing mitogen-activated protein kinase activation. Clinically, this

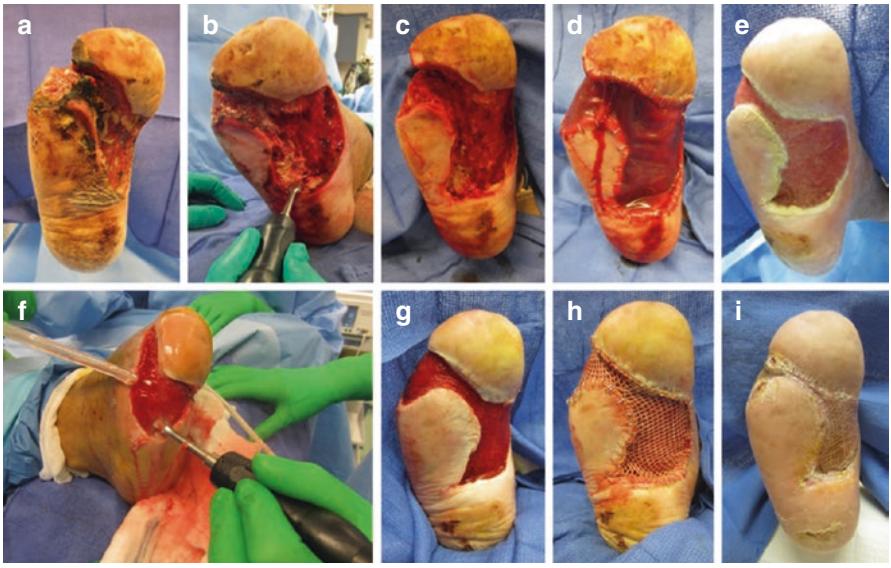

Fig. 7.1 (**a**) Right foot wound post infection debridement, (**b**, **c**) initial ultrasonic debridement staged procedure, (**d**) application of collagen allograft skin substitute, (**e**) appearance of foot after allograft take, pre-ultrasonic debridement in staged procedure for STSG application, (**f**, **g**) ultrasonic debridement and wound appearance, (**h**) application of STSG, (**i**) wound closure

is beneficial as it increases the cascade of neutrophils and macrophages and stimulates fibroblasts [40, 41]. ES has been shown to decrease bacterial load and increase transcutaneous oxygen levels. A randomized double-blinded placebo-controlled study by Peters in 2001 evaluated 40 patients with DFUs treated via ES. The study concluded that ES increased wound healing by 65% and wound area reduction by 86% (as compared to a control group) when treated by ES for 8 h nightly at 50 V for 12 weeks [41].

7.7 Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) delivered by vacuum assisted closure (VAC) therapy is a unique treatment system that offers reliable results when used appropriately. The VAC device has been an effective tool in simplifying wound care and creating more manageable wounds. It utilizes a uniform subatmospheric pressure on the wound bed to increase local blood perfusion, stimulate angiogenesis, and increase granulation tissue and cellular proliferation, while decreasing bacterial levels [42–44]. This process then allows the wound to be closed primarily, skin grafted, or to be suitable for advanced biological dressings. The VAC system is beneficial in treating acute, chronic and complex wounds [25, 40]. A multicenter randomized controlled trial for comparison of NPWT utilizing VAC to advanced

moist wound therapy (AMWT) in the treatment of DFUs demonstrated a greater proportion of foot ulcers achieving complete ulcer closure with NPWT (73/169, 43.2%) than AMWT (48/166, 28.9%) within the 112-day active treatment phase ($p = 0.007$). In assessing safety, no significant difference between the treatment and control groups was observed in relation to infection, cellulitis, and osteomyelitis within a 6-month period. NPWT appears to be as safe as, and more efficacious, than AMWT for the treatment of diabetic foot ulcers [44]. Another study analyzing VAC versus bolster dressing for securing skin grafts demonstrated that VAC group had improved wound healing, increased graft survival, required significantly fewer repeated splint thickness skin grafts (3% versus 9%), and decreased hospital stay (Fig. 7.2) [45].

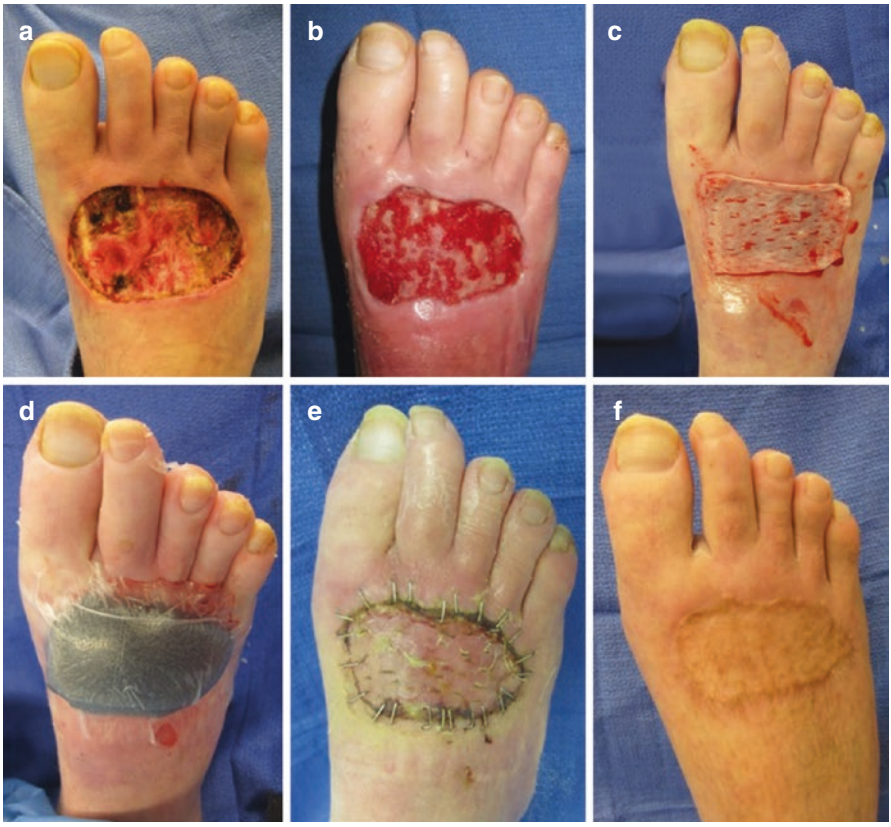

Fig. 7.2 Dorsal right foot wound treated with debridement, STSG application, and wound VAC therapy. (**a**) Dorsal right foot wound, (**b**) post debridement, (**c**) application of autologous STSG, (**d**) wound VAC application to site, (**e**) healing period, (**f**) completion of wound closure

7.8 Stem Cell Therapy

A newer treatment modality being utilized for the treatment of DFUs is stem cell therapy. Stem cells offer an alternative treatment aimed at increasing revascularization to reduce limb ischemia and promote wound healing. Generally, there are two types of stem cells: embryonic and adult. Embryonic stem cell have proliferative capacity and low differentiation maturity; while adult stem cells vary in the ability to differentiate based on tissue origin [46]. Current use of stem cells for DFUs include intramuscular and intraarterial injections, topical application, and grafts. While the use the stem cells is a fairly new concept, preliminary results appear promising [47]. Albehairy and colleagues demonstrated that patients with diabetes receiving autologous mesenchymal stem cell (MSC) injections around DFU borders had a significantly higher reduction in ulcer size at both 6 and 12 week follow-ups when compared to a control group. The results were 49.9% versus 7.67% at 6 weeks and 68.24% versus 5.27% at 12 weeks. The initial ulcer size for the MSC group in this study was larger than the ulcer size of the control group. This study shows that stem cells are a promising option for healing DFUs where standard treatments had limited effect [48].

7.9 Conclusion

In situations with recalcitrant wounds, advanced wound healing options are available and have demonstrated effective results. The associated morbidity and mortality in patients with these wounds are staggering; however, with appropriate treatment, wound healing and limb salvage can potentially be achieved. In this population, various comorbities, especially in deformities, vascular status, and neuropathy cause increasingly difficult wounds, leading to the need for initiation of advanced wound healing treatment plans. Without these treatment modalities, the risk of infection, complications, and potential loss of limb or life quickly escalates. Advanced wound healing options for DFUs are emerging and evolving regularly. However, while the array of advanced wound healing options for DFUs is plentiful, patient specific needs can always guide therapy. It is important to utilize evidence based medicine and effective treatment algorithms for the most predictable results. While all advanced wound healing modalities are unique and have individual guidelines, risks, and benefits, the underlying goal consistently remains to heal the wounds, prevent new ulcerations, reduce amputations, decrease mortality, and preserve both limb and quality of life.

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Chapter 8
Surgical Management: Neuropathic Foot

Stephen F. Lazaroff, Michael I. Gazes, and Peter A. Blume

8.1 Introduction

As the incidence of uncontrolled diabetes continues to rise, so do its resulting sequelae, including neuropathy. Diabetic peripheral neuropathy results in eventual sensory, motor, and autonomic neuropathy if left untreated. Sensory neuropathy results in the loss of light touch, vibratory, and pain sensation, thus decreasing the warning signs of impending problems [1]. Diabetics with sensory neuropathy are seven times more likely to develop foot ulcerations versus non-neuropathic diabetics [2]. Motor neuropathy yields abnormal neural supply to the intrinsic muscles of the foot, with resultant pedal deformities. These deformities cause abnormal plantar pressures, bony prominences, and shifting of fat pads, which cause plantar soft tissue breakdown and potential for ulceration of previously fitting shoe gear [1]. Autonomic neuropathy results in decreased sweat and oil gland function, putting skin more at risk for cracks, fissures, and edema from abnormal peripheral sympathetic vascular tone [1]. Charcot neuroarthropathy is also a serious concern for neuropathic patients with diabetes, and patients with peripheral neuropathy in general, as it results in fragmentation and dislocation of the foot, with subsequent rocker-bottom deformity.

Treatment of the neuropathic foot usually begins with conservative measures. For patients without wounds, preventative measures such as regular foot checks, accommodative inserts, and custom fitted shoe gear are all implemented. For uncompli-

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cated, non-infected ulcers, in office wound debridements and offloading measures are undertaken. When improvements with conservative treatments have stalled or failed, or infection has incurred, surgical management may be required.

8.2 Nerve Decompression

Diabetic neuropathy is estimated to effect at least half of all diabetics [3]. In the early 1990s, Dellon published research on rats showing that neuropathy did not occur when lower extremity nerves were not anatomically compressed [4]. Surgical decompression of lower extremity nerves has shown to increase sensation, improve balance, and decrease pain in neuropathic patients. The Dellon Triple Decompression technique, neurolysis of the peroneal nerve at the knee and the dorsum of the foot, and neurolysis of the tibial nerve in the four medial ankle tunnels, has been performed in an attempt to improve symptoms of diabetic neuropathy. Dellon published the results of fifteen peer-reviewed studies that used the inclusion criteria of (1) presence of symptomatic neuropathy, (2) positive Tinel sign over the tarsal tunnel demonstrating a site of compression, (3) no previous history of ulcer or amputation, and (4) use of the Dellon Triple Decompression technique (5). The review found an overall relief of pain in 88% and restoration of sensation in 79% of patients [5]. No new ulcers were observed after nerve decompression in patients without a history of ulcers [5]. In two reports, encompassing thirty patients with a history of ulceration or amputation, only one patient developed a new ulcer after nerve decompression [5]. The expected rate of ulceration for patients with diabetic neuropathy is 15%, and 50% recurrence rate for patients with a history of ulceration [5]. In 665 legs that underwent nerve decompression, the ulceration rate at 2.5 years was only 0.6%, and only a 2.25% recurrence rate was observed in 44 patients [5]. The conclusion of this study was that the effects of peripheral neuropathy can be reversed via nerve decompression, and the resultant restoration of sensation can greatly decrease the frequency of ulceration and subsequent amputation.

8.3 Forefoot Pressure Reduction

In a neuropathic patient, calluses, ulcers, and pressure points can be precursors to future problems. When these haven't responded appropriately to conservative treatments, they can be managed surgically. Hammer, claw, and mallet toes are common deformities seen in neuropathic patients. Depending on the degree and rigidity of the digital deformity, the dorsal aspect of the DIPJ and PIPJ, and distal tip of the toe become at risk areas for ulcer formation. Also, the retrograde force of the toe on the metatarsal head may lead to increased plantar pressure and subsequent callus formation or ulceration. For ulcers at the distal tip of the digit with a flexible deformity, a percutaneous flexor tenotomy can be performed [6]. Laborde published

a retrospective study on 18 patients that had a distal toe ulcer with flexible claw toe deformity. A percutaneous flexor tenotomy was performed, and yielded resolution of ulcer for all patients. Two patients required repeat tenotomy for recurrent contracture and ulcer formation, but were ulcer free at 17 and 34 months [7]. Tamir et al. performed a similar retrospective study with the addition of osteoclasis for rigid contractures at the PIPJ, and all wounds healed [8]. For rigid digital contractures, arthroplasty at the level of the deformity can be performed [6]. Capsular release at the level of the MTPJ may also be required for a rigid hammer toe deformity.

Sub metatarsal head ulcers without underlying osteomyelitis can be offloaded with osteotomies at the level of the surgical neck [6]. Tamir et al. performed 20 floating metatarsal osteotomies on 17 patients. The ulcer resolved after 6 weeks in 19/20 osteotomies, and didn't recur after a mean follow-up of 11.5 months [9]. One patient had a post-operative infection with osteomyelitis requiring debridement. A shortening metatarsal osteotomy can also be done for surgical offloading [6]. For ulcers with deep tunneling, an ulcer debridement with metatarsal head resection is recommended. Armstrong et al. published a retrospective study of 40 patients comparing fifth metatarsal head resection versus standard conservative treatment for a plantar metatarsal ulcer. He found a significantly faster healing time for the surgical group (mean 5.8 weeks ±2.9) versus the conservative treatment group (mean 8.7 weeks ±4.3) [10]. It is important to evaluate the remaining parabola after performing a metatarsal head resection [11].

Hallux limitus/rigidus, a decrease or lack of range of motion at the first MTPJ, results in increased plantar pressure of the hallux, predisposing the toe to ulceration in the neuropathic patient. In patients where orthotics do not effectively compensate for the lack of motion, ambulation will further damage plantar soft tissue. A Keller bunionectomy can be done to increase first MTPJ range of motion, thus decreasing plantar pressure. Berner et al. performed a retrospective study on thirteen Keller procedures done for eleven patients with plantar hallux ulcers that had been treated with conservative care for at least 6 months [12]. All patients had adequate vascular status without underlying osteomyelitis. Six months post-operatively, all primary ulcers healed. At 1-year follow-up, all primary ulcers remained healed; however, five transfer lesions developed. Armstrong et al. compared forty-one patients with plantar hallux ulcers, with twenty-one of those patients undergoing a Keller procedure. They found a significantly faster healing rate in the surgical group versus the conservative treatment group, and observed fewer ulcer recurrences at 6 months in the surgical group [13]. They concluded that a Keller procedure is effective in treating plantar hallux ulcers in non-infected, non-ischemic wounds [13].

During the pre-operative assessment, the presence of equinus should be evaluated using the Silfverskiold test. Ten degrees of ankle dorsiflexion is required during normal gait, with decreased range of motion resulting in increased plantar pressure in the forefoot [6]. Lavery et al. found that equinus (defined in their study as less than zero degrees of dorsiflexion at the ankle) exists in over 10% of all patients with diabetes, and those patients had significantly higher peak plantar pressures than those without equinus [14]. Rosenbloom et al. observed that decreased joint flexibility correlates with increased forefoot and midfoot pressures in several studies, which can lead to

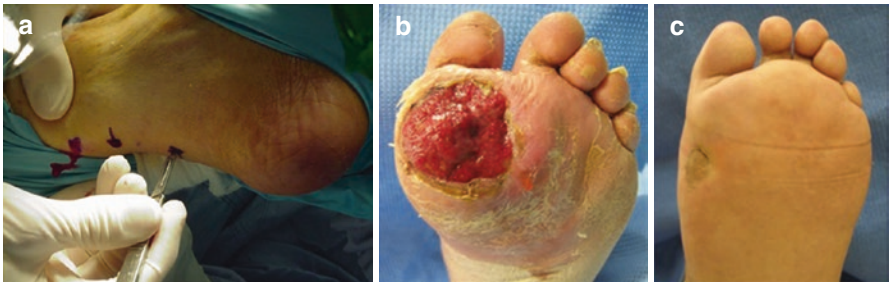

Fig. 8.1 Percutaneous tendoachilles lengthening to treat forefoot ulceration. (**a**) Three stab incisions for lengthening (**b**) forefoot ulceration, (**c**) closed wound site post tendoachilles lengthening

plantar ulcer development [15]. Armstrong et al. performed a study comparing mean peak pressures in the forefoot in diabetic patients with a recent history of healed forefoot ulcers. They used force-plate data collected just prior to percutaneous tendoachilles lengthening (TAL), and also measured the amount of ankle dorsiflexion. Post-operatively at eight weeks, these values were measured again. They observed a significantly decreased mean peak pressure in the forefoot post-operatively, and also a significantly increased amount of ankle dorsiflexion (Fig. 8.1) [16].

8.4 Charcot Foot

One of the most challenging aspects of dealing with the neuropathic foot occurs when managing a Charcot foot. Charcot occurs in roughly 1% of the diabetic population, and in about 30% of patients with peripheral neuropathy [6]. In the acute phase, this inflammatory neuroarthropathy often presents as a red, hot, and swollen foot [17]. The hypervascular foot causes bone resorption/fragmentation, dislocation, and eventual midfoot collapse resulting in the classic rocker-bottom deformity [17].

Management of acute phase Charcot focuses on prevention/limitation of joint subluxation. Non-weight-bearing is the mainstay treatment for acute phase Charcot [18]. Mitigation of deformity makes conservative treatment possible via accommodative footwear, ankle foot orthotics, or CROW boots after resolution of the acute flare.

Charcot increases the risk of ulcer development by 3.5-fold [19]. Chronic Charcot deformity recalcitrant to conservative treatments may be best managed surgically. Goals of surgery are to reduce plantar pressures, preserve skin integrity, and provide a stable foot [18]. The main indications for surgery are bony prominences that cannot be effectively offloaded, occurrence of infection, significant instability, and fixed deformity [17]. Exostectomy of bony prominences in a relatively plantigrade foot can enable accommodative bracing for prevention of ulceration [17]. Catanzariti et al. performed a retrospective review of twenty-seven procedures on twenty patients where exostectomies were done for midfoot prominences [20].

Eighteen ulcers were medial and nine were lateral. Twenty of the twenty-seven ulcers healed after exostectomy, with six of the seven failures occurring in the lateral wound group. There was a statistically significant higher rate of complication for the lateral ulcer group. The authors concluded that exostectomy for medial column wounds is a viable surgical option, whereas lateral column ulcers may require more complex reconstruction for limb salvage [20].

Rosenblum et al. also performed a retrospective study for non-healing neuropathic ulcers under the lateral column in Charcot feet [21]. Thirty-two feet were included, all of which underwent exostectomy. Seventeen feet also had ulcer excision with primary closures, eight had closure by rotational fasciocutaneous flaps with transpositional intrinsic muscle flaps, six had an incision placed adjacent to the ulcer, and one incision was made directly over the prominence in a healed ulcer. The authors observed an 89% success rate and proposed a soft tissue approach for wound closure, granted adequate exostectomy was performed [21].

Laurinaviciene et al. retrospectively analyzed twenty feet (nineteen patients) treated with exostectomy for midfoot Charcot ulcers [22]. In this study, nine ulcers were plantar to the medial column, nine were plantar to the lateral column, and two were plantar central to the midfoot. After exostectomy, eighteen of the twenty ulcers healed, with seven patients having recurrent ulcers at a mean time of 15 months. Most of the recurrences occurred in lateral column ulcers, with five patients requiring repeat exostectomy. Overall, fourteen of the sixteen patients alive at the end of the study (three patients died from other causes prior to follow up), had healed ulcers. The authors had similar conclusions to other studies in that exostectomy is a safe and effective treatment for ulcer cure, but that lateral column ulcers are at higher risk for recurrence [22].

When patients with Charcot foot fail conservative treatment and minimal surgical interventions, or the degree of deformity or instability is too significant to warrant these treatments, a reconstruction may be considered (Fig. 8.2). The timing and technique for reconstruction can vary greatly between surgeons, but the end goal of treatment is a plantigrade foot amenable to bracing. Despite a high rate of incomplete bony union in this patient population, arthrodesis can be useful in patients that have failed other treatments [23]. Since the location of joint destruction and quality of bone stock often varies in Charcot patients, the type of fusion and fixation required is patient specific.

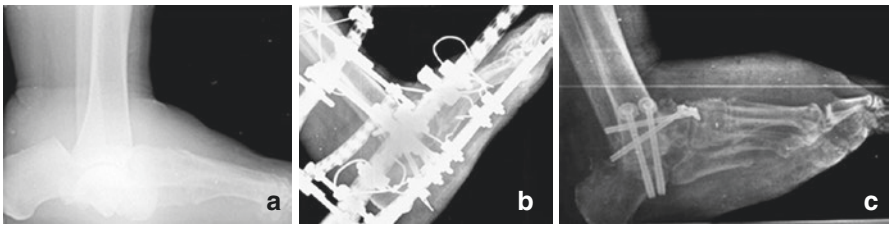

Fig. 8.2 (**a**–**c**) Pre-operative, reconstructed, and post-operative Charcot foot with use of internal and external fixation

The standard for treating Eichenholtz stage-1 Charcot foot has routinely been non-weight-bearing with total-contact casting [24]. Simon et al. argued that non-union or malunion may still result from this treatment, and evaluated fourteen patients who underwent early midfoot fusion for this condition. They compared plantar pressures of these fourteen patients to plantar pressures of fourteen patients with diabetic neuropathy who underwent a previous below knee amputation, and to fourteen patients with diabetic neuropathy without history of plantar ulcers. All midfoot fusions were successful, without post-operative complications, and enabled all patients to resume the same walking ability they had prior to the arthropathy occurrence [24]. No differences were observed via calculated confidence intervals between the midfoot fusion group versus the other two groups when comparing gait velocity, cadence, and stride; or with minimum, maximum, or total range of motion of each of the joints observed [24]. They concluded that early surgical treatment of Eichenholtz stage-1 Charcot foot can effectively restore anatomical alignment and improve function [24].

Mittlmeier et al. also evaluated the effect of early primary surgical reconstruction for Charcot patients. They retrospectively reviewed twenty-two patients (twenty-six feet) with midfoot or hindfoot reconstruction arthrodesis with a minimum 6-month follow-up [25]. Initially, there were eight ulcers, all of which healed without recurrence post-operatively. They observed increases in AOFAS scores from a mean 39 to 70 points (hindfoot) and 51 to 84 points (midfoot) from pre-operatively to post-operatively, and a complication rate comparable to patients undergoing secondary surgery after failed conservative treatments [25]. Similar to Simon et al., they concluded that early reconstruction can re-establish a plantigrade foot with an improved quality of life.

Midfoot, triple, or tibio-talo-calcaneal arthrodesis can all be implemented for reconstruction based on the location of the deformity [23]. Internal fixation techniques consist of pins, screws, nails, and plate fixation, and may be supplemented with external fixation [23]. Stone et al. performed three midfoot fusions and seven hindfoot fusions with autogenous iliac-crest bone graft for patients with Charcot deformity that had failed conservative treatment. Midfoot fusions were performed with cannulated screws and plates as necessary, while hindfoot fusions were achieved via tibio-talo-calcaneal intramedullary nail. They observed clinical and radiographic evidence of osseous fusion in five of nine patients, with the remaining four patients having a stable fibrous union [26]. During the follow-up, one patient had a failed hindfoot fusion, and below knee amputation was recommended. In the other nine cases, no further ulcers were observed and amputation was avoided [26]. They concluded that midfoot and hindfoot arthrodesis for Charcot arthropathy can re-establish a plantigrade foot and enable limb salvage, even if radiographic osseous union is not achieved [26].

Capobianco et al. discussed the use of an extended medial column arthrodesis for midfoot Charcot deformity [27]. They resected all medial column joints, performed osteotomies as needed for realignment, and applied a plate from the talus distally to the first metatarsal. A locking plate with a combination of locking and non-locking 3.5 mm screws were used, yielding stability and rigidity of the foot [27]. Since the

talonavicular joint is fused using this technique, rearfoot frontal plane motion is significantly restricted [28]. As a result, they recommend subtalar and ankle joint fusions only when residual instability remains after medial column fusion [27].

External fixation can also be used if further stabilization or offloading is required. The use of an external fixator when treating the Charcot foot has been described in isolation, or in combination with internal fixation. The external fixator resists torsional and axial stresses, and thus shields the fusion sites to enhance stability [27]. Also, the external fixator offloads the heel preventing decubitus ulceration, allows quiescence of soft tissue, and protects adjunct soft tissue procedures [29].

In 2007, Pinzur published work from a prospective study proposing an algorithm for treating Charcot patients. He first categorized patients as either having a plantigrade or non-plantigrade foot. The plantigrade patients were treated conservatively with total contact casting, and excluded from the study. The non-plantigrade patients were further categorized as low risk (no open wounds, no morbid obesity, and no significant diabetes-associated organ system comorbidities) or high risk. The low risk patients were treated with percutaneous TAL or gastrocnemius recession with internal fixation. The low risk patients were also excluded from the study. Twenty-six high risk patients were included in the study, and underwent percutaneous TAL, midfoot bone wedge resection to reestablish a plantigrade foot, followed by the application of a neutral ring external fixator to maintain position. At follow-up of at least 1 year, twenty-four of twenty-six patients were ulcer and infection free, and ambulated with depth-inlay shoes and accommodative orthotics [30]. This study concluded that patients with Charcot deformity, a non-plantigrade foot, and are at high risk for post-operative infection, can be effectively treated via this technique. Also, the algorithm proposed here can help guide treatment plans for this patient population [30].

8.5 Vascular Management

Treatments for neuropathic feet are becoming more complex with a trend towards earlier aggressive therapy to prevent amputation. Even though there has been a push for increased education and awareness of the deleterious effects of the neuropathic foot, ulcers still develop in roughly 15% of diabetic patients [31]. Diabetic foot infections are one of the leading causes of hospitalization in this patient population, with 85% of diabetic lower extremity amputations being preceded by an ulceration [32]. Once infection has occurred, surgical management is often required.

The pre-operative workup for an infected foot can be vital to the outcome. Clinical evaluation, labs, and imaging can all help elucidate the acuity and extent of infection. In non-emergent cases, a complete vascular workup to determine the limb's perfusion status is essential. In cases where amputation is required, the level of amputation is determined by both the extent of the underlying infection and the blood flow to the affected area.

As diabetic neuropathy is a major cause of lower extremity amputation, an understanding of the concomitant vascular disease in these patients is important. Peripheral vascular disease (PVD) is twenty times more prevalent in diabetics versus non-diabetics [33], with atherosclerotic disease having a predilection for the tibioperoneal vessels in diabetics [34]. The pedal vessels are often spared in diabetics however, which makes pedal bypass possible [34]. A thorough vascular exam and non-invasive tests can help determine the need for vascular intervention. Ankle-brachial index can be unreliable in diabetics however, as calcified vessels can result in falsely elevated values [35].

When there is concern for limb ischemia in the face of a chronic non-healing wound, arteriography can be done to visualize the arterial tree. Attinger et al. discussed the concept of angiosomes in the foot and ankle [36]. They described six angiosomes, three from the posterior tibial artery, two from the peroneal artery, and one from the dorsalis pedis artery [36]. Arteriography can help determine if a chronic wound or amputation site is in an angiosome not adequately perfused. The angiosome concept also becomes essential when determining incision placement, and flap formation.

Neville et al. retrospectively reviewed fifty-two non-healing lower extremity wounds in forty-eight patients treated via bypass. Pre-operative arteriograms were done to determine if a wound's angiosome was supplied, and patients were split into two groups, direct (bypass to artery directly supplying wound's angiosome) and indirect (bypass to artery not directly supplying wound's angiosome) revascularization. The results showed a 91% wound healing rate for the direct group, and 62% for the indirect group [37]. This value was statistically significant; however, no significant difference was noted in time to healing for all healed wounds [37]. The authors concluded that direct revascularization of a wound's angiosome yields a higher healing rate, and thus limb salvage [37].

Hinchliffe et al. reviewed forty-nine papers from 1980–2010 that evaluated the outcomes of revascularization for limb salvage in diabetics with ulcers and PAD. Patients were treated endovascularly or via open bypass. The median 1-year limb salvage rate for open bypass was 85% and 78% after endovascular revascularization, with 60% of ulcers healed at 1-year follow-up via either revascularization method [38]. The authors concluded that there wasn't sufficient data to determine which method is superior, but the results favor improved limb salvage rates via revascularization versus medically treated patients [38].

8.6 Wound Management

Eradication of tissue infection is paramount to limb salvage in the neuropathic and non-neuropathic foot. Differences in treatment strategies exist, but a regimen of both medical and surgical interventions is generally required. Treating osteomyelitis with antimicrobials alone is difficult as host defenses do not operate optimally within the bone, bacteria can adhere via impermeable glycocalyx biofilm, and antibiotic bone penetration is variable [39]. Surgical resection of infected or necrotic tissue is

therefore usually required. Debridement of soft tissue should be done until bleeding and granulation tissue is observed, and dense, hard bone with pinpoint bleeding is encountered [40]. The objective of resection is not only to eliminate infection, but also preserve function and decrease overall long-term morbidity and mortality [41]. Aggressive bone resection is important, as outcomes are poorer when margins are positive for residual infection. Atway et al. reported that 81.8% of patients with bone margins positive for osteomyelitis had poor long-term outcomes, and yields a higher risk for re-amputation and need for longer term antibiotics [42]. They concluded that bone margin cultures should be taken for all patients, and that excellent long-term results can occur when adequate soft tissue coverage is preserved after debridement [42]. Kowalski et al. also evaluated the rate of residual osteomyelitis via pathologic examination. They observed a 35.14% positive margin rate, with a higher prevalence in partial metatarsal amputations versus other amputations [43]. Also, the rate of re-amputation was higher with a positive bone margin [43].

Before any tissue is incised or resected, closure strategy, albeit primary or delayed, should be considered. The use of atraumatic technique, minimization of undermining, and knowing an angiosomal perfusion status for potential flap or graft closure can all help improve closure rates [44]. Janis et al. proposed a reconstructive ladder to guide wound closure strategies for a variety of soft tissue defects. The ladder is a stepwise approach from least morbid to most morbid techniques, and proposes that skin grafts and flaps should be considered when primary or secondary closure are not possible or ideal [45].

Primary closure, which is the first rung on the proposed ladder by Janis et al., is usually avoided following acute infection debridement, or not feasible due to extensive tissue resection. In these situations, wounds are packed open for repeat debridement and delayed primary closure [44], or left open for drainage and allowed to heal by secondary intention. Previously, the standard for healing via secondary intention was to pack wounds daily. This process is challenging however, as Visiting Nurses Association (VNA) services will be required for daily home dressing changes, the open wound is regularly exposed for potential further infection, and wound granulation can be lengthy as many patients have some component of peripheral arterial disease.

The advent of negative pressure wound therapy (NPWT) via wound VAC (vacuum-assisted closure), has been shown to expedite secondary healing. NPWT creates a moist wound environment, decreases edema, and promotes granulation tissue formation via increased perfusion from neovascularization [46]. Blume et al. observed the healing time for patients with diabetic ulcers using either NPWT or advanced moist wound therapy (AMWT), predominately hydrogels and alginates [46]. This was a multicenter randomized controlled trial with 73/169 NPWT patients achieving complete wound closure within the 112-day active treatment phase versus 48/166 AMWT patients. There were statistically significant fewer secondary amputations in the NPWT group, and the authors concluded that NPWT was as safe and more efficacious than AMWT for healing diabetic ulcers [46]. These results coincide with results from Argenta et al., who concluded that NPWT was beneficial for wound healing due to its ability to remove excess interstitial fluid, increase

vascularity, decrease bacterial colonization, and thus stimulate granulation tissue formation [47]. Saxena et al. also hypothesized that open pore foam dressings, as is used with NPWT, create micromechanical deformations in the wound surface [48]. This micro-deformation causes cell stretching and promotes cell division, thus stimulating granulation tissue formation [48]. NPWT is a commonly used therapy for wound healing, can be used to achieve wound re-epithelialization, or to promote a granular wound bed that is superficial enough to enable skin grafting.

8.7 Skin Grafts and Flaps

Skin grafting is the next step after NPWT according to the reconstructive ladder proposed by Janis et al. This technique entails harvesting skin from a donor site, and transplanting it to a recipient site. During this process, the harvested skin is separated from its local blood supply, and relies on the recipient site's blood supply for survival [49]. Split-thickness skin grafts (STSG), where the epidermis and only a portion of the dermis is obtained [44], are often used to enable wound closure.

Skin graft take is the process of transplanted skin to revascularize and reattach to the recipient site [49]. Prior to transplantation, it is imperative to aggressively prepare the recipient wound bed. Surgical wound bed preparation converts the wound from a chronic to an acute state, and a granular bed with pinpoint bleeding, increased skin lines, and neoepithelialization at the edges should be seen [50].

After harvest, the STSG can be either meshed or pie crusted. Meshing allows the graft to stretch and cover larger areas, increases adherence to irregular surfaces, and permits excess fluid to drain from the recipient bed, thus preventing hematoma or seroma formation under the graft [44]. Meshing tends to lead to a crisscross appearance once healed. Pie crusting also allows fluid drainage, but doesn't enable graft stretching or result in a crisscrossed appearance once healed [44].

Hematoma and seroma formation, and shear forces are the most common causes of graft failure [44]. Once the graft is applied and secured, either via staples or suture, a piece of Xeroform is applied followed by a bolster dressing. The bolster dressing applies pressure over the graft in an attempt to prevent hematoma and seroma formation, and decreases shear between the graft and the wound bed [44].

More recently, wound VAC application over skin grafts has been shown to improve take [51, 52]. Application of the wound VAC occurs in the operating room, and left running for 5 days uninterrupted [44]. The wound VAC is removed after 5 days, and a dry dressing is applied. Hegelson et al. reported greater than 90% wound closure rate with this treatment course [53]. Llanos et al. published results from a randomized, double-masked, control trial comparing the use of NPWT to a control group receiving the same dressing not connected to NPWT. In a 60 patient study, a STSG was applied to a wound bed after surgical debridement. The amount of STSG loss and the duration of hospital stay were recorded. They observed a statistically significant decreased median loss of STSG in the NPWT group (0.0 cm^2) compared to the control group (4.5 cm^2), and also a statistically significant shorter

median hospital stay in the NPWT group (13.5 days) versus the control group (17 days) [54]. They concluded that NPWT should be routinely used when applying STSG (Fig. 8.3) [54]. Several authors have advised against the use of skin graft application on weight-bearing surfaces however, as they may not withstand the pressure encountered in these locations [44].

In instances where skin grafts are not indicated, or direct wound closure can be obtained, flap closure can be implemented. A variety of local random flaps exist for the use in the foot and ankle, and include advancement, rotational, and transpositional flaps (Fig. 8.4). These types of flaps are perfused by a perforator artery from the dermis to the subdermal plexus [44]. These flaps differ from an axial flap, which has a direct cutaneous vascular supply [44]. Since random flaps rely on perforators for survival, the angiosome's perfusion is vital for random flap viability. The source artery supplying the potential flap's angiosome should thus be evaluated when planning this technique [44].

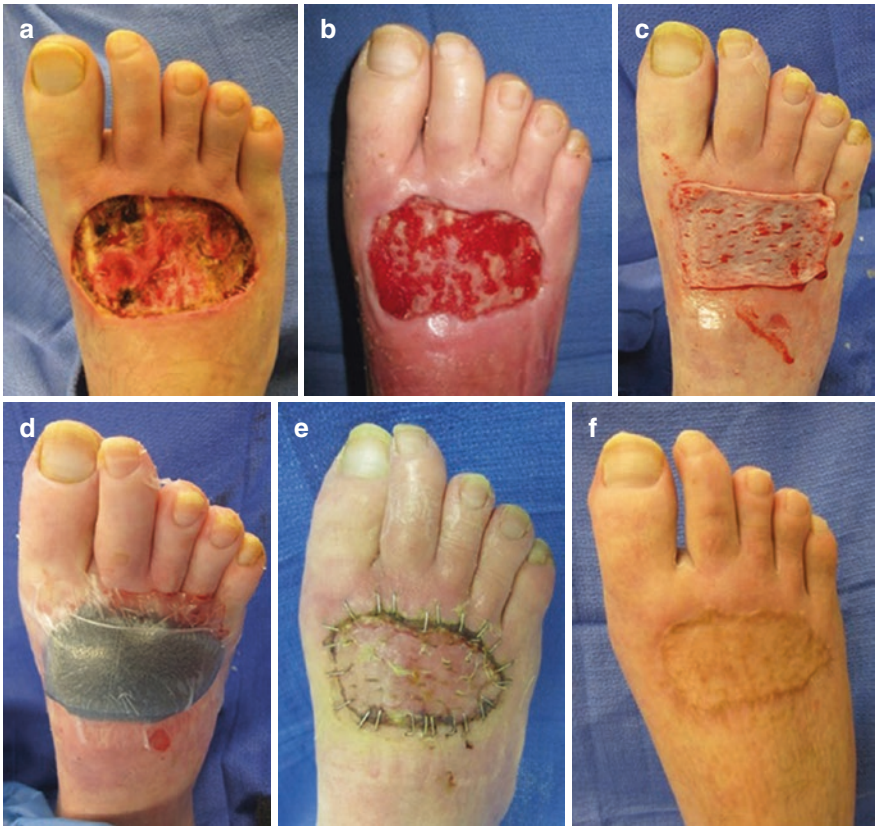

Fig. 8.3 Dorsal right foot wound treated with debridement, STSG application, and wound VAC therapy. (**a**) Dorsal right foot wound, (**b**) post debridement, (**c**) application of autologous STSG, (**d**) wound VAC application to site, (**e**) healing period, (**f**) completion of wound closure

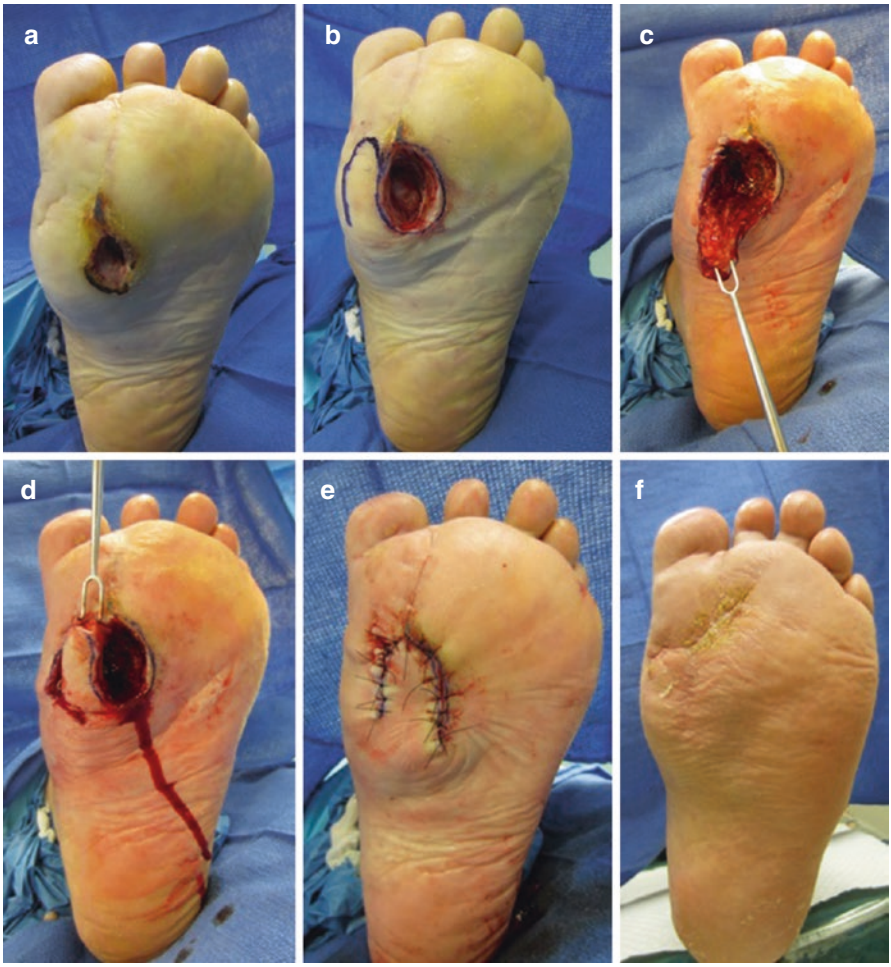

Fig. 8.4 (**a**–**f**) Single stage ulcer excision with flap formation and insertion

Choke vessels link adjacent angiosomes, and can be used to enhance perfusion to an angiosome [44]. The delay phenomenon is used to the surgeon's advantage by first raising a flap in the donor area. This results in the dilation of existing choke vessels within the flap, rather than an ingrowth of new vessels [55]. This is an active process resulting in an increase and enlargement of the cells of the vessel wall, and thus increased perfusion in the area [55]. The vessels dilate due to increased ischemia, causing a shift to anaerobic metabolism with a subsequent decrease in vessel pH [44]. Also, raising the flap causes a local sympathectomy, and thus vasodilation [44]. Choke vessel dilation was most pronounced between 48 and 72 h [55], at which point the flap can be set for wound closure.

When skin grafting and local random flaps are not suitable, distant axial flaps, tissue expansion, and free flaps, as proposed in the reconstruction ladder, may be

used for closure. These techniques are considered more complex, and have a higher risk for morbidity. Overall, many options are available for wound closure after surgical resection of infection. As the neuropathic foot can result in devastating consequences, and is often complicated by multiple comorbidities, a multi-disciplinary approach to surgical management is often necessary.

8.8 Conclusion

When infection is not present, non-operative and operative interventions can occur to keep patients with neuropathic feet safe from limb or life threatening developments. Prophylactic surgical interventions could benefit patients with bony prominences, which could develop into ulceration and a cascade of non-healing wounds, infection, and threat to limb or life. Charcot foot can have exostectomies, or complex reconstructive interventions to create a plantigrade foot amenable to bracing. Vascular integrity is imperative, especially in wound management. When wounds arise, regular care and evaluation are necessary to prevent negative results. NPWT, skin grafts, and skin flaps have proven to be effective modalities. Surgical management of the neuropathic foot is complex and should be guided by appropriate patient selection.

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Chapter 9
Limb Salvage for the Diabetic Foot

Thomas Hester, Camilla Jay Stewart, and Naveen Cavale

9.1 Introduction

The path to limb salvage in the diabetic foot is a challenge. Reasons such as pre-existing medical comorbidities, vascular insufficiency, abnormal bony anatomy, active soft tissue infection and underlying osteomyelitis can all be encompassed by a neuropathic foot that lacks the normal protective physiological responses. Our aim is to provide a practical guide to approach salvage of such feet.

Decisions are made in a multidisciplinary team setting, allowing medical issues to be optimised, orthotics to be planned and mobility issues to be pre-empted [1]. Vascular insufficiency is investigated with Doppler ultrasound (US) imaging and referral as necessary. Active foot infection must be dealt with thoroughly, with a low threshold for aggressive debridement until infection is under control. All wound margins are debrided back to healthy bleeding tissue, with awareness of concealed pockets of necrotic tissue. An approach to debridement is described in Chap. 29. Often magnetic resonance imaging (MRI) can show the extent of tracking along fascial planes or tendons. These must be sought out and debrided and the same is true of osteomyelitis which must be eradicated prior to starting reconstruction.

Once adequate bone and soft tissue debridement has been performed, samples for microscopy, culture & sensitivities (MC&S) are sent, empirical antibiotics started and negative pressure wound therapy applied. This aims to remove exudate leading to maceration, increase local growth factors (Cellular fibronectin (cFN) and

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transforming growth factor-β1 (TGF-β1)) [2], and reduce tissue oedema. Wounds are then reviewed regularly. When there is a downtrend in inflammatory markers and soft tissues have settled, reconstruction can begin.

Classically, the reconstructive ladder is considered, working primarily from healing by secondary intention, application of a split skin graft (SSG), soft tissue advancement, local rotational flaps and free tissue transfer [3] (Fig. 9.1). It is imperative to consider the location of the defect and the blood supply to that area. The foot and ankle are composed of six angiosomes that originate from three main arter-

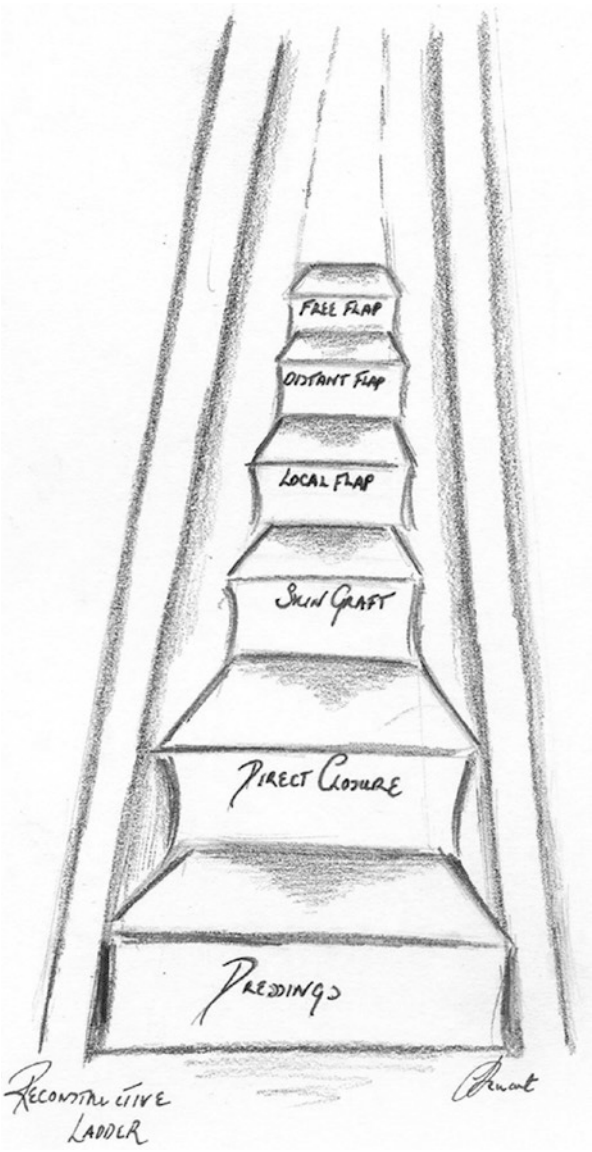

Fig. 9.1 The reconstructive ladder

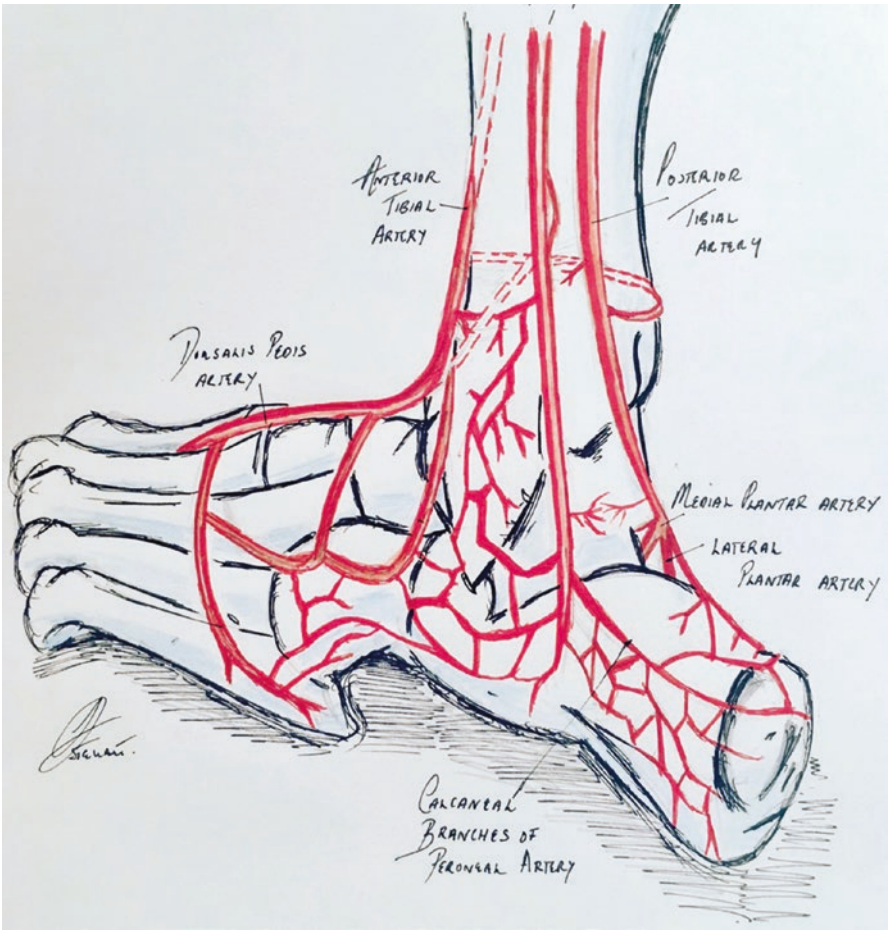

Fig. 9.2 Lateral blood supply to the hindfoot

ies. The posterior tibial artery supplies the medial calcaneal area (medial calcaneal artery) and the plantar foot (medial and lateral plantar arteries). The anterior tibial artery supplies the dorsum of the foot (dorsalis pedis artery). The peroneal artery supplies the lateral calcaneum (calcaneal branch) and the anterolateral ankle (anterior perforating branch) (Fig. 9.2).

9.2 Dorsal Defects

The dorsal lateral aspect of the foot can become secondarily infected from plantar ulcers or localised cellulitis. Debridement may see excision of the long extensor tendons, with extensor digitorum brevis (EDB) remaining which can be covered

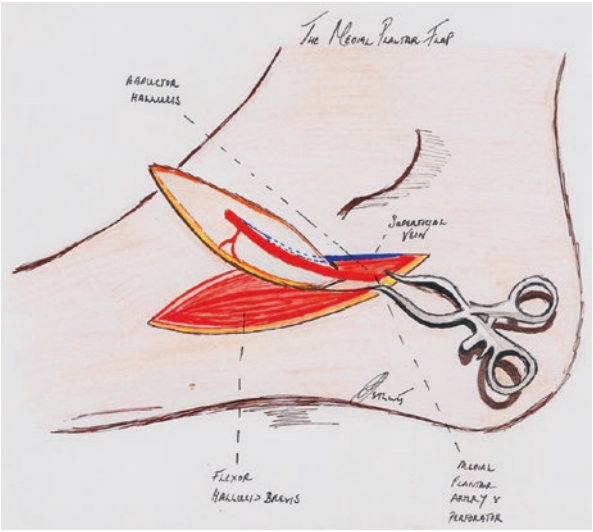

Fig. 9.3 Medial plantar flap based on the medial plantar artery

with SSG providing extensor paratenon remains intact. Local rotational flaps can be considered based on the dorsalis pedis artery (DPA) rotated to the malleolar areas. The flap is fairly versatile due to the size of the feeding vessel and can be fasciocutaneous or myocutaneous when including EDB.

The dorsal medial aspect of the foot can prove troublesome to SSG with the presence of exposed tibialis anterior tendon. If possible a dorsal flap can be raised based on the DPA or if this is looking doubtful then a medial plantar flap can be raised based on the medial plantar artery (Fig. 9.3).

9.3 Plantar Defects

Plantar weight bearing skin below the glaborous junction is very problematic to reconstruct after extensive debridement due to the mechanical properties of the plantar septae and their ability to resist shear. These properties are not replicated by most soft tissue coverage options, often resulting in continued ulceration. As such, local options are preferred if possible such as V-Y or local rotational flaps. However, the size of the defect is often limited to below 3 cm^2 (Fig. 9.4). The medial plantar flap can be utilised based on the medial plantar artery, or local muscle flaps can be utilised if they have not been resected or damaged by local bony prominences in the deformed foot e.g. flexor digitorum brevis, abductor hallucis brevis, flexor hallucis brevis.

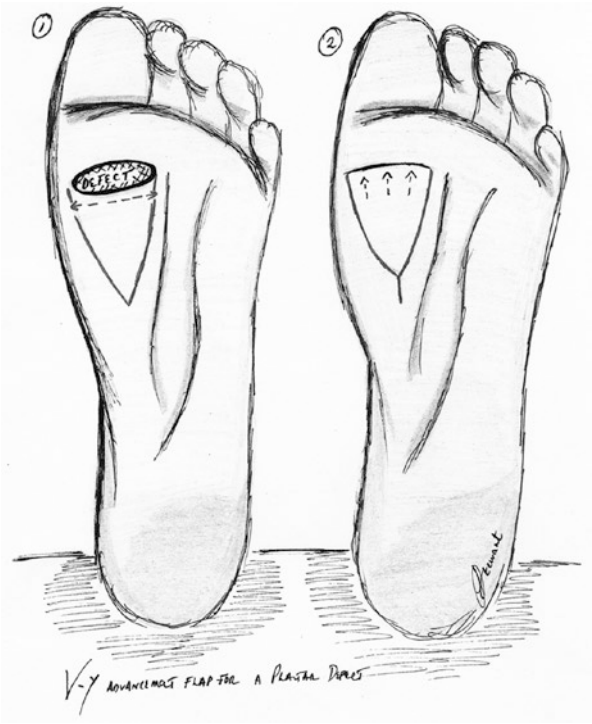

Fig. 9.4 V-Y advancement flap

9.4 Hindfoot Defects

Calcaneal wounds are frequently encountered due to the watershed between the two presenting angiosomes supplied by the calcaneal branch of the posterior tibial artery and the calcaneal branch of the peroneal artery. These defects are often difficult to treat with negative pressure wound therapy and SSG due to the lack of underlying muscle. Local options include the medial plantar flap or a perforator flap. The latter is based on a perforator from the posterior tibialis artery which consists of a fasciocutanous flap along the axis between the soleus and flexor digitorum longus.

9.5 Achilles Defects

Achilles defects are often associated with wound problems due to the presence of the peroneal angiosome from the lateral side and the posterior tibial angiosome from the medial side. As with tibialis anterior tendon, there is little soft tissue covering the tendo Achilles. A sural flap may be utilised based on a sural artery branch of the peroneal artery (Fig. 9.5).

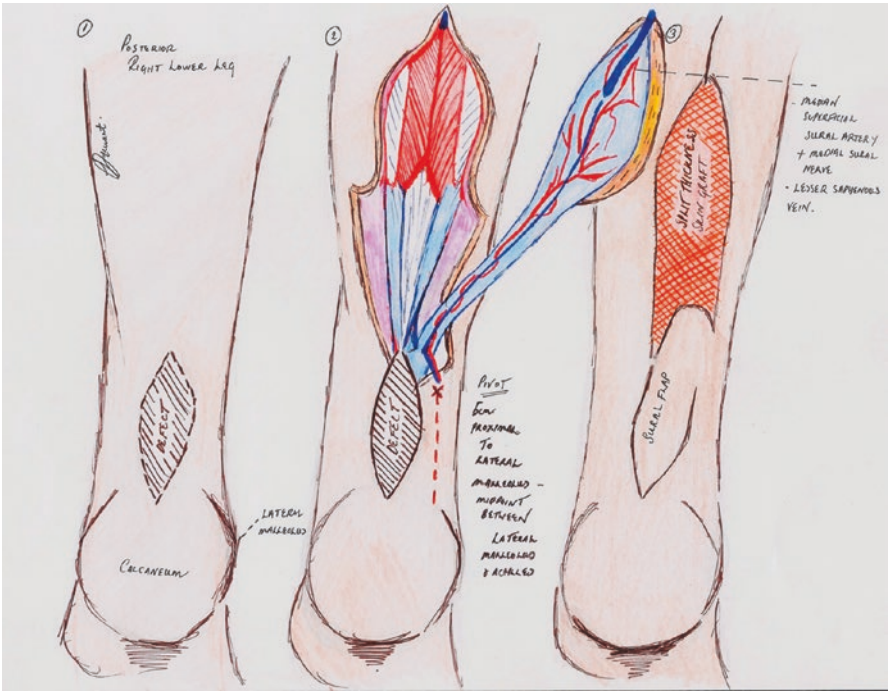

Fig. 9.5 Reverse Flow Sural Artery flap

9.6 Free Flaps

Free flap coverage to the foot is ideally provided by a very thin flap, to aid in accommodating footwear with suitable mechanical properties to resist shear, as it is often weight bearing. In this high risk group, it should also ideally have minimal donor site morbidity. A useful versatile free flap is the anterolateral thigh flap based on a perforator from the descending branch of the lateral femoral circumflex artery. The donor site can be closed primarily and the flap can be large and very thin (Fig. 9.6).

9.7 Should Other Procedures be Considered at the Same Time as Soft Tissue Reconstruction?

The majority of chronic ulcers are on the plantar aspect and is often associated with increased plantar pressures caused by tightness in the posterior chord causing equinus deformity. It has been shown that by lengthening the Achilles this can reduce

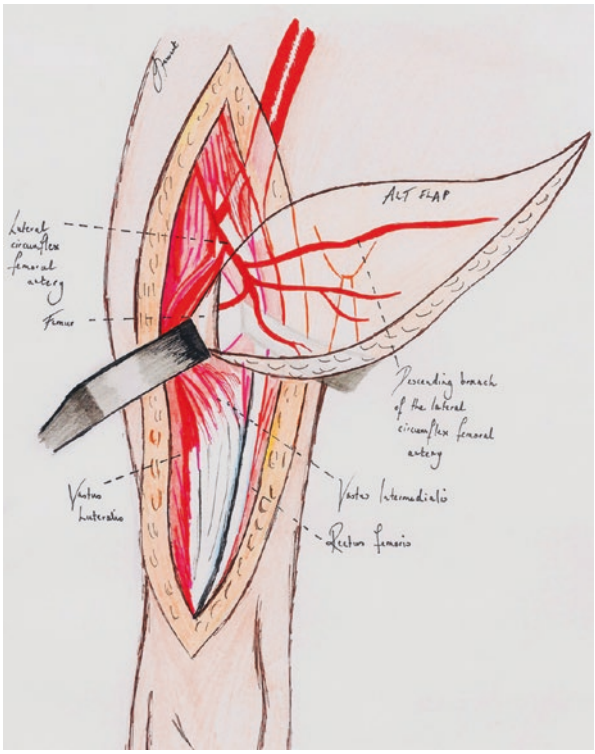

Fig. 9.6 Antero -lateral thigh free flap for large defects

the rate of recurrent ulceration with minimal loss of ankle plantar flexion [4]. This can be done by triple section (Hoke triple hemisection technique) with minimal associated comorbidities [4].

9.8 Alternatives to Split Skin Grafting

With the huge financial and time burden this places on both the patient and the health service, emerging novel techniques are being developed. Epidermal grafts harvested by suction blisters provide autologous keratinocytes with minimal donor site trauma. This can all be performed in the outpatient setting. By means of the application of heat to 40 °C and 200 mmHg of negative pressure, the device creates and harvests either 42 epidermal microdomes to cover an area of 2.5 × 1.75-cm or, with a larger harvester, 128 epidermal microdomes. The blisters, or microdomes, are cleaved and can then be placed on the defect [5].

Autologous, heterogeneous skin cell suspension that includes keratinocytes, and fibroblasts in combination with SSG has also demonstrated promise. A small 1 cm donor skin sample is taken and added to a proteolytic solution. This can then be used to cover up to 80 cm^2 [6].

9.9 Post OP Dressings

9.9.1 SSG Donor Site

An adhesive fabric porous dressing such as Mefix (Molnlycke Healthcare Ltd) is applied straight on to the donor site. This is temporarily padded with gauze and bandaging which is removed after 1 week. The Mefix is left in place and trimmed as it is allowed to separate. The idea of using a dressing that is in direct contact with a raw, painful area may seem counterintuitive but by doing so, shearing forces from dressings moving against the wound are reduced, which dramatically reduces pain in the donor site—a common complaint after split skin-grafting.

9.9.2 SSG Recipient Site

A non stick silicon or paraffin gauze layer is applied followed by gauze padding and bandaging. Alternatively, a non stick layer with negative pressure wound therapy (NPWT) is applied for 1 week. The dressing should then be applied twice weekly although the NPWT should be discontinued after the first week. If the negative pressure dressing fails to maintain a vacuum seal at any time during this week, it is better to remove it altogether and replace with a conventional dressing. Reapplying a negative pressure dressing to a skin graft can shear it off the wound, leading to failure.

9.9.3 Standard Dressings

9.9.3.1 Postoperative Care

A non stick layer of silicon base or paraffin gauze is applied with gauze padding and bandaging and changed after 1 week and then as frequently as needed. This is usually twice a week to begin with, reducing in frequency as the skin graft settles in and becomes drier.

9.9.3.2 Elective Incisional Wounds

For wounds that have been sutured, Micropore tape (3M PLC) is applied in a double layer and left in place for a week. It is removed after 1 week when sutures are removed. The patient can shower after 24 hours with the tape in place. The tape can be dried with clean gauze or tissue paper after showering. It might require replacing for a further week, but provided adequate wound healing is evident, the incision can often be left exposed at this stage [7].

9.9.3.3 Elective Bony Correction

Elective bony correction and subsequent soft tissue closure is associated with higher wound complication rates. Incisional NPWT can be used either with the traditional sponge system or with self contained units with single use power packs. This has been used in multiple high-risk groups including diabetic patients without significant associated dressing complications, and can also be considered in these cases.

9.10 Amputation

Many partial foot amputation methods are available to assist with diabetic limb salvage when appropriate. A below or above knee amputation is often mentioned early on as the level of choice, However this is not without its problems and most patients will benefit from maintaining a functional plantigrade foot for ambulation, whilst minimising the chance for ulcer recurrence.

The benefit of local amputation, is that by removing the underlying bone the local amputation flaps often allow primary closure of the wound. Knowledge of foot and ankle angiosome principles is important because amputation-related flaps generally involve the medial or lateral plantar artery. The flaps should be created in a full thickness fashion without undermining or layered dissection. Bone is resected in such fashion that that cartilage is removed and bony prominences avoided by bevelling or filing the ends. If there is any concern about residual infection then the stump should be left open and a second stage planned. Closure is performed in a full thickness fashion with interrupted sutures, with care being taken to avoid excessive tension on the local soft tissues.

9.11 Conclusion

This chapter has summarised the main principles of soft tissue coverage in the diabetic foot and described a straight forward practical guide to approach limb salvage of such feet.

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Part II
Charcot Foot

Chapter 10
Introduction to the Charcot Foot: Limb Salvage Pathway and Algorithm

Nina L. Petrova, Bauer E. Sumpio, Wegin Tang, and Michael E. Edmonds

10.1 Rationale for Modern Management

It is imperative to diagnose the Charcot foot early. Thus it is important to have a high index of suspicion when a patient presents with a hot swollen foot (Chap. 11). Favourable outcomes depend on proper recognition and early management [1]. The Charcot foot is precipitated by minor trauma such as tripping or twisting the ankle. Rarely, pain may be severe. The Charcot foot may follow injudicious mobilisation after surgery, a period of bed rest or casting. The Charcot foot is defined as acute or active when there is ongoing bone damage and joint disruption. Clinically, this is reflected in erythema and oedema of the foot which is at least 2°C hotter than the contralateral foot. It should be investigated initially with X-ray but if the diagnosis is unclear on X-ray by magnetic resonance imaging (MRI) and single photon emission computed tomography/computed tomography (SPECT/CT) bone scan (Chap. 12).

The aim of management is to convert the Charcot foot from the active into the inactive state. If the diagnosis is made sufficiently early, when the X-ray is normal, deformity can be prevented by casting (Chap. 13). The X-ray can be preserved as normal, the Charcot foot can be completely healed and there will be no progressive changes.

If deformity does occur, then it should either be accommodated in footwear or if there is minimal risk to the skin envelope it should be corrected by surgical reconstruction (Chaps. 14 and 15).

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Recently, patients with longstanding Charcot deformity have presented with established peripheral arterial disease which needs attention before surgical reconstruction (Chap. 28).

10.2 Management of the Active Charcot Foot

10.2.1 Step 1. Casting

The active Charcot foot needs immobilisation and offloading (Fig. 10.1). Patients with no deformity may be casted with a total contact cast or a removable cast. Casting is continued until the foot becomes inactive (Chap. 13). Patients with deformity will need a bespoke cast, namely a total contact cast.

The evidence for pharmacological treatment of the active Charcot foot is limited. Initial experience with a single dose of receptor activator of nuclear factor κβ ligand (RANKL) antibody resulted in a faster fracture resolution in a small cohort of patients [2].

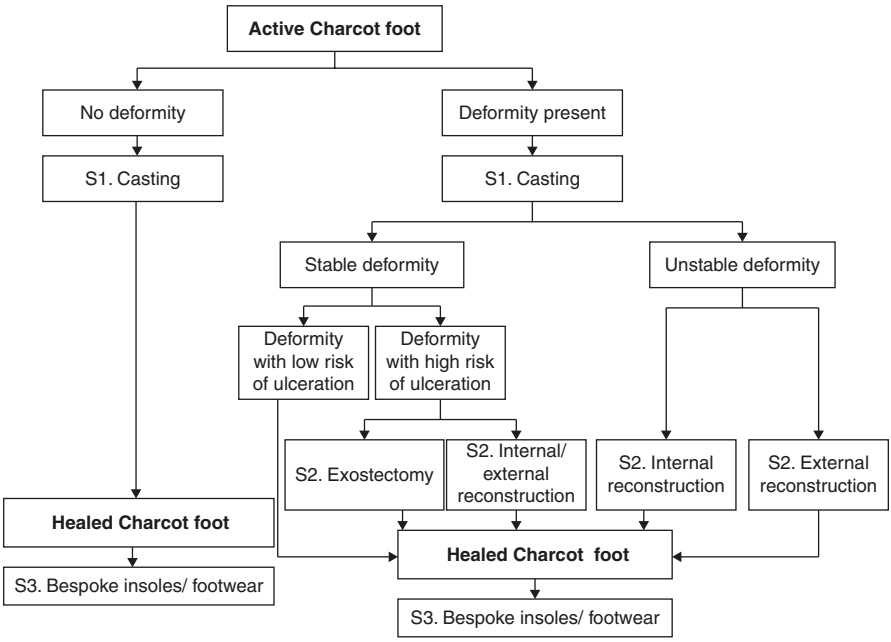

Fig. 10.1 Algorithm for limb salvage pathway of the Charcot foot. The WIfI gradings of wound, ischaemia and infection are explained in Chap. 1. The prefixed numbers (S1–3) refer to the intervention steps described in the text

10.2.2 Step 2. Exostectomy/Surgical Reconstruction

The deformed Charcot foot needs to be assessed as to whether the deformity is stable or unstable (Fig. 10.1). If the deformity is stable, the risk to the skin envelope and that of ulceration needs to be considered. If this is judged as low risk, casting is continued until the Charcot foot becomes inactive. If there is high risk of ulceration, then either exostectomy or surgical reconstruction is carried out (Chaps. 14 and 15).

If the deformity is unstable, then internal or external reconstruction is indicated. Satisfactory outcome for corrective fusion of severe deformities of ankle and hind foot has been attained with an intramedullary nail leading to ulcer healing, limb salvage, deformity correction and return to independent activities of daily living. In a recent series, twenty nine patients (83%) were able to fully weight bear in surgical shoes or custom orthoses at the time of follow-up and six patients were in a bivalved total contact cast, three of them awaiting orthotics [3].

A further recent study has reported clinical outcomes following operative correction of Charcot ankle which comprised single-stage debridement of active infection and ankle arthrodesis with 70% of patients having application of a circular external fixator when infection was present and 30% having retrograde locked intramedullary nailing in the absence of infection [4]. Fifty per cent of patients achieved a favourable (excellent or good) clinical outcome.

In a further series, the rate of successful limb salvage in patients deemed reconstructive candidates was 90% [5]. The presence of a Charcot-related foot wound at presentation increased the likelihood of a major lower extremity amputation. Other risk factors that were associated with major amputation in patients included active infection at presentation, non-union or instability after reconstruction, and a postoperative wound problem.

There are two main pathways to major amputation in the Charcot foot. Firstly, the acute active Charcot foot can lead to bone and joint disruption and deformity with subsequent ulceration and then infection as in Stage 4 of the Simple Staging System (Fig. 1.1, Chap. 1). This can lead to extensive tissue necrosis as in Stage 5, and if this is overwhelming, major amputation is inevitable. Secondly, an unstable hind foot and ankle can make walking impossible and if the foot cannot be reconstructed, mobility can only be restored by a major amputation and the fitting of a prosthesis.

Thus, if the foot is unreconstructible or if there is overwhelming infection secondary to ulceration, major amputation may be necessary and techniques are discussed in Chap. 16.

10.2.3 Step 3. Bespoke Insoles/Footwear

The healed inactive Charcot foot is taken out of casting and rehabilitated with bespoke insoles and footwear ((Fig. 10.1) Chap. 13).

10.3 Conclusion

It is crucial to make an early diagnosis of the Charcot foot when the X-ray is still normal utilising either MRI or SPECT/CT. Prompt immobilisation can convert the acute active Charcot foot into a inactive foot and prevent deformity. If deformity occurs or already has developed at presentation, it must be either accommodated in bespoke footwear or the foot should undergo internal or external reconstruction to correct the deformity.

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Chapter 11
Charcot Foot: Presentation

Nina L. Petrova

11.1 Introduction

Charcot neuropathic osteoarthropathy (CN) or Charcot foot is a severe foot complication of diabetes in which there is considerable bone and joint destruction. It bears the name of the French neurologist, Jean Martin Charcot, who reported the condition in tabes dorsalis in 1883. Later, Charcot joints have been described in other neuropathies, including leprosy, congenital sensory neuropathy, familial amyloid neuropathy, alcoholic neuropathy and more recently in human immunodeficiency virus (HIV) -induced neuropathy [1–4].

The first description of CN in diabetes was reported by Jordan in 1939. Although, the Charcot foot has been considered initially as a rare complication of diabetes [5], in the last 40 years, there has been a marked increase in the reported cohorts of cases. It is now largely accepted that in the twenty-first century, diabetes is the leading cause for CN. Moreover, with the predicted global increase in the prevalence of diabetes (http://www.idf.org/sites/default/files/Atlas-poster-2014_EN.pdf), the burden of neuropathy and its related adverse complications including CN is also expected to rise (http://www.idf.org/diabetesatlas/5e/mortality).

In diabetes, the Charcot foot is characterised by varying degrees of bone and joint disorganisation, secondary to underlying peripheral neuropathy and trauma leading to fracture, bone fragmentation and ultimately foot deformity. It commonly presents in the midfoot but it may also occur in the fore-foot and hind foot. There may be a history of minor trauma such as tripping, falling over an object, twisting the ankle or walking over rough surfaces such as cobbles.

The acute presentation is characterised by unilateral erythema and swelling (Fig. 11.1). The foot is usually at least 2 °C hotter than the contralateral foot as measured with a skin thermometer. It is very important to have a high index of

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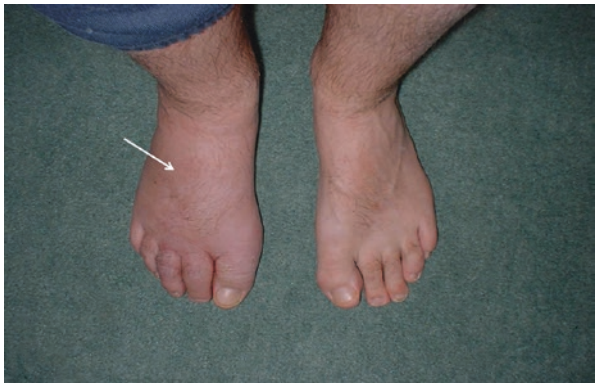

Fig. 11.1 Swelling of the right foot which was also warmer compared with the left foot

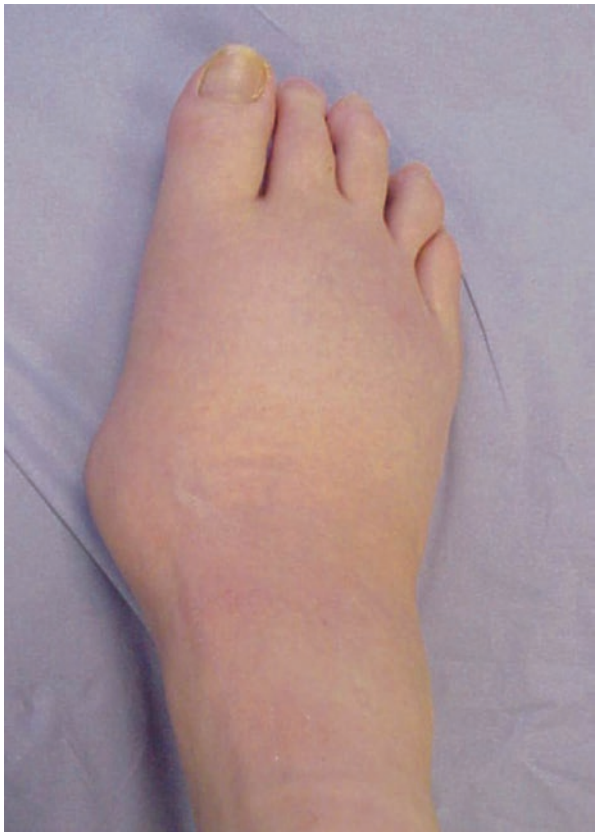

Fig. 11.2 Medial convexity deformity

suspicion when a patient presents with a hot swollen foot. In the late presentation, deformity can present in the forefoot, mid-foot or hind foot and ankle. The mid-foot is the commonest site of presentation of CN and is recognised clinically by the medial convexity (Fig. 11.2) and rocker bottom deformity (Fig. 11.3). The rocker

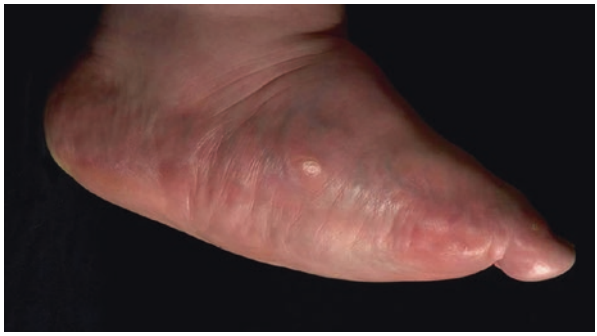

Fig. 11.3 Rocker bottom deformity

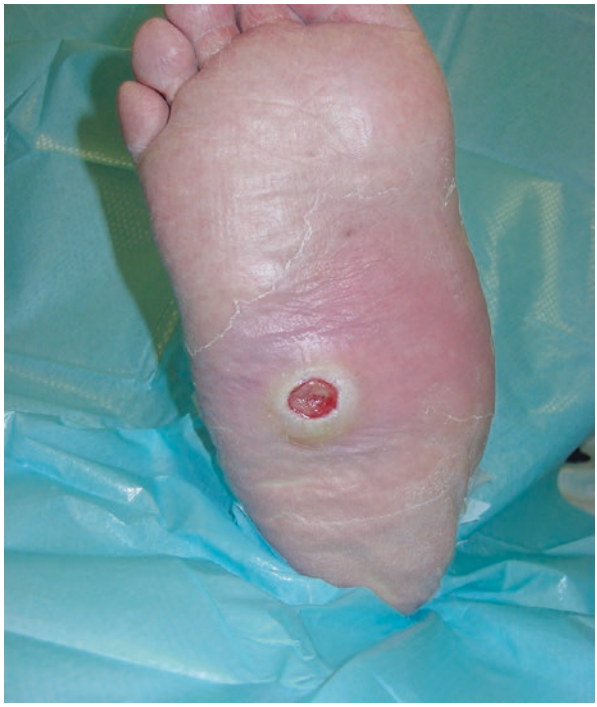

Fig. 11.4 Rocker bottom deformity with plantar ulceration

bottom deformity develops when there is disintegration and displacement of the cuneiforms or the proximal tarsal bones, resulting in collapse of the mid-foot. Rocker bottom deformity is often associated with plantar ulceration (Fig. 11.4), which can become infected and if not promptly managed, it can lead to an amputation [6]. Thus, it is important to be aware of the initial presentation of the Charcot foot in diabetes so as to recognise the condition early, institute timely management and prevent adverse outcomes.

This chapter will discuss the incidence and prevalence of Charcot foot in diabetes, predisposition and common risk factors with a specific reference to their relevance to type 1 and type 2 diabetes.

11.2 Incidence and Prevalence

The true prevalence and incidence of CN in diabetes are not fully known. The prevalence in diabetes varies from 0.1% to 8% and there is a disparity between centres and countries. For example, in the United States, a recent analysis of the Department of Veterans Affairs inpatient and outpatient administrative datasets, reported that in 2003, a new diagnosis of Charcot foot was noted in 0.12% of all cases with type 2 diabetes [7], whereas an earlier report from Denmark denoted an annual incidence of 0.3% [8]. Interestingly, a retrospective analysis of foot and ankle radiographs indicated evidence of radiological changes associated with Charcot foot in up to 10% of patients with diabetes and neuropathy. With regard to the incidence of this condition, early studies reported one case per 680 people with diabetes developing Charcot foot [5], whereas in a further series, there was one case per 333 people with diabetes [8].

Some of these regional differences could be related to a lack of consistency with the nomenclature of this condition [9], which has now been standardised to Charcot neuropathic osteoarthropathy or Charcot foot at a recent Task Force meeting [10]. A further explanation could be the lack of consistency in using established international disease codes. A recent study in Italy showed that three different international disease codes were used to record newly diagnosed cases of Charcot foot [11]. Codes were selected according to the original clinic to which the patient presented [11]. A further retrospective analysis in Ireland that recorded which healthcare professional made the initial diagnosis of CN reported that 35% of cases were diagnosed by an endocrinologist, 20% of cases by a podiatrist, 20% by an orthopaedic surgeon and 15% by a vascular surgeon [12]. In the remaining 10%, it was not identified who diagnosed the condition [12]. The prevalence of active Charcot disease of the foot during a single month was assessed at seven secondary care services in the East Midlands region of England. A total of 90 cases were identified, representing 4.3 per 10,000 of the 205,033 total diabetes population of the region [13].

Thus there is a need for large population based studies using consistent nomenclature and coding system to confirm the true incidence and prevalence of this condition in people with diabetes.

11.3 Predisposition

There is a notable increase in the awareness of this complication in people with diabetes. Recent reports, published from various parts of the world, have described typical contributing factors together with some region-specific features (Table 11.1) [12, 14–17]. This indicates that the Charcot foot is more common than previously thought.

The Charcot foot occurs in both type 1 and type 2 diabetes [8, 18]. Patients present with a varying degree of microvascular (nephropathy, neuropathy and retinopathy) and macrovascular complications (coronary artery disease, peripheral arterial disease and stroke) (Table 11.1). A relative preponderance of type 1 diabetes has been suggested [18], and a recent report indicated that the odds ratio for a patient with type 1 diabetes to develop CN is 3.9 times greater than the odds ratio for a patient with type 2 diabetes [19]. Moreover, some contributing factors are more pronounced in type 1 compared to type 2 diabetes or vice versa [18].

Table 11.1 A list of recent reports including cohorts of patients presenting with CN in various parts of the world: common and region-specific features

Study	Malaysia (Fauzi et al.) [14]	Brazil (Nóbrega et al.) [16]	Jordan (Al Mousa M et al.) [17]	United Kingdom (Game FL et al.) [15]	Ireland (O'Loughlin A et al.) [12]
Study design	Retrospective hospital based case-control study in type 2 diabetes	Matched case-control study in individuals with type 2 diabetes	Case-control study	Web-based survey of new cases of acute Charcot foot at 76 different centers in the UK and Ireland	Case finding by searching the SYNGO radiology information system, Hospital Inpatient Enquiry database of hospital inpatient discharges and combined list from podiatry, endocrinology, vascular surgery and orthopaedic clinics
Study period	June 2010–June 2011	February 2000 September 2012	1 November 2009–1 February 2010	June 2005 to February 2007 (20 months)	2006 to 2012
Total sample size	100 48 Charcot cases/52 diabetic patients	235 47 Charcot cases/188 controls	112 (20 Charcot cases/92 controls)		
Charcot foot patients identified	48	47	20	288	40
Age at diagnosis, years (mean ± SD)	50.2 ± 7.1	53.6 ± 10.2	58.5 ± 8.9	57.0 ± 11.3	58 ± 10
Males (%)	42%	68.1%	45%	71.2%	68%

(continued)

Table 11.1 (continued)

Study	Malaysia (Fauzi et al.) [14]	Brazil (Nóbrega et al.) [16]	Jordan (Al Mousa M et al.) [17]	United Kingdom (Game FL et al.) [15]	Ireland (O'Loughlin A et al.) [12]
Type 2 diabetes (%)	100%	100%		70%	73%
Duration of Diabetes (years)	89% (>10 years)	12.1 ± 6.8	23 (mean)		15 ± 9
BMI kg/m^2	83% (>23 kg/m^2)	28.5 ± 6.1	33.5 ± 8.8		
Neuropathy	89% (mild to severe neuropathy symptom score)	100%	95% (abnormal monofilament test)		100%
Retinopathy	83%		75%		50%
Nephropathy	63%				43%
Peripheral arterial disease		6.7%			2%
Coronary artery disease					18%
Cerebrovascular accident					5%
Hypertension		46.8%	85%		
HbA1c					65 ± 16 mmol/mol (on diagnosis)

11.3.1 Demographic Characteristics

There are differences in the demographic features of patients with type 1 and type 2 diabetes, developing this condition [18]. Patients with type 1 diabetes and Charcot foot are significantly younger compared with patients with type 2 diabetes. In type 1 diabetes the reported peak age of presentation of CN is the third and fourth decade, whereas in type 2 diabetes, it is the sixth and seventh decade.

Patients with type 1 diabetes have longer duration of diabetes than patients with type 2 diabetes. In the latter, diabetes and the Charcot foot can be diagnosed at the same time.

We have noted a classical Charcot foot presentation in subjects who have subsequently developed diabetes. More recently, CN has been linked with prediabetes [20]. Individuals with prediabetes especially those who are susceptible to trauma and have early evidence of nerve damage, may develop Charcot foot more commonly than expected [21].

Thus it is important to be aware of these differences in the presentation of patients with type 1 and type 2 diabetes (and prediabetes) developing Charcot joints for improved recognition of this complication.

11.3.2 Impaired Glycaemic Control

Longstanding impaired glycaemic control has been suggested to predispose to Charcot foot, although evidence to support this association is controversial. A significant link between raised haemoglobin-A1c (HbA1c) of 7% or more and increased incidence of CN has been recently reported [7]. This is in contrast with a further large 15 year retrospective study which indicated that the cumulative glycaemic burden was associated with the development of diabetic foot ulceration but not with CN [22]. Nevertheless, poorer glycaemic control increases the risk of diabetic neuropathy, which is one of the main predisposing factors to CN.

11.3.3 Elevated Body Mass Index and Obesity

Elevated body mass index (BMI) and obesity have been suggested as possible contributing factors. Subjects with type 2 diabetes and both obesity and neuropathy were 21 times more likely to develop CN compared with persons without obesity or peripheral neuropathy [7]. The association between obesity and Charcot foot has been predominantly noted in subjects with type 2 diabetes, but this has not been confirmed in mixed cohorts of type 1 and type 2 diabetes [19]. Thus BMI and obesity in conjunction with neuropathy (and increased mechanical forces) seem more common in type 2 diabetes and Charcot foot.

11.3.4 Diabetic Neuropathy

Peripheral neuropathy links all conditions that present with Charcot joints. It is also a well-recognised contributing factor to Charcot foot in diabetes. Despite the unifying importance of this factor, patients with Charcot foot and diabetes present with varying degrees of nerve damage [18]. Recent clinical observations indicate that the number of patients with type 1 diabetes developing Charcot foot in their early twenties is rising. These patients have predominantly small fibre neuropathy (abnormal threshold to hot and cold stimuli) but preserved large fibre function (i.e. they have normal monofilament tests and normal or near normal vibration perception threshold), [23]. This is in contrast to patients with type 2 diabetes in whom a combination of both small and large fibre neuropathy is usually present [18]. In the subset of patients with type 1 diabetes, their young age, together with the lack of classical signs of peripheral nerve damage contribute to a frequent misdiagnosis. This can often result in a delayed referral to a specialised treatment centre only after a significant bone and joint destruction and typical Charcot deformity have been acquired. Thus it is important to consider CN in people with type 1 diabetes and history of trauma even in cases in whom standard nerve function tests are within a normal range.

11.3.5 Trauma

Trauma to the foot is a frequent forerunner of CN and often predicts the site of involvement [24]. In people with diabetic neuropathy, isolated injury to the foot or repetitive mechanical loading due to limited joint mobility and increased plantar pressures [25, 26], can lead to stress bone injury and ultimately to CN [27]. Hypoglycaemia, impaired vision and abnormal gait increase the risk of falls in people with diabetes [28]. In a series of patients, metatarsal fractures were strongly associated with the subsequent development of CN [29]. Although the role of elevated body mass index as a significant predictor of the acute Charcot foot is not fully established [7, 19], body weight is positively associated with increased mechanical loading of the foot [30].

Due to the underlying neuropathy, trauma may often remain unnoticed by the patient. Indeed, in a recent cohort of 288 cases of CN, only 36% of patients recollected a history of trauma prior the development of the Charcot foot [15]. Moreover, pain and discomfort are rarely reported by the patients [31].

Overall unawareness of trauma and lack of symptoms in the neuropathic foot account for both delayed presentation and frequent misdiagnosis of the condition. Thus, in a patient presenting with a red hot swollen foot, detailed history to depict precipitating trauma is of paramount importance.

11.3.6 Diabetic Foot Ulceration and CN

The link between foot ulceration and CN is well established. According to different studies, a history of foot ulceration has been noted in up to 80% of cases [14, 17, 32]. The adjusted odds ratio for a patient with a history of diabetic foot ulceration to develop Charcot foot is 4.84 (CI 1.62–14.51) [16]. Moreover, patients with established Charcot deformity have a four-fold risk of ulceration compared with the overall risk of foot ulceration in diabetic feet [33]. A history of previous foot ulceration, foot surgery or a combination of both has been reported in up to 70% of the patients [15]. Although the temporal relationship between surgery and subsequent development of a Charcot foot has not been fully investigated, a recent audit of Charcot foot disease in the UK (CDUK) reported that 12% of patients had had some surgical intervention to the index limb in the preceding 6 months before case registration. Furthermore, this web-based survey reported that active foot ulceration was noted in 35% of the cases at registration and in 7% of these, it was associated with an osteomyelitis [15].

Thus diabetic foot ulceration, osteomyelitis and foot surgery are well recognised drivers to CN and should be promptly managed.

11.3.7 Simultaneous Pancreas and Kidney (SPK) Transplantation

Another group at risk are patients with type 1 diabetes who have undergone simultaneous pancreas and kidney (SPK) transplantation. A diagnosis of CN was made in 4.6% of SPK transplant recipients during the first year post-transplantation [34].

Although the true prevalence of CN in post-transplant patients with diabetes is unknown, the link between transplantation and Charcot foot in diabetes is well established [35].

Risk factors that contribute to the development of Charcot foot in the SPK transplant patient include higher pre-transplant values of HbA1c, more frequent use of cyclosporine and azathioprine, and higher cumulative corticosteroid use [34, 36].

Moreover, patients with SPK transplant and Charcot foot have significantly higher mortality, greater graft failure rates and acute rejection rates [36]. Recently, Charcot foot has been less frequently noted in patients with SPK transplantation probably because of the transition to tacrolimus-based immunosuppressive therapy and lower doses of corticosteroids [36, 37].

In post-transplantation, patients often lack classical clinical symptoms (unilateral inflammation and heat), due to immunosuppressive therapy [38]. Clinicians should be aware of this modified clinical phenotype of CN to avoid a delay in the diagnosis and treatment [38].

11.4 Conclusion

This chapter acknowledges the improved global recognition of CN in diabetes, summarises the impact of common risk factors and enhances some specific features more commonly associated with either type 1 or type 2 diabetes.

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Chapter 12
Charcot Foot: Investigations

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12.1 Introduction

Charcot neuropathic osteoarthropathy (CN) is a bone and joint complication of diabetes which poses a significant challenge in clinical practice. Trauma to the neuropathic foot triggers an excessive inflammation and increased osteoclastic activity, which rapidly progresses to fracture, bone fragmentation and joint destruction, and ultimately leads to severe foot deformity i.e. the Charcot foot [1]. A high index of suspicion is needed to make the earliest diagnosis and institute prompt management.

This chapter will discuss our clinical approach in patients presenting with a suspected active Charcot foot. It will summarise the main findings from the medical history, clinical assessment, biochemical tests and imaging studies, frequently used in the investigation of this condition.

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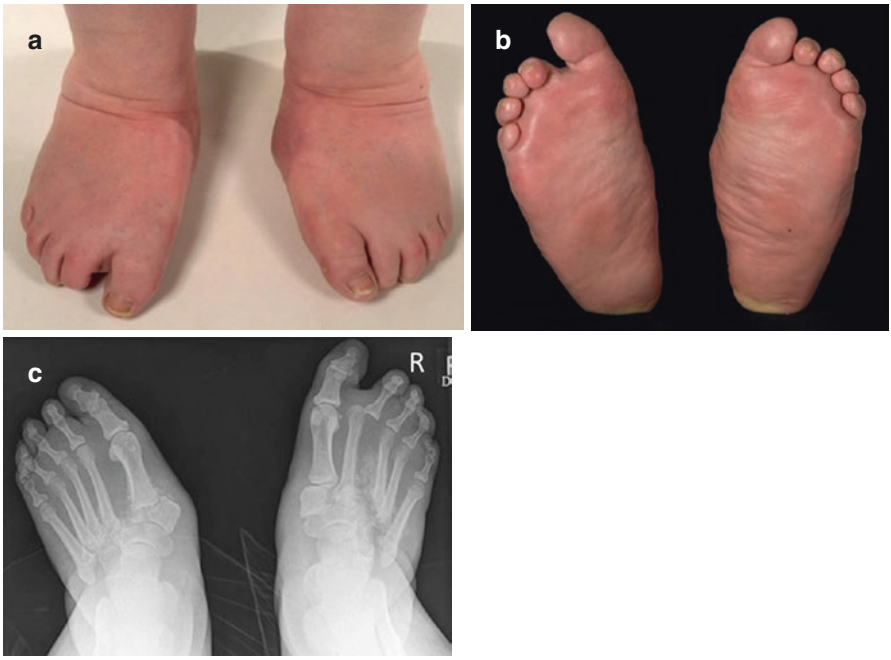

Fig. 12.1 (**a**) A patient presenting with bilateral acute red hot swollen Charcot feet (**b**) showing rocker-bottom deformity of each foot (**c**) corresponding dorsoplantar radiograph showing bilateral metatarsal-tarsal fracture dislocation and right second metatarsal-phalangeal dislocation

12.2 Presentation

The active Charcot foot presents with classical features of inflammation, including redness, swelling, heat, dull ache/discomfort and loss of function. It is most commonly unilateral and a red hot swollen foot in people with diabetes and peripheral neuropathy should be considered and managed as a Charcot foot until proven otherwise. Simultaneous bilateral involvement is rare and is challenging both for diagnosis and management (Fig. 12.1).

The foot is the most common presentation and the anatomic patterns of involvement defined by Sanders and Frykberg's classification include the metatarsal-phalangeal joints (pattern I), metatarsal-tarsal joints (pattern II), tarsal joints (pattern III), ankle joint (pattern IV) and posterior process of the calcaneum (pattern V) [2].

12.3 Medical History

A detailed medical history is essential for prompt diagnosis and timely management. Although trauma to the foot is a well-recognized forerunner of the Charcot foot, in many cases it may remain unnoticed by the patient due to underlying

neuropathy. Some probing questions may help the patient to recollect recent events which may have initiated the process of bone and joint destruction. In addition to trauma, recent surgical debridement, revascularisation or mobilisation after prolonged bed rest can also predispose to CN.

Unilateral foot swelling is frequently reported by patients. It is more prominent after weight-bearing and may subside partially after bed-rest. It is important to enquire about a history of deep vein thrombosis as the latter should be ruled out.

In addition to swelling, pain is another classical symptom, Patients report ache or discomfort of the foot which is different from their usual "throbbing nerve pain and tingling sensation". However, in a subset of patients, pain may be absent, despite the underlying extensive bone and joint destruction, and this often can lead to a delayed presentation.

A past history of CN either in the index foot or in the opposite foot makes a new Charcot episode likely. Redness and swelling of the established Charcot foot may indicate either a relapse of the previous bone and joint damage or a further episode with a new pattern of involvement. Contralateral involvement is common and it may occur within 2 years of the initial presentation of the index foot. Moreover, bilateral Charcot feet have been reported in almost 40% of patients. Thus in a person with diabetes and past history of CN (either of the index foot or of the contralateral foot), a red hot swollen foot is a Charcot foot until proven otherwise.

12.4 Clinical Assessment

Bedside tests should include assessment of neuropathy (vibration perception threshold (VPT) and monofilaments), assessment of peripheral blood supply and measurement of skin foot temperature with infrared thermometry.

12.4.1 Peripheral Neuropathy

Standard tests to detect nerve damage demonstrate a variable degree of impairment in patients with CN. Numbness of the lower extremity is one of the most frequently reported symptoms. Patients with Charcot foot demonstrate impaired sensation to hot and cold stimuli (small fibre neuropathy) and also a reduced VPT (large fibre neuropathy) when compared to controls [3]. Abnormal VPT to 128 cycle/s tuning fork is common and in one series, it was observed in 93% of patients with CN [4].

Although it is widely accepted that patients with CN have profound neuropathy, we have noted a group of patients with type 1 diabetes who present with impaired sensation to hot and cold stimuli but have preserved VPT [5]. These patients have longstanding diabetes and because of their young age and "lack of typical neuropathy", the development of CN is often overlooked. Rarely, patients suspected of developing CN may have no signs of neuropathy on clinical examination but this should not prevent the diagnosis of active CN.

12.4.2 Peripheral Blood Supply

It is generally accepted that CN develops in a well perfused foot with palpable bounding peripheral pulses. Foot pulses may not be readily palpated in patients with a widespread swelling and these should be referred for vascular assessment. In the presence of heavily calcified arteries, measurement of ankle/brachial pressure indices is unreliable. However, blood flow assessment which shows a Doppler three-phase blood flow signal is indicative of preserved blood supply.

Recently, longstanding CN has been linked with the later development of peripheral arterial disease, and, one should be aware of this unusual presentation especially if surgery is planned [6] (Chaps. 14, 15 and 28).

12.4.3 Skin Foot Temperature

The Charcot foot presents as a hot foot which is significantly warmer compared with the contralateral foot. The heat can be detected with the back of the hand and measured with infrared thermometry. A variety of hand-held thermometers has been used in clinical practice and the skin temperatures at corresponding sites between the affected and contralateral foot are recorded for the fore-foot, midfoot and hind foot.

It is widely accepted that the Charcot foot is at least 2 degrees Celsius warmer compared with the contralateral foot, although in some patients with active Charcot foot the temperature difference between feet can be lower. We recommend that in a patient with clinically suspected Charcot foot, it is imperative to carry out imaging studies to look for bone damage even in cases presenting with a temperature difference of less than 2 degrees Celsius.

12.4.4 Blood Tests

The diagnosis of CN is primarily based on clinical findings and at present, there are no established disease markers. In the active Charcot foot, there is dissociation between the presence of local signs of inflammation, as demonstrated by increased skin temperature in the Charcot foot, and the lack of systemic inflammatory response, with a normal to slight increase in serum C-reactive protein levels (CRP), normal white cell count, and mild increase in erythrocyte sedimentation rate [7]. In contrast, the concentration of C-reactive protein levels and the erythrocyte sedimentation rate are significantly raised in diabetic foot infection. Recently, the usefulness of procalcitonin, to distinguish between diabetic foot osteomyelitis and diabetic foot infection has been reported, although the role of this marker in CN is not fully known [8].

In addition to inflammatory markers, bone turnover markers have been also studied in the pathological osteolysis which characterises both CN and osteomyelitis.

Measurement of the serum concentration of bone resorption and formation markers has been limited to research studies and the reported changes were non-specific for either condition [9, 10]. Therefore, bone turnover markers are not recommended for routine clinical use.

12.4.5 Imaging Studies

Imaging is central to the diagnosis of CN. Foot and ankle radiographs are the first line investigation. A patient with a suspected Charcot foot should be referred for weight-bearing foot and ankle radiographs (preferably straight, oblique and lateral foot X-rays and straight and lateral ankle views). These projections allow full assessment of the foot and ankle anatomy.

The radiological evolution of the Charcot foot was documented by Eichenholtz in 1966. In his monograph "Charcot joints" he described a cohort of 68 patients in whom Charcot joints were associated with diabetes (n = 12), syphilis (n = 34), alcoholism (n = 4), syringomyelia (n = 3) and leprosy (n = 1), [11]. Based on the X-rays, he summarised the changes into three stages: (1) development, (2) coalescence and (3) reconstruction and reconstitution (Table 12.1).

Recent advances in imaging modalities have enabled the detection of initial signs of inflammation and underlying bone damage before overt bone and joint destruction has occurred. When patients present early in the acute active phase, the X-ray may be normal. Further investigations are then necessary. Initially a ^{99m}technetium methylene diphosphonate (^{99m}TcMDP) bone scan can detect early evidence of bone damage by demonstrating focal areas of increased uptake of radionuclide. Recently single-photon emission computed tomography/computed tomography (SPECT/CT) can be carried out in addition to the conventional bone scan (Fig. 12.2a–g).

Table 12.1 Eichenholtz's description of the natural course of the Charcot joint (radiological features and foot presentation)

Stages	Radiological features	Foot presentation (appearance)
Stage 1 Development	Debris Fragmentation Disruption Dislocations	Redness Swelling Warmth Bounding pulses
Stage 2 Coalescence	Sclerosis Absorption of fine debris Fusion of most large fragments	No redness Reduced swelling No warmth
Stage 3 Reconstruction and reconstitution	Lessened sclerosis Rounding of major fragments Attempts at reformation of joint architecture	Ultimate foot deformity Rocker bottom deformity Medial convexity Ankle subluxation

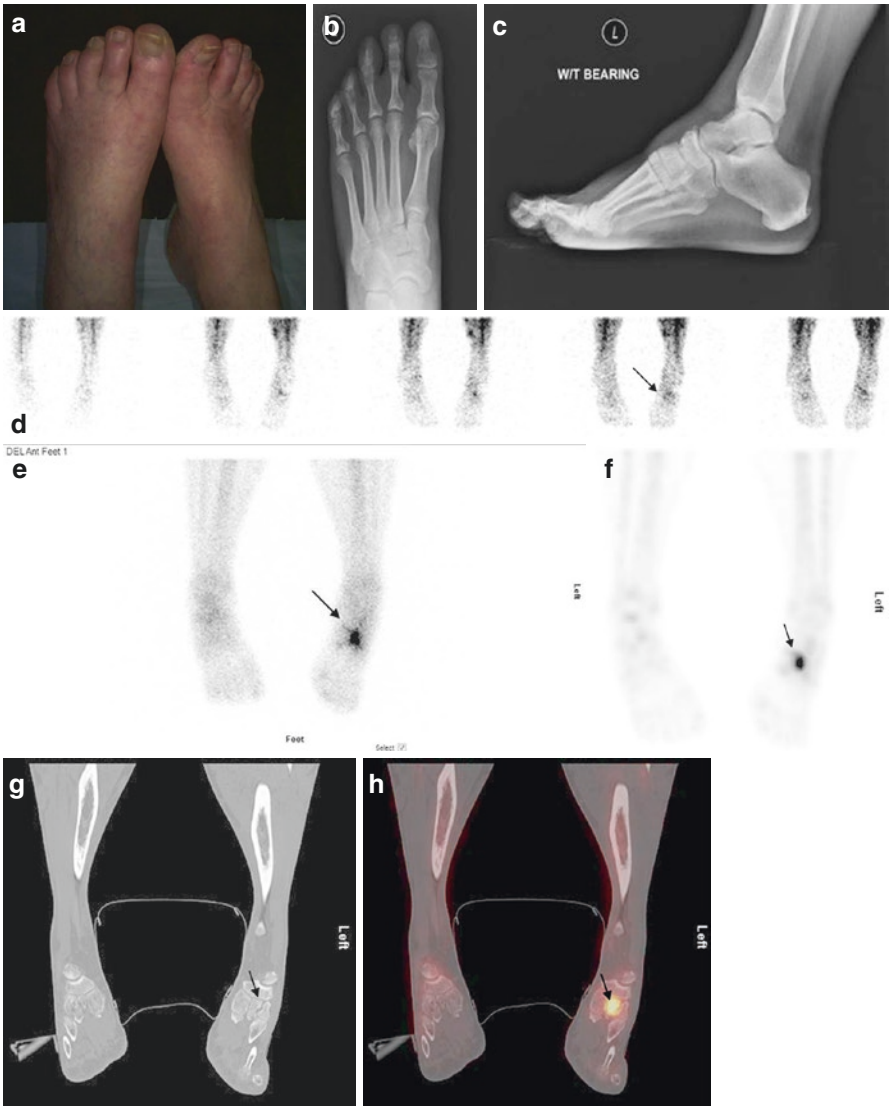

Fig. 12.2 Left foot stage 0 Charcot foot (X-ray negative, SPECT/CT positive). (**a**) A patient presented with pain and swelling of left foot following an episode of prolonged walking. The temperature difference between feet was less than 1 °C and C-reactive protein was 2 mg/L. (**b**) dorsoplantar radiograph normal (**c**) lateral foot radiograph normal. (**d**) The patient was referred for a SPECT/CT bone scan, which showed increased blood flow to the left midfoot (arrow), the blood flow to the right foot was normal; (**e**) on delayed imaging of bone scan, there is minor increase in the uptake in the midfoot (arrow) (**f**) SPECT shows increased uptake in the middle cuneiform (arrow) (**g**) CT shows lucency in the middle cuneiform but no definite fracture (arrow), (**h**) fusion of CT image and SPECT shows increased uptake localised to middle cuneiform (arrow)

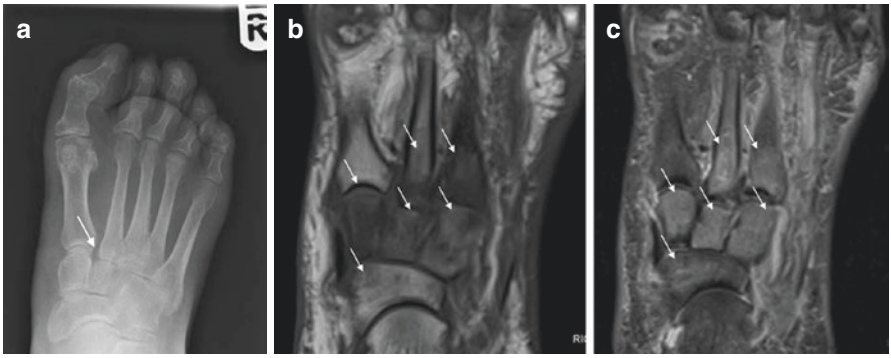

Fig. 12.3 Right stage 0 Charcot foot (X-ray negative, MRI positive). A patient presented with a painful red swollen right foot 2 °C warmer compared with the contralateral foot. C-reactive protein was 9 mg/L. (**a**) dorsoplantar radiograph shows mid-foot soft tissue swelling with only a very subtle step at the medial margin of the second metatarsal-tarsal joint (arrow) (**b**) axial T1 and (**c**) STIR MR imaging show prominent bone marrow oedema (reduced signal on T1 and increased signal on STIR) within the proximal diaphyses of the second and third metatarsals, the cuneiforms, and the navicular (arrows)

In a recent Charcot Task Force document, magnetic resonance imaging (MRI) of the foot has been recommended in the diagnosis of a stage 0 Charcot foot (X-ray negative stage). The MRI features of CN include soft tissue swelling, bone marrow oedema, microfractures and bone bruising (Fig. 12.3a–c).

This X-ray negative, MRI positive CN presentation is recognised as stage 0 (grade 0) Charcot foot in the modified Eichenholtz classification proposed by Chantelau. The acute active CN is divided into a low severity stage (grade 0) or high severity stage (grade 1) according to the absence or presence of cortical fracture [11]. Grade 0 is characterised by mild inflammation, soft tissue oedema, normal X-ray but abnormal MRI scan showing evidence of microfracture, bone marrow oedema and bone bruising. Grade 1 is characterised by severe inflammation, soft tissue oedema, abnormal X-ray with macrofractures, abnormal MRI scan showing evidence of macrofracture, bone marrow oedema and bone bruising [11]. A summary of the characteristics of grade 0 and grade 1 is schematically presented (Fig. 12.4).

Close communication between the physician and the radiology/nuclear medicine department is critical to enable optimal protocolling of complex imaging studies as well as appropriate, clinically relevant interpretation of imaging findings. Referrals should always include details of the presence and precise location of any foot ulceration, and details of previous surgical interventions as well as all other relevant clinical data. Any current and relevant previous imaging, including conventional radiography should also be available to the reporting radiologist/nuclear medicine specialist.

Patients who are suspected of having CN and are awaiting SPECT/CT bone scan or MRI should be treated as if the diagnosis has been confirmed (Fig. 12.5). Several reports have now shown that prompt offloading with a below knee cast can arrest the arthropathy, preserve the foot shape, and maintain the X-ray normal [12–15].

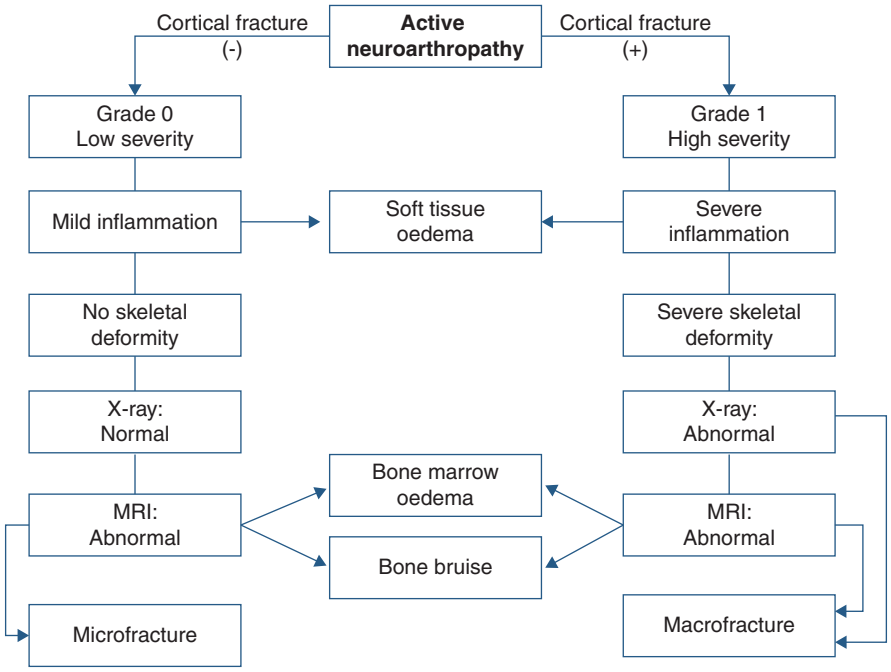

Fig. 12.4 Categories of active Charcot neuroarthropathy based on MRI scan

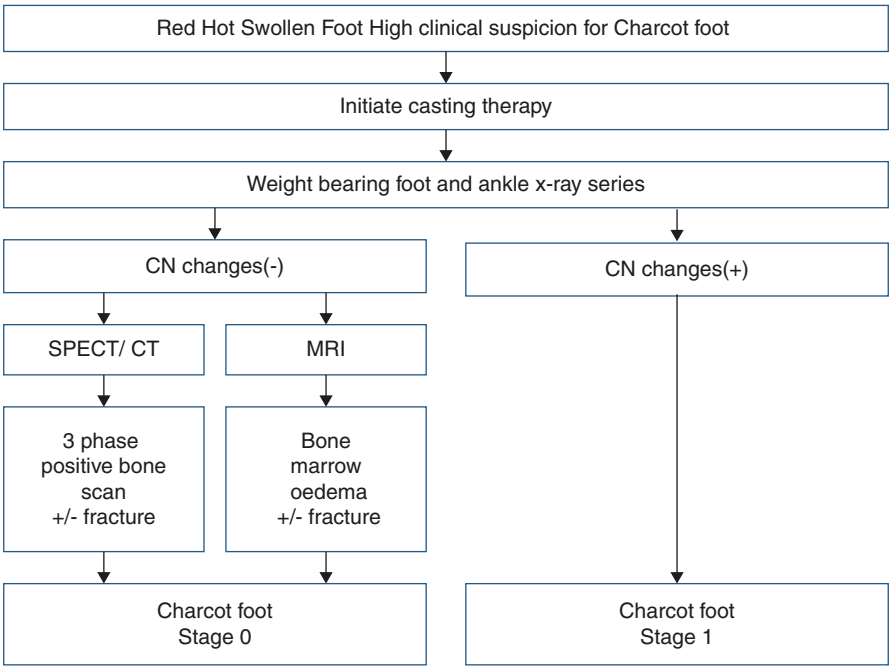

Fig. 12.5 Clinical practice recommendation in a patient with a suspected Charcot foot

If CN is not recognised and managed at this stage, extensive irreversible bone and joint destruction can occur [13] associated with severe foot deformity, leading to ulceration and possible amputation [15].

12.5 Conclusion

A high clinical suspicion is needed to recognise the early presentation of CN in diabetes. Interdisciplinary approach in the diagnosis and management are key for an improved outcome of this devastating complication of diabetes.

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Chapter 13
Conservative Treatment of Charcot Neuroarthropathy

Raju Ahluwalia

13.1 Introduction

Charcot neuropathic osteoarthropathy (CN) occurs in the background of a peripheral neuropathy with diabetic neuropathy being the commonest etiology. The combination of trauma, sensory-motor somatic neuropathy, autonomic neuropathy and metabolic abnormalities of bone results in an acute localized inflammatory condition. This leads to a clinically symptomatic hot swollen foot which if not treated may lead to varying degrees and patterns of bone destruction, subluxation, dislocation, and deformity. Radiographic changes of CN are typically delayed and have low sensitivity [1].

Key points of conservative treatment are to:

1. Prevent the foot progressing to deformity.
2. Allow the Charcot process to resolve and reduce time to resolution.
3. Prevent a recurrence or a further episode of CN.

13.2 Conservative Treatment of the Diabetic Charcot Foot

The current best practice in managing CN is immobilization, offloading and contact pressure reduction on the traumatized foot. Such offloading is needed to protect the foot from physical forces that may cause further bone and joint destruction. Otherwise the loss of pain sensation from the neuropathy would allow ongoing uninterrupted ambulation and further injury. This reduction in contact pressure

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will relieve ongoing stress and trauma, prevent deformity and lead to the healing stages of CN [2]. The current gold standard for offloading is thus achieved by casting to keep the foot plantigrade which can then allow weight-bearing in a shoe or brace [3].

13.3 Casting Therapy

The process of casting increases the total surface area of contact over the foot evenly distributing vertical forces of ambulation and thereby minimizing peak contact pressure distribution areas on the foot. Total contact casting (TCC) was introduced in 1930s, by the orthopaedist Milroy Paul in Sri Lanka for treating non-healing ulcers in Hansen's Disease. Paul Brand used the technique for similar patients as well as for patients with diabetes and brought the technique to the United States.

TCC is now the most commonly described technique of offloading and leads to a number of biomechanical changes that prevent further stress and trauma on the foot as outlined below:

- It leads to a shortening of his/her stride length, which in turn decreases gait velocity and therefore reduces vertical loading forces on the foot [4].
- The saggital plane motion at the ankle is eliminated, thereby removing the propulsive phase of gait, resulting in the eradication of vertical loading forces at the metatarsal heads and thus reducing mechanical trauma [5].

The TCC has been shown to reduce plantar pressures by 32%, 63%, and 69% on the fifth, fourth, and first metatarsal heads, respectively, 65% on the great toe and 45% on the heel [6]. This reduction in pressure reduces oedema significantly and limits bone and joint destruction [7]. Resolution of bone marrow oedema and healing of microfractures have been reported after casting treatment [8].

13.4 Practicalities of Applying a TCC

The TCC is applied in such a way to make intimate contact with the exact contour of the foot and hence is called the "total contact cast." A prerequisite is that the foot must have an adequate blood supply, and the foot must be carefully monitored throughout the duration of casting.

1. An experienced technician must apply the cast.
2. This is best carried out in a multidisciplinary foot clinic.
3. The ankle should be bent to a neutral position and the technician will need access to the sole of the foot.
4. A thin layer of stockinette is applied to the foot and leg and protective cast padding applied between the toes.

5. Cast padding is applied very thinly up the limb and then secondary foam padding is applied over the toes at the bony prominences especially on the inner and outer side of the ankle, sides of the cast and the front of the shin.
6. Then, an undercoat of plaster or in modern practice cast tape of synthetic material, is applied very carefully and smoothly to the foot and leg, completely encasing the toes and going up the leg.
7. The sole of the cast is carefully molded to the contours of the foot.
8. Any "valleys or troughs" are then filled in with cast tape of synthetic material so that the sole of the cast is flat.
9. The cast is point reinforced by fiberglass and a special curved or rocker-bottom sole is applied to relieve the stresses of walking if the patient is to be allowed to bear weight
10. When the cast is removed, the Charcot foot is washed in a warm soapy foot bath. This maintains patient hygiene and reduces the "aerosol effect" when a cast is removed.
11. Patients should be educated to look for danger signs (cast cracks, leakage or staining), to monitor routinely their blood glucose and body temperature and to present immediately if concerned about any complications (cast structural problems, unexplained hyperglycaemia or fever). A communication network to enable the patient to obtain urgent advice is important for successful management of total contact casting.

13.5 Controversies in Cast Application and Variation in Practice

13.5.1 Weight Bearing

The traditional management recommendation for acute CN of the foot or ankle is strict non-weight-bearing cast immobilization [9]. In many cases it is difficult to be completely non-weight bearing because the patients have multiple co-morbidities including loss of proprioception, postural hypotension, high body mass index and, in some cases, neuropathy of the upper limbs, all of which can make it difficult for them to use crutches to facilitate non-weight bearing. Furthermore, a wheelchair existence is often impractical in many home environments.

There are no firm guidelines as to whether patients treated with TCC should be allowed to bear weight. Clinical outcomes of patients treated with weight-bearing casts indicate no significant complications in two small series [10, 11]. In a study of ten patients with Charcot foot in an acute Eichenholtz stage I and treated with weight bearing total contact cast and biweekly cast changes, all subjects were successfully managed and were able eventually to use commercially available depth-inlay shoes and custom accommodative foot orthoses [10]. In a further study of thirty four Charcot feet treated with weight bearing total contact casts, thirty three

did not report any deleterious effect from weight bearing, specifically with regard to skin ulceration or rapid deterioration of the osseous architecture [11]. There is limited published evidence to suggest that a degree of protected weight bearing may be a safe treatment option [12]. Allowing weight bearing has not been shown to result in increased development of deformities; however, immobilization times can be increased (by up to 5 weeks) compared to those times with adherence to non-weight bearing prescription [9]. Although non-weight bearing may be ideal, a practical approach is to allow restricted weight bearing supported when possible by assistive devices [13, 14].

13.5.2 Monitoring Resolution

The duration of offloading is guided by clinical assessment of healing of CN based on resolution of oedema, erythema, and skin temperature difference.

Casting is continued until the swelling has resolved and the temperature of the affected foot is within 2 °C of the contra lateral foot [15] and this may be measured accurately with an infrared skin thermometer [16]. This is a well-established tool for assessment of cast cessation [17]. It reflects the overall gradual cooling of the foot, which is on average 0.022 ± 0.0005 °C per day [18].

Evidence of healing on X-rays or MRI strengthens the clinical decision to transition the patient into footwear. Typically, radiographs will demonstrate reduction in deformity progression and consolidation. In the initial diagnosis of Charcot foot, when differentiating MRI from osteomyelitis, MRI may not be definitive [19]. However, for monitoring treatment outcome, MRI is becoming the modality of choice. Improvement of MRI findings has been correlated with improvement in clinical findings (amount of oedema and pain found on physical examination) [20]. These MRI findings may resolve after cast immobilization for 6 months [21]. In a prospective study of 40 patients with acute Charcot foot, each patient had an MRI performed every 3 months until deemed healed, and the estimated mean time to clinical healing was 6.8 months and the mean time to resolution of MRI findings was 8.3 months [22]. Thus the MRI is useful to judge the appropriate duration of immobilization for the conservative management of acute CN.

Other indicators such as the Doppler spectrum of the first dorsal metatarsal artery (i.e. blood flow measurements) can be used to monitor disease activity and guide treatment. In the acutely active stage, the Doppler spectrum of the affected foot showed monophasic forward flow. All patients were treated in a well-padded non–weight bearing cast until the Doppler spectrum patterns returned to normal after a mean of 13.6 weeks (range, 6–20) of immobilization [23].

Biochemical markers such as the pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) have been evaluated prospectively in the natural history of the Charcot foot in patients treated with casting therapy. Concentrations of TNF-α, interleukin-1β, (IL-1β), and IL-6 were slightly but significantly raised compared with control subjects and decreased after recovery to

values similar to those noted in control subjects [24]. A further study has shown that there is a sustained increase of IL-6 and TNF-α starting shortly after offloading and paralleled by accelerated bone healing on radiographs [25].

13.6 Duration of Casting Therapy

Practices vary regarding the actual duration of casting therapy. Studies carried out in the UK report a longer duration of casting (median of 10 months) [26], compared to studies in the US (varying between 9 and 16 weeks) [10, 11, 15]. These differences may be attributable to the lack of reliable indicators to determine the clinical resolution of CN.

In summary, casting may be necessary for 12–18 months and is discontinued on the basis of clinical, dermal, thermometric and radiological signs. Serial plain radiographs should be taken during the acute phase to evaluate progress, with MRI being added towards the end of this period to confirm resolution. Reduction of bone marrow oedema and fracture healing has been graded by a recently developed semi-quantitative-scoring proforma [27].

13.7 Results of TCC

Many studies have shown the efficacy of TCC in CN over the last 30 years [28]. The current literature has tried to identify prognostic indicators for treatment. Chantelau found that an increased time from diagnosis to casting could lead to an increased duration of casting [29]. Eleven patients were referred with early incipient Charcot foot, (the case group), and in 13 patients referral was delayed (the control group). Both groups were immediately treated with off-loading and total contact casting. Only 1 out of 11 incipient Charcot patients developed extended foot fractures and severe deformity, compared with 12 out of 13 in the delayed Charcot patients.

The outcomes of stage 0 CN or incipient feet depend on early recognition and management [30]. Treatment of Stage 0 or Stage 1 Charcot patients with TCC immobilization resulted in stabilization without deformity in 50% of patients [31]. Given these findings, early diagnosis with conservative treatment is crucial for the management of Stage 0 and Stage 1 Charcot. However, healing times do vary according to the location of the disease with hind foot and mid-foot involvement requiring longer offloading in TCC compared with that of the forefoot. Forefoot pathology heals in two thirds the time needed for mid and hind foot pathology [13].

Although some studies have reported an average time of casting of 18 weeks [21], some patients may need a cast for over a year. In 46 patients with acute CN, median duration of casting was 11 months and this is compatible with previous MRI studies [22, 32]. The mean time of return to permanent wearing of shoes was 28.3 weeks. Male patients required a longer period of immobilization and took

longer to return to wearing shoes compared to women, 21.8 versus 15.2 weeks and 30.2 versus 26.4 weeks, respectively. In a further study, TCC immobilization provided effective resolution with maintenance of a stable, plantigrade foot in 75% of cases [28]. Furthermore, 88.9% remained with a stable, plantigrade foot at 32 months following treatment. Thus TCC remains the mainstay of treatment for acute CN.

In summary the average time spent in a cast seems to range between 8–52 weeks [33]. The variation in the literature may reflect the lack of reliable indicators to determine the onset of CN and the clinical resolution of the CN and differing practices in managing resolution.

13.8 Complications

The majority of complications associated with casting therapy are minor [10] and their rate may be as low as 5% [34]. The complications include pressure rubs, and infection. The odds ratio of a complication with a TCC depends on the indication for the application. Even when the TCC is applied by an experienced provider, the odds ratio for a complication was 1.46 in cases of Charcot deformity and 0.69 for patients with neuropathic ulceration [33, 34].

Many people with CN are obese and have peripheral neuropathy. This leads to the inability to determine how much weight is being placed on the foot and also to impairment of balance and proprioception which leads to falls. Poor strength and co-ordination make the use of ambulation assistive devices difficult. Many patients do not have the cardiovascular reserve to use crutches effectively and undertake walking with a cast. Increased dependence on the unaffected foot with significant hopping can be a traumatic event and lead to a contralateral Charcot process. Many patients have poor eyesight secondary to diabetic retinopathy. These factors need to be assessed before embarking on immobilization and pressure off loading. To minimise the risk of complications, it is essential that a safety network is in place to reassure the patient [35, 36].

Although not a specific complication of casting, relapse of CN will be evident from further swelling and heat in the foot and may be detected in up to 30% of feet. Total duration of casting treatment required thereafter can be 20 months [32].

13.9 Alternative Treatments to TCC

TCC application is both labour intensive and time consuming and this may explain the underuse of this technique as well as the fear of iatrogenic complications. A survey of the practice patterns in the treatment of the Charcot foot in the US indicated that non-removable cast was the first choice of management in only 49% of the cases [37]. An online survey showed that only 34% of patients were offered a non-removable cast at any one time point for the management of the acute Charcot foot [26]. Alternative treatment is a prefabricated walking cast, such as the Aircast®

Walker [38]. However, immobilization times with these devices are longer compared to those of non-removable devices as patients may remove the device and ambulate without them [9].

13.10 Rehabilitation from Casting Therapy to Footwear

Once the swelling of the foot is decreased and it is no longer changing shape, with the radiographs showing evidence of consolidation the patient should be assessed for made to measure footwear.

Custom footwear includes extra-depth shoes with rigid soles and a plastic or metal shank. When such footwear is available, the patient should be provided with a removable bivalve cast or a cast walker. The patient should take a few short steps in the new footwear and then return to the cast for the remainder of the day. The patient should monitor the foot and if there is no increase in warmth, swelling and redness, then the patient can walk a few more steps the next day, and very carefully build up to a reasonable amount of walking. Finally, the patient may progress to the permanent wearing of bespoke shoes. Patients should be instructed to look specifically for swelling or pain or discomfort and to seek advice immediately if there is concern that CN has reactivated. The relapse rate can be as high as 30% and some patients may require additional casting therapy.

When the patient comes out of the cast there will be joint stiffness and wasting of the calf muscles and the patient will need physiotherapy. The rocker bottom foot with plantar bony prominence is a site of very high pressure. If ulceration does occur, an exostectomy may be needed (Chap. 8). The clinician and physiotherapist must be aware of the dangers of reactivating the bony destruction phase by excessively rapid mobilization or protracted weight bearing in the early stages of rehabilitation [39].

When rehabilitating patients with hind foot Charcot osteoarthropathy, many types of braces may be used, including a patellar tendon-bearing brace, a Charcot restraint orthotic walker (CROW), and a double metal upright ankle foot orthosis (AFO) [40]. The CROW is a bespoke bivalved total contact device which externally fixates the ankle. It is fitted with a bespoke moulded insole to accommodate any existing deformity and to redistribute plantar pressures. A rocker bottom, crepe sole facilitates roll-off during walking. It is used after swelling is controlled and progressive destruction has been resolved by total contact casting. The AFO is a device used to stabilize the foot and ankle. There are two main forms of AFO, the traditional conventional metal and leather calliper and the newer thermoplastic types which are more cosmetically acceptable.

13.11 Follow-Up of Patients with Charcot Foot

Patients need follow-up in a multidisciplinary diabetic foot service. Occasionally there may be a relapse in an already established but stabilized foot with CN. This will present with erythema, swelling and warmth. Patients should be treated as if

they were again in the acute phase. Up to 30% of patients may develop CN in both feet. All patients with CN should therefore be taught to check their feet and ankles regularly for warmth and danger signs. In essence, lifetime surveillance is advised to monitor for signs of recurrent or new CN episodes as well as other diabetic foot complications [41].

13.12 Other Treatment Modalities for CN

Evidence to support the use of pharmacological therapies in the management of CN is not robust. Anti-resorptive therapies (bisphosphonates and calcitonin,) used in addition to casting therapy have been investigated in clinical trials in small cohorts of patients with CN [42–44]. Anti-resorptive therapies reduce the osteoclastic activity of bone breakdown, promote healing, and decrease local inflammation but have minimal effect on bone formation. Although these systemic anti-resorptive therapies demonstrated a significant reduction in bone turnover, none of these therapies showed a significant effect on temperature reduction between active treatment group and control [45]. Moreover, treatment with zolendronate resulted in longer cast immobilisation compared to placebo [46].

Recently, a double blind randomized control study in patients with acute CN to evaluate the possible benefit of 1–84 recombinant human Parathyroid hormone on fracture healing has been carried out [47].

The inflammatory response to trauma in the Charcot foot consists of an increased release of cytokines from activated monocytes including raised concentrations of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, and reduced secretion of anti-inflammatory cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10) [48]. Serum concentrations of TNF-α and IL-6 are raised in the active stage of CN and they positively correlate with serum biochemical markers of bone resorption [24]. Indeed, in the active Charcot foot, there is increased osteoclast mediated bone resorption which is not coupled with osteoblast bone formation resulting in negative bone balance. Osteoclasts generated from monocytes isolated from Charcot patients and cultured on bovine or dentine bone discs exhibit increased resorbing activity in response to the osteoclast activator, receptor activator of nuclear factor kappa-B ligand (RANKL) [49, 50].

Furthermore, it is possible that peptides normally secreted from nerve terminals may be important in the expression of RANKL and thereby take part in the regulation of the inflammatory response to trauma. Substance P and calcitonin gene-related peptide (CGRP) are essential neuropeptides involved in fracture repair. They are potent vasodilators and have an osteotrophic effect. Calcitonin gene–related peptide (CGRP) is known to be necessary for the maintenance of normal joint integrity and antagonize the synthesis of RANKL. Hence, any reduction of CGRP through nerve damage will result in an increase in RANKL expression, which could facilitate joint dislocation A recent immunohistological study showed a trend

towards reduced expression of CGRP in CN bone specimens compared with controls [51]. Initial experience with a single dose of RANKL antibody seems promising, as treatment with this agent leads to a faster fracture resolution in a small cohort of patients [52].

Currently low-intensity ultrasound or pulsed low-intensity ultrasound has been shown to transmit micromechanical force and strains to the fracture site and to promote bone formation. Studies have demonstrated acceleration in healing and an increase in strength at the callus site [53]. Finally, the use of electrical stimulation and of magnetic field therapy to stimulate bone formation has been discussed in a few case reports. These therapies have shown some benefit in accelerating healing times. However, there are no prospective studies to indicate a positive effect [54].

13.13 Conclusion

Casting therapy remains the mainstay tool in the management of this condition. Timely intervention can arrest deformity and keep the X-ray normal. If deformity develops despite treatment, there is a role for surgery to stabilize the foot and prevent progression (see Chaps. 14 and 15).

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Chapter 14
Surgical Management: Internal Stabilisation

Venu Kavarthapu

14.1 Introduction

The presence of severe deformity and/or instability makes the foot vulnerable to ulceration due to the increased plantar pressures despite adequate offloading. Chronic non-healing ulcers that do not respond favourably to offloading measures or exostectomy can develop repeated infective episodes leading to deep bone infection. Such infective episodes often increase the risk of amputation. Surgical reconstruction and corrective fusion may be considered in the presence of severe or unstable deformity that does not respond to offloading measures. There has been a recent shift towards the surgical reconstruction of Charcot deformities as more published data is now available with medium-term outcomes [1–4]. However, most published series have demonstrated a high incidence of non-union of the surgically fused bones following such deformity corrective procedures. Even though, non-union or pseudoarthrosis was considered as an acceptable outcome in such difficult pathologies, it has become an established concern that non-union or an unstable pseudoarthrosis in a neuropathic foot will most likely lead to recurrence of progression of foot deformity over a period of time.

The surgical aim of CN foot reconstruction is to achieve a normal shaped, plantigrade and stable foot that allows full weight bearing. Stability of the reconstructed foot is ideally achieved by obtaining full bone fusion. Non-union can lead to instability of the corrected foot, resulting in progressive change in the foot shape causing recurrence of ulceration and raising the risk of amputation. It is desirable to achieve sound bone fusion of the reconstructed CN foot that only requires routine modified footwear for full weight bearing mobilisation. This is best achieved with rigid internal stabilisation and optimal bone opposition through an open surgical approach.

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14.2 The Concept of Internal Stabilisation in the Presence of a Non-Healing Ulcer

Internal fixation during CN reconstruction in the presence of previous history of foot ulcer or osteomyelitis is a concern to the surgical team. Even in the absence of history of infection, retention of an internal fixation device in a diabetic foot carries a risk of future infective episodes around the internal fixation metal work. Metal work prominence can cause high pressure points that could potentially get infected, leading to a chain of events that may ultimately jeopardise the limb survival. Diabetic patients with multiple medical comorbidities are also vulnerable to episodes of systemic infections and the bacteraemia associated with this could potentially settle and spread around the metal work. However, our experience has shown that aggressive surgical and medical management of an ulcerated or previously infected CN foot under the care of a dedicated multidisciplinary team results in a low risk of metal work related infections and reduced amputation rate [3, 5]. Other reports also describe the use of internal fixation in patients but without a wound or any recent history of deep infection [4]. However, in patients with open wounds, active infection or with a history of infection, some authors prefer the use of external fixation [4].

14.3 Optimal Timing of Surgical Reconstruction

There is no consensus on the optimal Eichenholtz stage in which the deformity corrective procedure is best performed. Traditionally, surgery is delayed until the consolidation (inactive) stage of CN is reached [4, 6]. Surgery during stage 1 has historically been a relative contraindication due to the increased risk of complications such as infection, non-union and hardware failure. However, some recent studies with a small series have shown improved results [7]. This is most likely due to the recent improvements in the fixation methods and the access to multidisciplinary care. The standard management of a deformed Charcot foot, however, is offloading in a total contact cast or an univalent brace until Eichenholtz stage 3 is reached, followed by surgical reconstruction. Most of the current literature recommends reconstructing in stage 3. However, some studies have shown good outcomes in stage 2 [8, 9]. Furthermore, a recent study, demonstrated the effectiveness of hindfoot arthrodesis by stable fixation across all the Eichenholtz stages of Charcot neuroarthropathy involving ankle and peritalar joint [10].

14.4 Preoperative Considerations

There are patient factors that must be taken into consideration before proceeding to surgery. Patients with CN due to diabetes often present with significant comorbidities, including neuropathy, retinopathy and chronic renal disease. Limb perfusion is

assessed with vascular studies and optimised as required pre-operatively. Patients with peripheral vascular disease are initially managed by the vascular team and are revascularised prior to fusion. The skin, tendons and other soft tissues in the foot and ankle are assessed for contractures that might require release during surgery. A contracted Achilles tendon is often encountered in this group of patients. Care must be taken to ensure a safe home environment and adequate physical and psychological support is provided postoperatively.

14.5 Internal Stabilisation Principles

The general principles of surgical correction of limb deformity are applicable to CN. The detailed surgical techniques for hindfoot and midfoot deformity corrective surgery are described in the paragraphs below. The general principles for internal stabilisation include the following:

- Descaling of skin: most patients are in a brace or cast for a considerable period of time prior to the reconstruction procedure and develop extensive skin scales that harbour skin flora. An exfoliating cream is applied a few days prior to the planned surgical procedure to remove these scales. Foot scrub using chlorhexidine preparation is performed prior to the routine limb preparation and draping.
- Lengthening of contracted Achilles tendon: CN deformity often presents with contracted Achilles tendon. This can be lengthened either percutaneously using a triple hemisection method or through an open approach (Fig. 14.1).
- Single major incision for correction on the convex side of the deformity: multiple major incisions carry greater risk of wound infection and tissue necrosis. When possible, most deformity correction should be achieved using a single

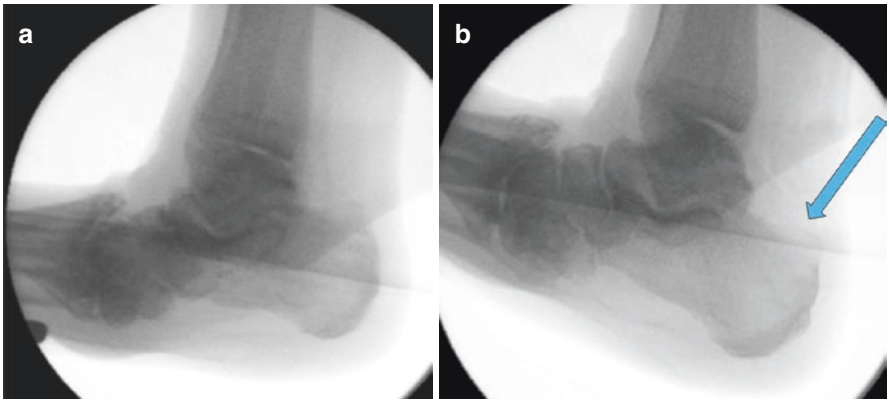

Fig. 14.1 (**a**) and (**b**) Intraoperative fluoroscopy images showing the improvement in the calcaneal pitch following percutaneous lengthening of Achilles tendon (arrow)

major incision, supplemented with other smaller incisions that are sufficiently apart, as required.

- Deep tissue flaps: thick deep soft tissue flaps should be developed to preserve the soft tissue circulation.
- All joints intended for bone fusion are exposed and surgically prepared.
- For hind foot deformity, a large lateral approach (transfibular) is used for varus deformity correction that provides access to the ankle and subtalar joints (Fig. 14.2). Hindfoot valgus correction requires an anteromedial approach to the ankle joint as the major incision and a separate smaller approach for the subtalar joint for preparation.
- If simultaneous hindfoot and midfoot deformity correction is performed, the hindfoot is performed first, followed by midfoot correction.
- During reconstruction, the priority is given to achieve a normal looking stable plantigrade foot. It is however crucial not to jeopardise the foot's vascularity and soft tissue integrity in order to achieve absolutely normal radiological angles.
- Deep tissue specimens are taken from all suspicious areas in the presence of previous infection and labelled separately for microbiological cultures. Appropriate surgical prophylactic antibiotic is administered after harvesting the tissue specimens.
- Super construct fixation: durable long segment rigid internal fixation is performed with optimal bone opposition.
- Dead space management: in the absence of any history of previous foot infection or ulceration, particulate bone autograft or allograft may be used. If there was a previous history of infection, antibiotic embedded injectable bone graft substitute or similar product may be used to fill the voids.
- Aggressive wound lavage is done through out the procedure. Tension free wound closure is performed with or without a suction drain.

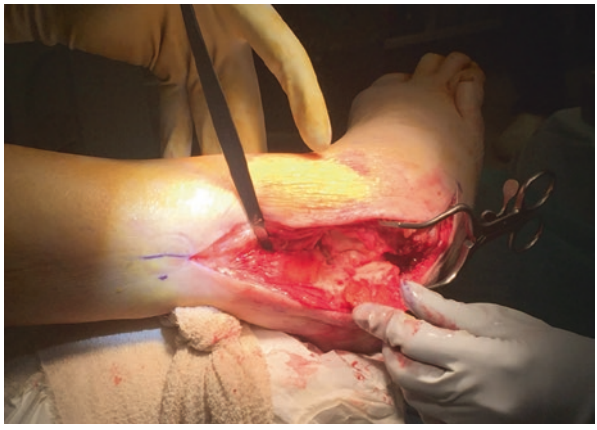

Fig. 14.2 An intra-operative photograph showing the trans-lateral malleolar extended lateral approach that provides access to the ankle and subtalar joint in a varus hindfoot CN deformity

14.6 Super Construct Fixation

The superconstruct technique was first described by Sammarco et al. [11]. Its principles include: (1) bone fusion is extended beyond the affected joints and include joints that are not affected; (2) bone resection is performed to shorten the skeleton to allow for adequate reduction of the deformity correction without undue tension on the soft tissue envelope; (3) the strongest device that can be tolerated by the soft-tissue envelope is used; and (4) the devices are applied in a position that optimize their mechanical function. The internal fixation construct should be robust enough to provide a durable and rigid fixation that would maintain axial, bending and rotational stability until the bone fusion is achieved.

14.7 One Stage Reconstruction in the Presence of Non-Infected Ulcer

If an ulcer is present, this is thoroughly debrided at the beginning of the procedure. Any previous scars or sinuses are included and removed in the planned incisions whenever possible. Bone debridement at the ulcer base is performed to healthy bleeding bone. The instruments used are disposed of and the foot is re-draped. In the presence of a history of previous or recent ulceration or infection, multiple bone and soft tissue samples are collected throughout the procedure from previously infected areas. It is important that each specimen is handled with an uncontaminated separate set of instruments. These specimens are sent for microbiological cultures and histological examination.

Those with an infected ulcer are treated in staged manner to initially eradicate infection. Surgical debridement followed by NPWT together with deep tissue culture specific antibiotic administration is carried out as a first stage before planning definitive deformity corrective fusion (Chap. 37).

14.8 Hindfoot Deformity Correction

Hindfoot deformity correction is achieved by performing bone wedge resections using a single major incision on the convex side of the deformity and internally stabilising with a rigid long-segment internal fixation construct applied along the lines of the weight bearing forces. Various internal fixation devices including Steinmann pins, staples, screws, standard plates and angled plates, have not yielded successful results. This is often due to the associated poor quality of bone, the degree of bone and soft tissue loss and mechanically weaker fixation construct achieved

with these options. An intramedullary (IM) hindfoot fusion nail (tibio-talar-calcaneal nail) can overcome these obstacles in most situations. The forces that operate on the ankle joint during weight bearing are predominantly in compression mode and the IM nail can facilitate this favorable environment for bone healing [12]. The subtalar joint in CN foot is often stiff and markedly deformed due to significant displacement and angulation. Following wedge bone resections and soft tissue releases, this malalignment and lateral shift in the subtalar joint are corrected and the joint plane is converted to more horizontal. In this mode, the IM nail offers stable fixation along the weight-bearing axis allowing better deformity correction and higher rates of bone fusion (Fig. 14.3).

Durability of the fixation construct in Charcot hind foot fusion is paramount, as the time to fusion is often much longer than taken in non-neuropathic patients. The extramedullary internal fixation devices such as plate and angled plate are subjected to excessive bending forces as they are away from the line of weight bearing axis. This, along with reduced bone contact and bone strength in CN foot, results in greater risk of plate breakage. The IM nail has been shown to have much higher bending and torsional stiffness compared to the plates and yet is subjected to reduced forces as it is placed along the line of weight bearing axis. It can also provide intra-operative compression and post-operative dynamic compression options, unlike the other internal fixation devices. However, the distal locking screws that are usually inserted into talus and calcaneus through the IM nail are subjected to significant bending and torque forces and this can potentially result in screw migration or breakage. It is recommended that a nail that has threaded distal screw holes would improve the screw-nail engagement and thereby reducing the risk of telescopic migration of the screw. Hydroxyapatite (HA) coating to the locking screws has been used in a series with marked reduction in the screw migration [3]. HA coating has been shown to increase the torque of screws during insertion and extraction compared to standard screws in some studies. In addition, the potential for bony on-growth on the screws may further increase the self-loosening threshold of these locking screws. However, if the degree of bone loss in the ankle and subtalar joints is marked, the IM nail may not provide rigid fixation, as there is often some rotational instability in the nail construct. In such situations, an additional retrograde screw fixation across the calcaneus and distal tibia running parallel to the IM Nail, or extension of plate fixation from distal tibia to talus or medial column increases the stability of the construct (Fig. 14.4).

14.9 Midfoot Deformity Correction

The midfoot is the most commonly affected region in CN of the foot and ankle. This often results in collapse, leading to rocker bottom and forefoot abduction deformity. The Charcot midfoot deformities generally fall into one of three patterns: (1) rocker bottom forefoot abduction, (2) dorsal subluxation/dislocation, (3) forefoot adduction. The rocker bottom forefoot abduction pattern is the commonest and results in

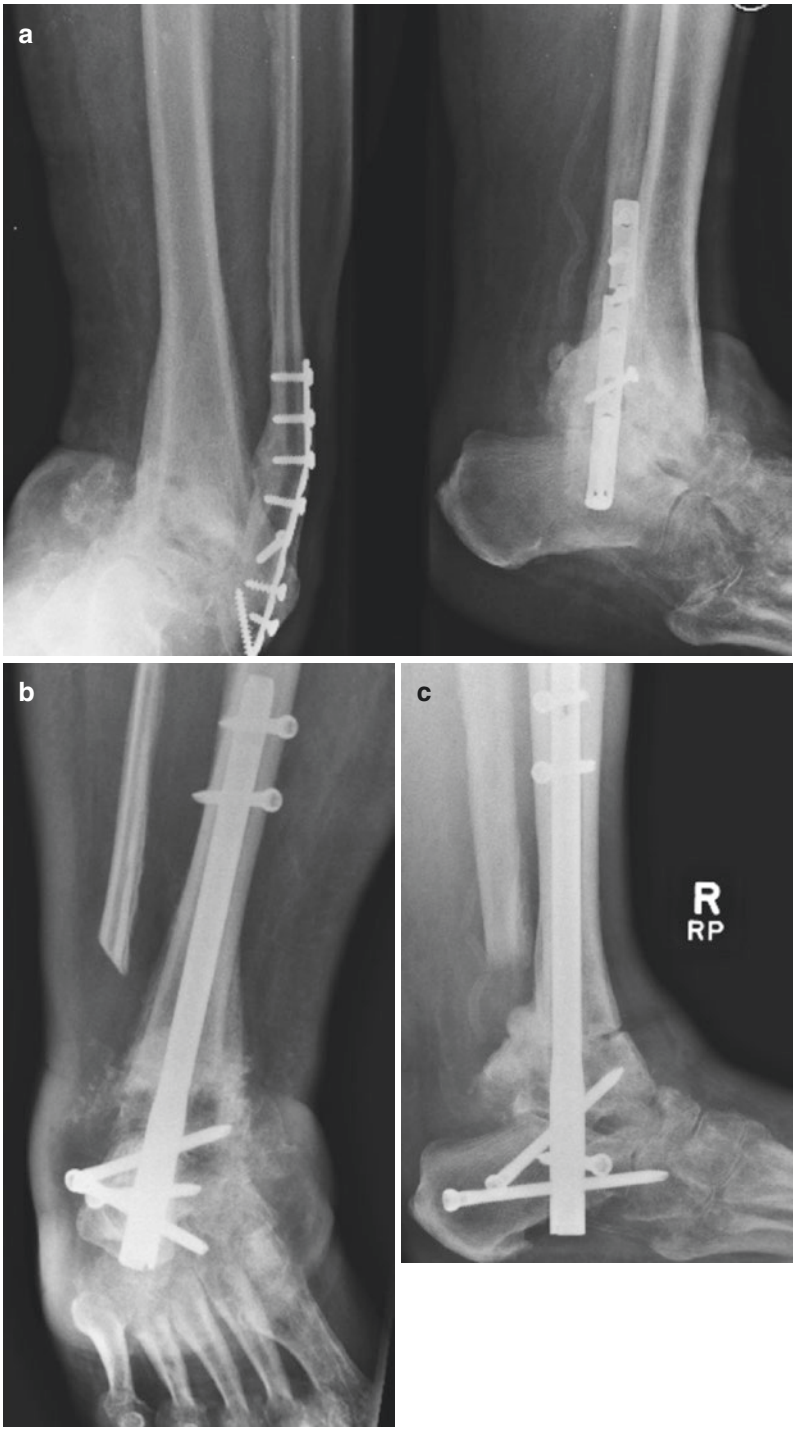

Fig. 14.3 AP and lateral radiographs (**a**) showing CN of ankle and subtalar joint following an internal fixation of ankle fracture resulting in marked varus deformity and chronic ulceration at the tip of lateral malleolus. Post-operative AP (**b**) and lateral (**c**) radiographs following surgical correction

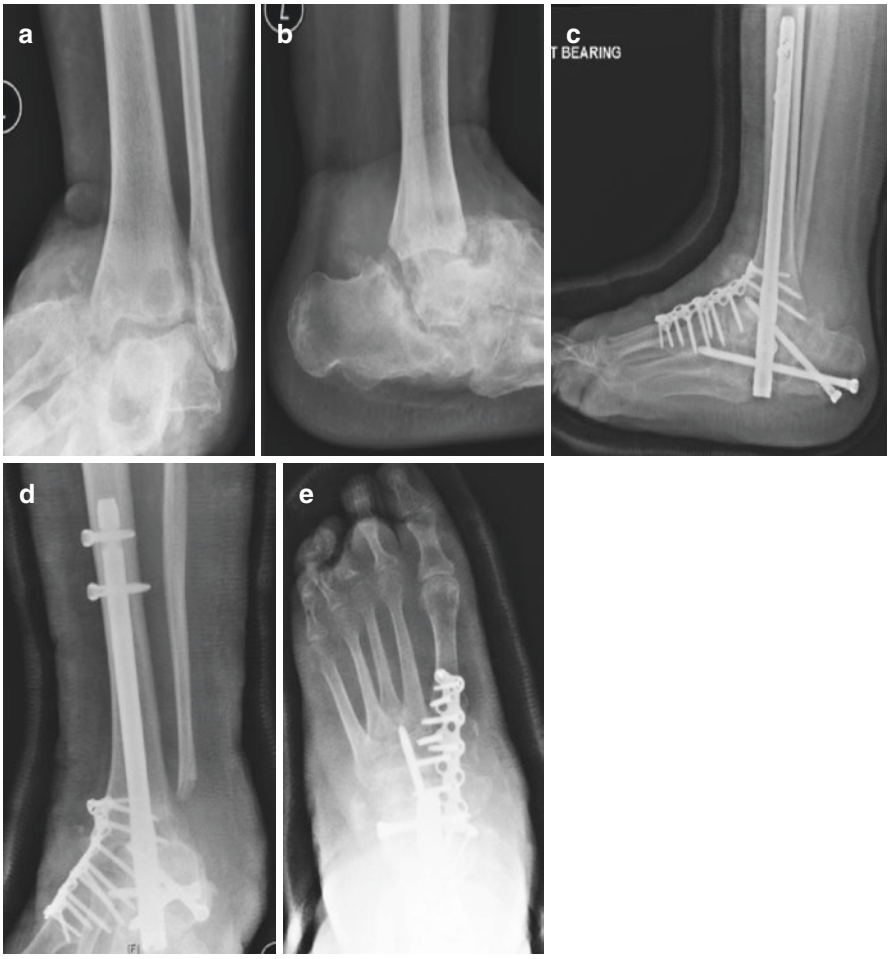

Fig. 14.4 AP (**a**) and lateral (**b**) radiographs showing CN of ankle, subtalar joint and midfoot articulations with severe deformity. Post-operative lateral (**c**) and AP (**d**) radiographs the ankle and DP view (**e**) of the foot following surgical correction showing combined ankle, hindfoot and midfoot reconstruction

significant reduction of calcaneal pitch, contracture of Achilles tendon and dissociation of the Meary's angle and talar-1st metatarsal angle in the dorso-plantar plane. The dorsal subluxation/dislocation pattern is due to the dorsal subluxation or dislocation of the forefoot, with the plantarly displaced and tilted intact talocalcaneal articulation taking some tarsal bones which are left attached to it. The forefoot adduction pattern is uncommon and may be associated with fracture of bases of lateral metatarsals and peroneus brevis dysfunction.

The midfoot reconstruction is usually performed using an extended medial approach exposing the medial column. It is recommended to use the Doppler probe

routinely to identify the patent vessels of the ankle and foot, and especially the dorsalis pedis artery before draping the foot, as in severe deformities, it varies significantly and often lies very close to the dorsomedial incision. Its course on the foot is marked on the skin with an indelible marker.

After adequate surgical exposure, an appropriate sized medial and plantar-based wedge osteotomy is performed under fluoroscopy guidance. The distal cut of the wedge osteotomy is done through the base of the 1st - 3rd metatarsals, just distal to the articular surface. The proximal cut of the wedge osteotomy usually goes through the cuneiform/navicularis/talar head medially depending on the degree of the deformity and the size of the wedge. The plantar part of the wedge often includes most of the plantar prominence. The apex of the osteotomy is aimed to within the cuboid bone mid-substance so that the lateral cortex of cuboid bone is carefully preserved. This intact lateral cortex acts as a strong hinge, and the cancellous midsubstance can easily collapse into a closing wedge. This allows plastic deformation of the lateral cortex of the cuboid during correction and the application of tension band plating principle for medial column fixation. The correction is provisionally held in place with two 2 mm Kirschner wires.

The initial reduction and fixation of the osteotomy is done using either one to two cannulated lag screws across the osteotomy or an intramedullary medial column beam inserted through the head of 1st metatarsal into the body of talus using a cannulated technique. The aim of these fixation techniques is to achieve compression across the osteotomy site. The stability of the fixation is then enhanced by using a

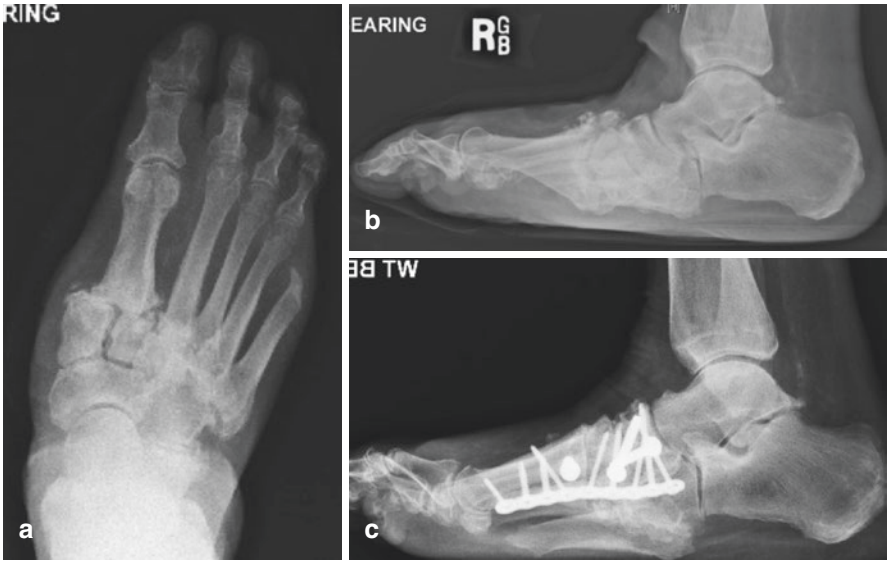

Fig. 14.5 DP (**a**) and lateral (**b**) radiographs showing CN of midfoot, predominantly affecting the Lisfranc articulation. Post-operative lateral radiograph (**c**) showing the deformity correction and plantar plate fixation of the medial column, sparing the talonavicular joint

locking plate fixation. A low profile, contoured, strong and durable locking plate fixation system is used. For most deformities, one locking plate placed plantar-medially or dorso-medially is sufficient (Fig. 14.5). For complex deformities that require excessive wedge resection or with previous divergent dissociation of the Lisfranc joint, a second plate fixation is used bridging the base of 2nd or 3rd metatarsal to the tarsal bones. Careful assessment of the position and length of the plates and screws is done under fluoroscopy throughout the procedure to avoid any metal work prominence. Any addition, removal or exchange of screws is performed as required.

The tibialis anterior tendon is reattached in optimal tension. The deep soft tissues and skin are closed in a layered fashion over a suction drain if there is any residual active wound oozing. A below knee back slab is applied over sterile dressings with a well-padded layer of wool.

14.10 Exostectomy During Reconstruction

When possible, the wedge resections should include the exostosis associated with CN deformity. It is essential that a thorough inspection is done at the end of the procedure for any residual bone prominences and a further exostectomy is performed as required.

14.11 Post-operative Care of Reconstructions

Postoperatively the leg is kept elevated for 48 h, and then after, as often as possible, to reduce swelling. In the absence of any previous history of infected foot ulcers in the operated area, only prophylactic perioperative antibiotics are given. Otherwise, parenteral antibiotics are administered according to the pre and intraoperative microbiological culture results and continued until there is clinical and serological evidence of infection eradication. The wound inspection is done 2 days post operatively, when the suction drains are removed if used. The leg is placed in a bivalved non-weight bearing total contact cast when the foot swelling is reduced. The patient is discharged when safe mobilisation is achieved and adequate home microenvironment is ensured. A total contact cast is applied when there are no wound concerns and it is changed every one or 2 weeks. A non-weight bearing status is recommended until there is radiological evidence of progression of bone union, usually at around 3 months after surgery. Partial weight bearing in a total contact cast is then initiated under regular radiological monitoring for progression of bone healing, implant failure or loss of correction and clinical monitoring for skin breakdown. After a period of a few weeks of uncomplicated recovery, custom made orthotics or even normal shoes are used for independent ambulation.

14.12 Conclusion

Single stage corrective fusion for hind foot deformity and also mid foot deformity in CN are effective procedures when delivered by a skilled multidisciplinary team. These can be carried out in the presence of foot ulceration which must not be infected.

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Chapter 15
External Stabilization of the Charcot Foot

Ryan N. Cantwell, Michael I. Gazes, and Peter A. Blume

15.1 Introduction

Charcot arthropathy of the foot and ankle is a progressively deforming disease requiring long-term treatment and prompt recognition from the trained physician. The disease process often leads to increased morbidity, instability, recurrent ulcerations, and even amputations [1–4]. Charcot arthropathy has been associated with leprosy, syringomyelia, exposure to toxins, multiple sclerosis, trauma, and diabetes. Diabetes with neuropathy is the leading cause and Charcot arthropathy is a complication in up to 7.5% of diabetics [1, 5, 6]. Although the first reported case of Charcot arthropathy was over 300 years ago, it still remains a very difficult disease to not only identify, but also to manage and treat [1]. External fixation and stabilization of the Charcot foot has proven effective in management.

The use of external fixation has several advantages for correcting complicated deformities of the foot and ankle. Its use allows for gradual correction, the ability to revise during correction, and reduce damage to vital neurovascular structures [7]. External fixation also provides opportunities to operate on what was once considered a nonsurgical foot. For example, the trained surgeon can operate on osseous pathology with significant soft tissue damage and infections. The capability to preserve joints, joint function and maintain or gain bone length are strong considerations with the use of external fixation of the Charcot foot. The ultimate goal for all deformity corrections is to create a stable, aligned, comfortable foot below a well-aligned leg [7].

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Choosing the surgical candidate and when to operate on the Charcot foot can be quite the challenge. One complication the surgeon will consider when choosing external fixation is the possibility of deep infections or pin tract infections. The presence of neuropathy alone increases the risk of surgical site infection, even in the absence of diabetes [8]. Poor glycemic control and increased tourniquet times are also associated with increased risks of surgical site infections [8–10]. In addition to infections, reconstructing a chronic deformity can lead to compromised blood vessels and ischemia necessitating amputation [8]. A case review on limb salvage by Kucera et al. recommends regional anesthesia with a vasodilation effect and surgery without the use of a tourniquet to prevent ischemia.

15.2 Acute Charcot Joints

Surgeons are sometimes concerned as to when it is safe to operate on a foot with a Charcot deformity. In the acute stage of Charcot, patients often present with a unilateral erythematous and edematous lower extremity, which may or may not be painful [11]. The majority of these patients do not recall a single traumatic event; however, often there was a recent increase in activity or exercise. Although minimal, this repetitive trauma to the neuropathic foot can be devastating. Early imaging is strongly encouraged as well as a thorough clinical exam. Radiographic abnormalities may be absent in the acute Charcot foot, further emphasizing the importance of a clinical exam [11, 12]. Clinically, elevation of the affected limb will lead to a diminished appearance of erythema, unless there is an underlying infectious process [11]. Appropriate lab work should be considered in the presence of an infection. Suspicion of osteomyelitis should potentiate the need for further imaging as well as a two-stage procedure. In the first stage, meticulous debridement is suggested, followed by reconstruction in the second-stage [8]. The next obstacle is then to appropriately select effective antibiotics during the perioperative period [8, 13].

Controversy exists in literature regarding surgical intervention of the acute Charcot foot and ankle. Strict non-weight bearing and cast immobilization of the affected limb is crucial to the early management of acute Charcot [11]. Although this treatment can be effective, a nonunion or malunion may still result. The consequent deformities may lead to complications including pedal ulceration and need for operative treatment [14]. Most authors advocate surgical intervention in the coalescent or consolidative stages [11, 15, 16]. However, early arthrodesis with internal and external fixation has been reported during the developmental stage [11, 14, 15, 17]. These authors recognized the highly variable and individualized nature of each Charcot foot and do not encourage a generalized treatment algorithm for the Charcot deformity [11].

A Charcot foot unmanageable with conservative care and offloading should necessitate the need for surgical intervention. Surgical intervention should be done at the earliest signs of a potential ulceration, presence of osteomyelitis, or if the deformity endangers the intact skin envelope [11]. The decision to use external

fixation for stabilization or fusion of an acute stage Charcot foot should keep in mind repeatedly infected wounds caused from plantar ulcers [18]. Avoiding inoculation of infection into surrounding bone via hardware should be highly considered. There is convincing literature that reports greater than 90% limb salvage after major foot and ankle reconstruction in patients with a Charcot deformity [11, 16, 19].

Regardless of the decision of when to operate, the goals for every patient with a Charcot deformity should be to maintain or achieve structural stability of the foot and ankle, prevent ulceration, and to preserve a plantigrade foot [1, 20].

15.3 Offloading Wounds and Flaps

A problem often arising with a Charcot deformity is the development of a non-plantigrade foot leading to ulceration. Collapse of the foot or ankle architecture can predictably advance to plantar deformity, ulceration, and ultimately infection and amputation [11, 21]. Up to 15% of diabetics have a lower extremity amputation in their lifetime with Charcot proving a clear amputation risk factor [11, 21]. Offloading these wounds is shown to be very beneficial for limb salvage.

The majority of ulcerations are located at the plantar medial foot secondary to the dislocation of the navicular or medial cuneiform bones and eventually the talus. Dislocation of the cuboid bone is also common leading to plantar lateral ulceration. There is much debate regarding the treatment protocol for relief of plantar ulcers [8]. Saltzman et al. presented a retrospective study of the standard conservative treatment protocol for diabetic feet and determined that even with strict adherence to conservative treatment, there are poor results [4, 8]. Operative treatment may be superior to conservative management for plantar ulcerations [8, 14].

With plantar wounds being a common event following a Charcot event, wound management quickly becomes an additional problem to tackle. Each wound following a Charcot event can cost up to an additional $40,000 [22]. The use of external fixation can prove beneficial in the healing plantar wounds. Clark et al. proposes the use of external fixators for offloading plantar heel wounds, finding the external fixators to be a very versatile tool deserving inclusion as an adjunctive procedure to reduce pressure to the affected area. External fixation can allow immediate or gradual correction in all 3 planes (sagittal, frontal, and transverse). The use of external fixation is also an acceptable choice for offloading plantar or posterior flaps (Fig. 15.1). Clark et al. routinely employs the use of external fixation for stabilizing and protecting fragile flaps or grafts in patients that motion about the foot could damage the graft.

The rates of pin tract infections for offloading plantar wounds and flaps are not significantly different than what is reported in other uses of external fixation [22]. Contraindications must be recognized before the use of an external fixator. Appropriate patient selection can be difficult in the situation of plantar wounds and patient compliance is of utmost importance. Strict non-weight bearing orders for the involved extremity during the course of external fixation could provide better

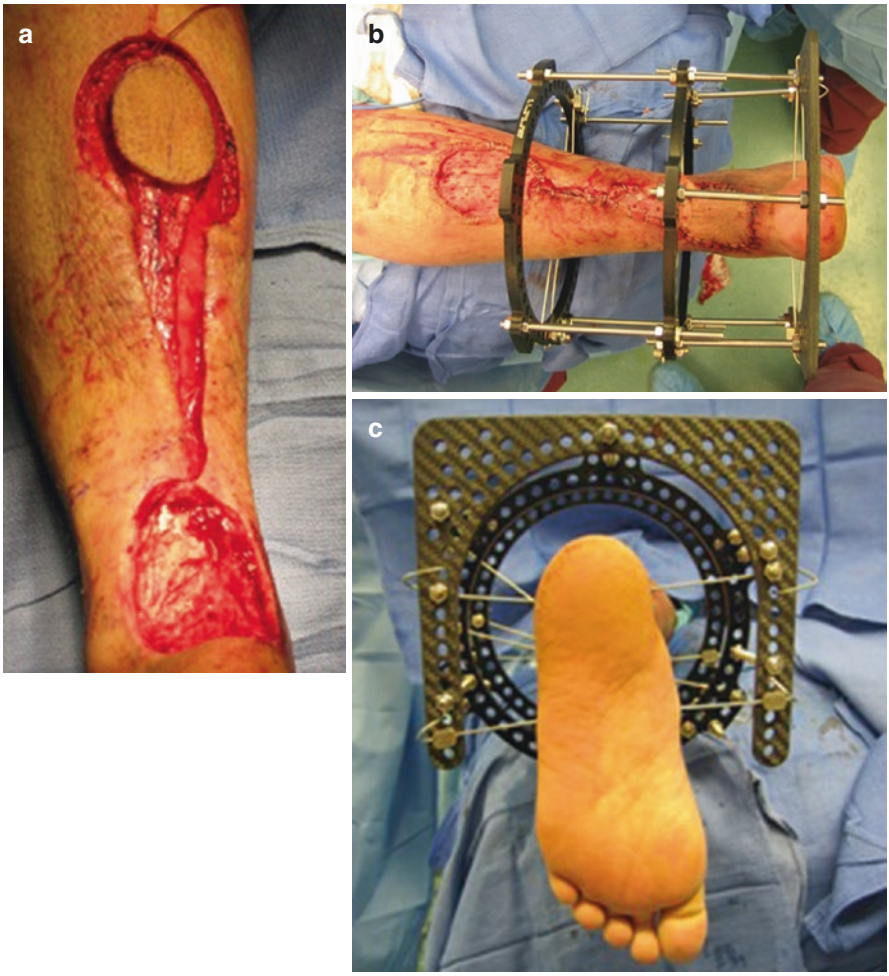

Fig. 15.1 Reverse Flow Sural Artery Pedicle Flap. (**a**) Preparation of flap site, (**b**, **c**) Protecting flap with use of external fixation with adequate space for offloading between frame and flap

results. Other contraindications to consider are compromised soft tissue envelope, pin placement across infection sites, insufficient blood supply, and a poor bone stock that would compromise the integrity of the bone-pin interface [22].

15.4 External Cast

The use of external fixation continues to evolve as well as its diversity for the treatment of various pathologies. In the past, external fixation was a last resort treatment, but has now developed into a mainstream technique used to treat a variety of bone

and soft tissue pathologies as its benefits are numerous [23]. Comparing external fixation to internal fixation, external fixation causes less disruption of the osseous and soft tissue blood supply and less damage to the periosteum [23, 24]. Unlike internal fixation, the external fixator also allows for postoperative adjustability and easy wound management.

When using external fixation on a neuropathic patient, careful postoperative radiographs should be reviewed throughout the postoperative course. Unadvised weight bearing with the lack of protective feedback can lead to loosening of the pins, leading to the declination of structural support as well as increased risk of infection around pin sites. Although motion about pin sites is strongly discouraged, micro motion about fracture sites is a significant benefit when comparing external fixation to internal fixation. Kenwright et al. found that tibia fractures treated with a dynamic unilateral fixator allowed for axial micro motion at the fracture site, which showed noteworthy clinical and mechanical healing [25]. Kenwright et al. also noted that although a rigid locked frame allows for earlier weight bearing, it prevents axial interfragment motion, delaying the healing process [24, 26].

Axial loading plays an important role in fracture healing. In the presence of adequate blood supply, lack of axial loading will cause resorption at the interfragment site [23, 26]. Moreover, weight bearing alone in the absence of adequate blood supply will inhibit osteogenesis. Weight bearing with poor fixation will also cause resorption at the fracture site [23, 26]. The combination of sufficient blood supply, osseous stability, and axial loading should be sought after, as it will provide the optimal environment for osteogenesis [23].

Although the external fixation device has its benefits when used alone, the trained surgeon often finds its use in the Charcot foot to be assisted with internal fixation due to the severity of the disease (Fig. 15.2). The operative approach for the Charcot

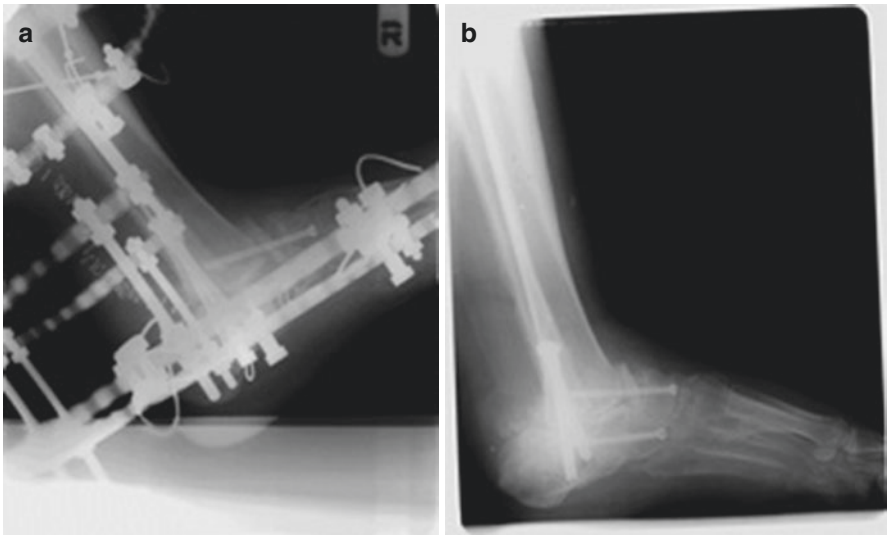

Fig. 15.2 Fusion utilizing external (**a**) and internal (**b**) fixation

foot often consists of tendo-achilles lengthening, resectional arthrodesis of the Lisfranc joint, and arthrodesis and realignment of the midtarsal joints [8, 27]. The addition of the external fixator allows for additional compression, resulting in optimal fusion and stability across joints. Additionally, it maintains the ability to bridge sites of infected bone and the availability to access and treat plantar wounds during the healing process [8, 28].

15.5 Septic Fusions

The trained surgeon who frequently treats Charcot often comes to the obstacle of an actively or previously infected joint. The ability to avoid putting internal hardware into an infected site is extremely imperative. External fixation is proven to be an effective choice for fusion of joints with recurrent osteomyelitis or other septic joints (Fig. 15.3) [23, 29]. The use of a hybrid external fixator provides a successful alternative for limb salvage for the arthrodesis of infected ankle joints when

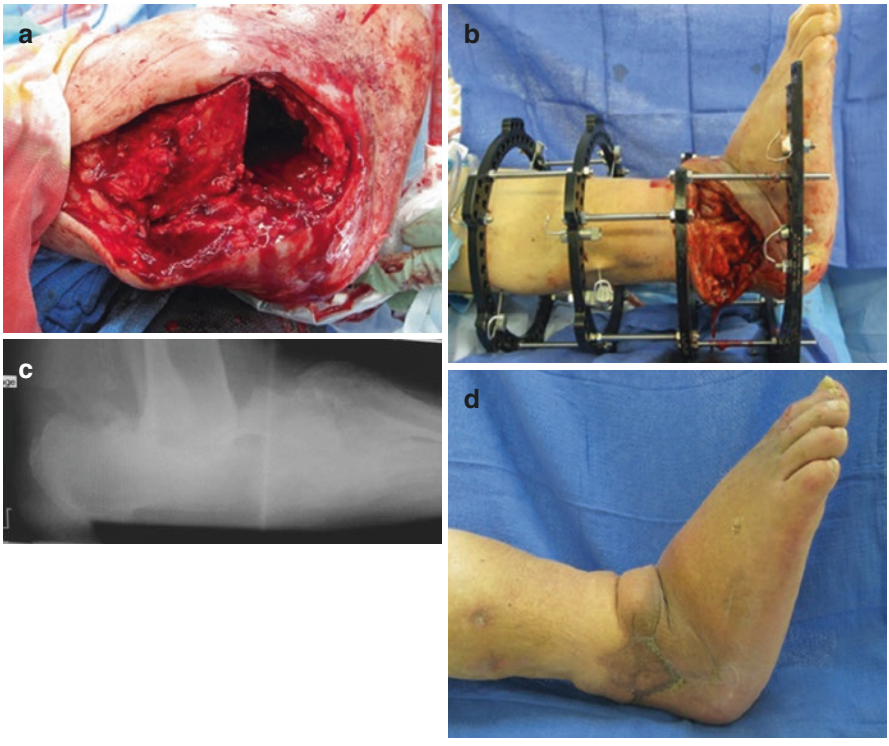

Fig. 15.3 Septic fusion utilizing external fixation. (**a**) Joint preparation, (**b**) Application of external fixation with no internal fixation utilized, (**c**) Post-removal of external fixation, (**d**) Plantigrade foot

infection or poor soft tissue envelopes are present [30]. In the aseptic joint, fusion can be successful in 88–100% of patients with internal fixation [30]. However, in the presence of infection this number plummets to 71% with a 25% chance of amputation [30].

Kollig et al. performed a study of fifteen joint fusions with the use of a hybrid external fixator [30]. All of the patients had a combination of both osseous and soft tissue infections, with Staphylococcus aureus being the major culprit. The study spanned a two-year period with fifteen ankle fusions. Limb salvage and solid ankle joint fusions were achieved in 93% of the patients evaluated. All patients that achieved successful fusion went on to full weight bearing without complications in their 12-month follow up.

Strong controversy exists with the management of open wounds, exposed bone, and osteomyelitis. Questions arise to whether there should be resolution of the osteomyelitis before attempting to correct the acquired deformity. With the incidence of diabetes increasing, Pinzur et al. performed a large retrospective case series to determine the outcome of a single-stage procedure to correct both the deformity and eliminate the osseous infection [31]. 71 patients underwent a single-staged surgery to correct a diabetes associated Charcot deformity in the presence of osteomyelitis with a 95% success rate for limb salvage and ability to ambulate. Pinzur et al. reported resection of the infected bone and appropriate antibiotic therapy selection followed by maintaining the desired correction with external fixation can be beneficial for limb salvage [31].

Limb salvage is the ultimate goal in the patient with a septic joint or chronic osteomyelitis. A common strategy in the treatment is using thin tension wires that do not span any portion of infected bone or soft tissue, using a wound VAC for any remaining open wounds, and appropriate IV antibiotic therapy selection. Often, physicians recommend 6 weeks of intravenous antibiotic therapy following these procedures; however, Swiontkowski et al. showed that a shorter course of intravenous antibiotics followed by culture-specific antibiotics is effectively equivalent to a 6-week course of intravenous antibiotics in the treatment of chronic osteomyelitis [32].

15.6 Stabilizing Spacers

Complications and injuries involving bone loss in the foot or ankle often leave the trained surgeon with very few options regarding reconstruction. The majority of these situations often have multiple components to assess, such as the presence of infection, scarring, osteoporotic bone, and neurovascular damage, including from primary or subsequent injury [33, 34]. Any of the above issues are a contraindication for the use of internal fixation, leaving external fixation a practical choice for correction and limb salvage (Fig. 15.4). Careful decision of pin placement should be made in osteoporotic bone due to possibilities of pin loosening, loss of frame stability, and delayed soft tissue healing [33, 35]. Loss of the distal tibia or the talus as the

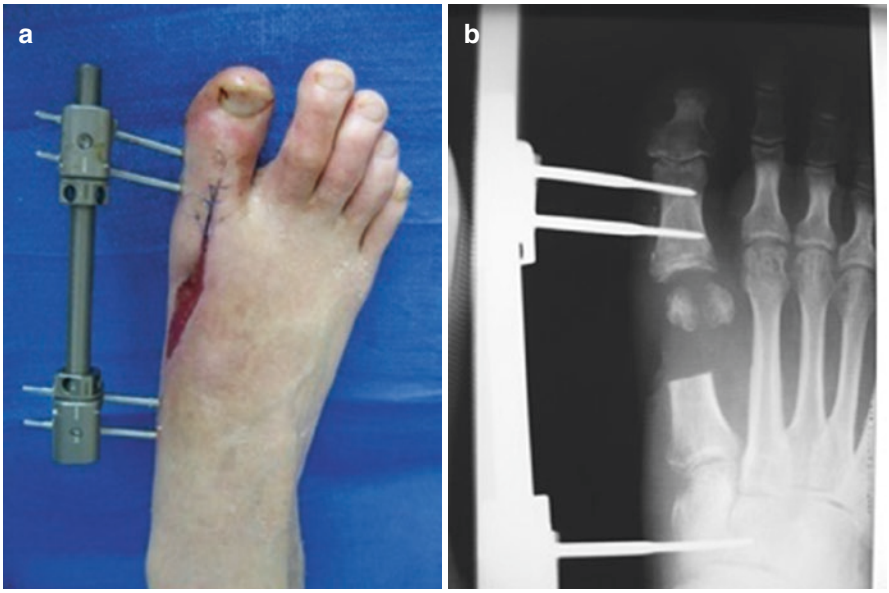

Fig. 15.4 Clinical (**a**)and radiographic (**b**) image of external fixation used as a spacer

result of injury or subsequent infection is a very serious problem, and ankle fusion often a main alternative to amputation. The choices for reconstruction using fusion are bone transport with external fixation or a vascularized bone graft [33, 36, 37].

In the event of bone loss, progressive compression at a rate of 1 mm/day is advised. Kovoor et al. presented a study of ankle fractures involving bone loss, which recommended distraction at the corticotomy site starting seven to 10 days after operation and continued until the bone ends had docked or limb-length discrepancy had been equalized. The frame was removed when the ankle fusion had united and the regenerated bone matured [33].

15.7 Conclusion

Charcot arthropathy is a serious disease and is often accompanied by several associated complications. Its management is crucial and limb salvage is the optimal goal in treatment and patient satisfaction. Early detection of a Charcot foot is critical. Appropriate lab work, imaging, and clinical examination should be performed. External fixation has proven effective in use of all stages of Charcot foot. In acute Charcot foot, it stabilizes to avoid an increase in malpositioning of the bones frequently formed in the arthropathy. When reconstructions are performed, both internal and external fixation can increase rates of success, as the external fixation is versatile and can be utilized as a compressive device or as an external cast. External

fixation has been effective in protecting wound sites, graft sites, and flap sites, eliminating deforming forces and allowing for efficient healing. Space can be maintained with the use of external fixation and septic fusions can be achieved in situations that require it. The use of external fixation has proven to be an excellent choice during surgical correction of the Charcot foot with or without the presence of infection.

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Chapter 16
Strategies for Leg Amputation in Patients with Charcot's Arthropathy

Julia Fayanne Chen and Bauer E. Sumpio

16.1 Introduction

Painless bony and articular destruction of the foot was first described in neuropathic patients with syphilis by Jean-Martin Charcot in 1868. Charcot arthropathy later came to encompass any painless bone and joint destruction caused by longstanding neuropathy. In the modern day, diabetic mellitus is now the leading cause of Charcot's arthropathy [1]. Unfortunately, due to the painless nature of this deteriorative process, many patients do not seek medical attention until significant irreversible musculoskeletal deformities and tissue loss have occurred. While a number of techniques for foot and ankle fixation and/or reconstruction are available [2–5], in patients who have developed ulcers, osteomyelitis or severe ankle instability and deformity, major proximal lower extremity amputation may be indicated [6–8]. However, because of the underlying nature of the disease, healing an amputated limb that has been affected by Charcot's arthopathy can prove challenging. We will review in this chapter amputation strategies and post-operative care unique to this patient population.

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16.2 Hypervascularity and Edema Associated with Charcot's Arthropathy

Charcot's arthropathy is a progressive, degenerative process, which is a consequence of denervation of the foot and ankle joints. The etiology and pathophysiology of this process remains unclear, however, despite vigorous studies investigating this devastating complication [9–11]. Two well-respected theories have traditionally been relied upon to clarify the pathogenesis of this disorder: the French neurotrophic theory (Fig. 16.1a) [12, 13], and the German neurotraumatic theory [14, 15] (Fig. 16.1b).

As research has progressed on the molecular level, the validity of each of these theories has only become more solidified, and their pathways more interwoven. For example, recent studies have pointed to the disturbance of the inflammatory cycle as a trigger to the course of events described in each theory. Charcot patients have been shown to have an imbalance in pro vs. anti-inflammatory cytokines as a result of lack of CGRP (calcitonin gene-related protein), a neuropeptide that plays a key role in inhibiting proinflammatory cytokines [16–18]. As a result, Charcot patients not only experience repetitive trauma due to insensate foot, they also undergo abnormally intense and prolonged inflammatory responses following each trauma. This

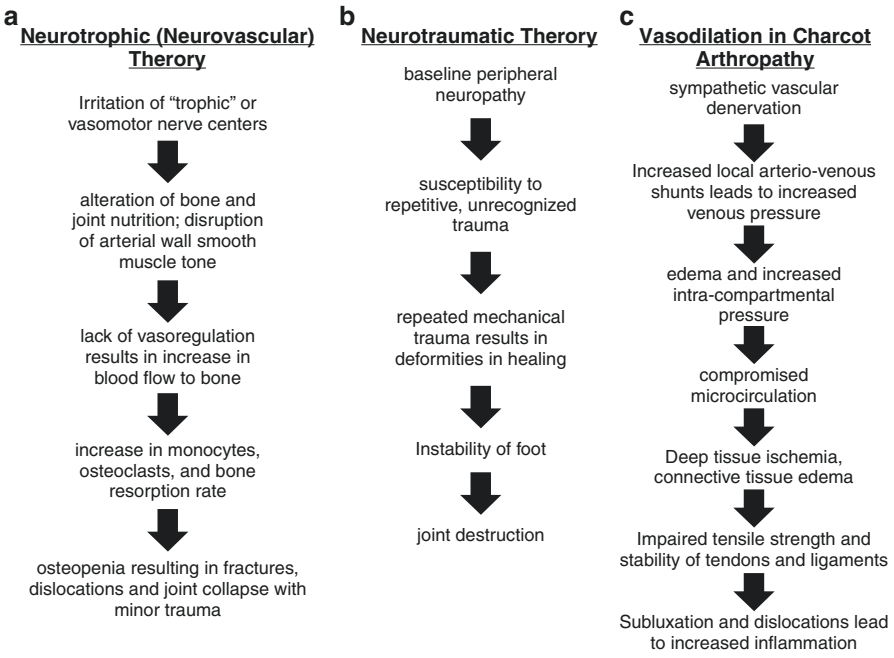

Fig. 16.1 (**a**) Neurotrophic (neurovascular) theory; (**b**) Neurotramatic theory; (**c**) Vasodilation in Charcot arthropathy

results in excessive osteoclastic activity leading to increased bone turnover, ultimately leading to osteolysis [18–20].

Furthermore, the role of vasodilatation (Fig. 16.1c) resulting in increased bone perfusion, as initially implicated by Charcot, has also been further elucidated. The rarity of Charcot arthropathy could lie in the fact that an intense inflammatory response in a neuropathic limb nevertheless relies on a sufficiently intact vasomotor response. The neuropathic limbs must retain the ability to increase blood flow in response to a stimulus, which is not typically the case [20]. Two studies [21, 22] have suggested that, when compared to patients with diabetic neuropathy alone, Charcot patients are unique in that they retain the ability to vasodilate. For example, maximum microvascular hyperemia has been shown to be significantly high in patients with diabetic Charcot compared to patients with diabetic neuropathy alone [22]. Additionally, it has been shown that Charcot patients and healthy patients have comparable levels of skin blood flow and vasomotion compared to patients with diabetic neuropathy [21]. Conversely, it has been noted that peripheral arterial disease appears to have a protective effect on the development of Charcot arthropathy [23], possibly as a consequence of the limited vasodilation ability of affected arteries (Fig. 16.1c). This cycle of pathophysiology results in a pathologically vascular and edematous limb, posing inherent obstacles to healing after amputation.

16.3 Amputation and Wound Care Strategy

The amputation strategy for Charcot arthropathy is based on the fact that the Charcot-affected limb is in a pro-inflammatory, edematous, hypervascular state, which is not ideal for primary closure. A surgical procedure will only incite more inflammation and edema, increasing the likelihood of wound dehiscence. Thus, we have advocated a two-stage procedure in combination with negative pressure wound therapy (NPWT) [24]. Specifically, the algorithm consists of an initial open ankle disarticulation, followed by NPWT for 5–7 days to the open stump combined with leg elevation. This strategy provides for control of any residual infection and leg edema. A completion below-knee amputation (BKA) with posterior flap is then performed. In many patients with persistent edema, we just perform a partial closure to the level of the fascia, and further application of NPWT at the skin and subcutaneous level until the wound heals by secondary intention.

The efficacy of NPWT has been demonstrated repeatedly in literature, with positive results including reduction in post-operative inflammation, stump edema, wound dehiscence, in addition to increased granulation tissue formation [25]. The goal of NPWT following the first-stage ankle disarticulation is to optimize the lower leg by decreasing edema and inflammation. During the period of NPWT between the first and second stages, leg elevation and compression is encouraged. Following completion BKA, NPWT is also frequently applied over closed fascia to ensure successful definitive closure.

16.4 Case Study: (Patient RO)

This is a 36 year-old male with poorly controlled type II diabetes mellitus and Charcot arthropathy on his right lower extremity with an open plantar ulcer. Previous MRI had demonstrated no evidence of osteomyelitis, and arterial studies were obtained pre-operatively to confirm arterial vascular sufficiency prior to amputation (Fig. 16.2).

He underwent right ankle disarticulation using a tourniquet just below the right knee (Fig. 16.3). An incision was made along the ankle joint, and sharp dissection was used to remove the foot in entirety. Brisk bleeding was noted from the lower extremity vasculature, and a considerable amount of time was spent achieving hemostasis using electrocautery and suture ligation of small vessels. At the completion of the procedure, the tourniquet was removed and the wound was dressed with a betadine-soaked kerlix dressing followed by ACE bandage for compression.

The following day, NPWT was applied to the open stump. This was changed every other day until the second stage completion BKA (Fig. 16.4).

As noted in Fig. 16.4, edema is significantly decreased by the time patient underwent completion BKA, which was performed 1 week later with a standard posterior flap. A tourniquet was again applied as previously described in the first stage procedure.

A Jackson-Pratt drain was placed into the lateral aspect of the wound, and the stump was then closed to the level of fascia using 2–0 Vicryl sutures. The subcutaneous wound was then again irrigated with normal saline and pulse irrigation. This level of tissue was left open and NPWT was applied intra-operatively to the

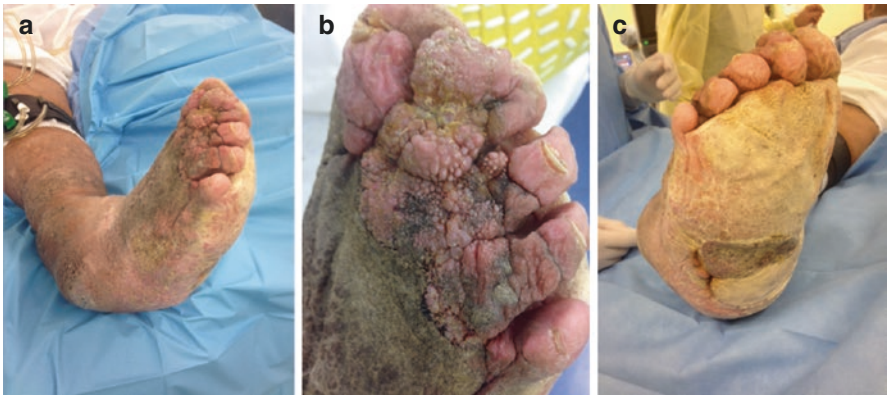

Fig. 16.2 Pre-operative right foot. (**a**) note inversion and swelling of ankle indicative of late-stage deformity; tourniquet applied prior to ankle disarticulation (**b**) extensive verrucae from chronic edema; (**c**) plantar surface; note rounded bottom from mid-foot arch collapse and wound from previous attempted surgical repair

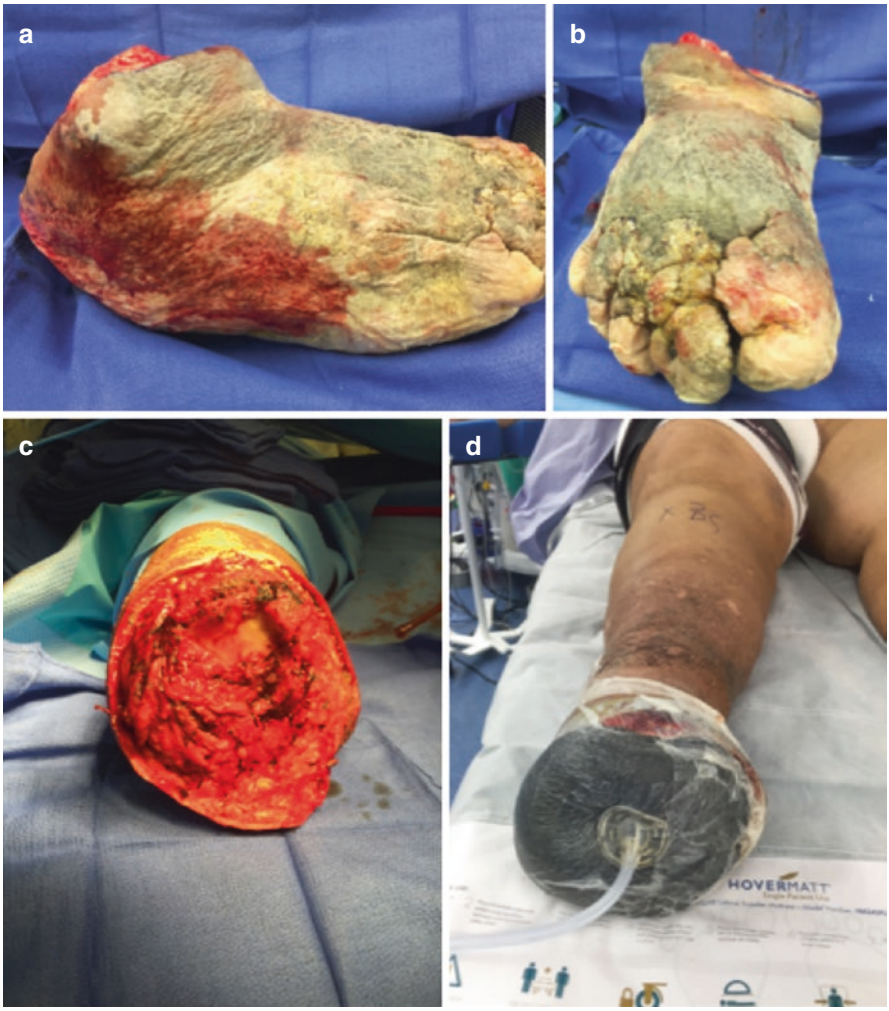

Fig. 16.3 Open ankle disarticulation. (**a**) lateral view of amputated foot; (**b**) AP view of amputated foot; (**c**) open wound immediately following disarticulation; (**d**) application of NPWT to open wound

area over the closed fascia. Immediate post-operative prosthesis (IPOP) was then applied.

This patient was discharged to rehab after one VAC change in the hospital. He continued to undergo VAC changes every 48–72 h, with discontinuation of the VAC approximately 7 weeks post-op. The wound fully healed shortly thereafter, and he was independent on a prosthetic by 2 months (Fig. 16.5).

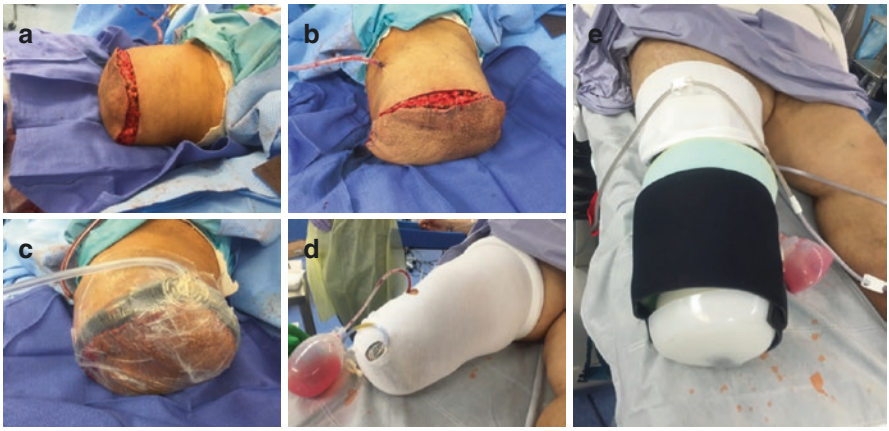

Fig. 16.4 Completion below-knee amputation. (**a**) medial view of BKA stump with fascia closed and subcutaneous tissue left open; (**b**) AP view, note Jackson-Pratt drain; (**c**) NPWT applied; (**d**) protective stocking placed over stump prior to IPOP placement; (**e**) IPOP in place

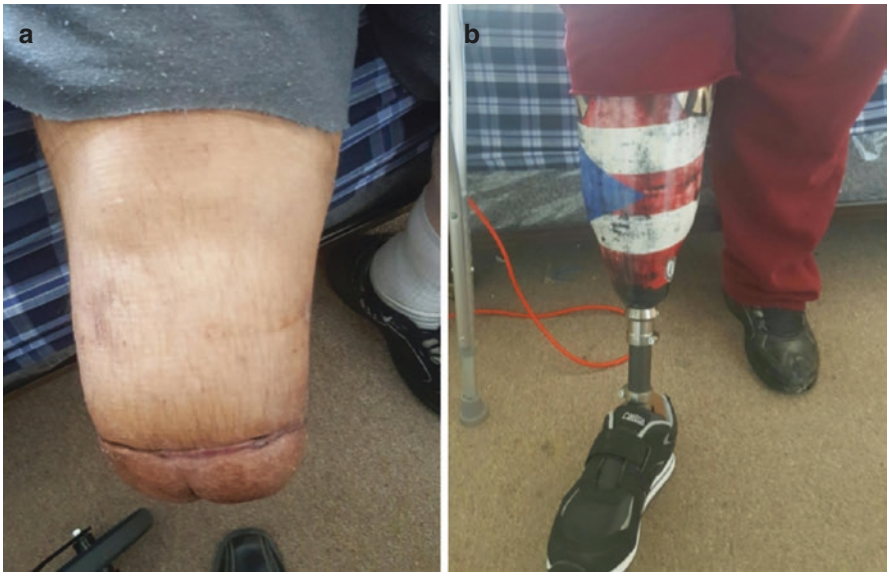

Fig. 16.5 (**a**) Two months post-op with a healed stump; (**b**) Ten weeks post op with fitted prosthetic

16.5 Negative Pressure Wound Therapy (NPWT)

The primary available commercial device to deliver localized negative pressure to a wound is the vacuum assisted closure (VAC) device (KCI, TX). The benefits of VAC were first described by Argenta and Morykwas [26, 27] in 1997, and it has since

been demonstrated to be effective in healing wounds of all types, including infected wound beds, traumatic injuries, surgical incisions and diabetic foot wounds. The mechanism of NPWT remains somewhat elusive [25], but the general understanding is that negative pressure promotes angiogenesis and microvessel maturation [8, 28], in addition to upregulation of biochemical factors that lead to formation of granulation tissue and increased collagen deposition [29], all of which result in accelerated wound healing.

With respect to patients undergoing two-stage amputation for Charcot arthropathy, NPWT plays separate roles at each stage. Following ankle disarticulation, the primary objective of VAC placement is to decrease edema, assist with bacteria clearance and thus reduce inflammation. The VAC is not placed directly in the operating room in order to first ensure adequate hemostasis 24–48 h following ankle disarticulation. The Charcot limb is hypervascular and immediate application of NPWT could result in moderate blood loss. Following completion BKA, the purpose of NPWT is then to improve wound healing, especially in patients that have persistent subcutaneous fluid. In this case, the VAC is placed immediately in the operating room because the surface area of the wound is less and the subcutaneous fat is less likely to bleed.

16.6 Immediate Post-operative Prosthesis (IPOP)

The final step in our algorithm is application of an immediate post-operative prosthesis (IPOP) in the operating room immediately following BKA. Traditionally, soft compressive dressings have been used to manage post-operative BKAs. These dressings are changed daily until complete stump healing before initial prosthesis fitting. On the other hand, the IPOP is a rigid dressing typically made of plastic, fiberglass, or a combination of both. In addition to maintaining an extended knee, it is designed to control edema and shape and protect the limb. Anecdotal evidence has suggested that this type of dressing helps reduce pain. Perhaps more importantly, recent studies have also shown that use of an IPOP reduces the rate of surgical revision and encourages early ambulation and rehabilitation, resulting in psychological benefits and decreased complications from prolonged bedrest [30–33].

16.7 Conclusion

Our approach to amputation of the Charcot limb has been carefully designed, taking into account the unique pathophysiology of this disease in order to optimize patient outcomes. The algorithm is grounded in a two-stage amputation that assumes the newly amputated Charcot limb will require further conditioning prior to closure. This is achieved with the use of NPWT, which plays key roles in reduction of edema and inflammation followed by accelerated wound healing. Additionally, application

of the appropriate post-operative dressing, in this case the IPOP, further ensures a favorable outcome. Our amputation strategy acknowledges the complexity of healing not just a diabetic wound, but a diabetic Charcot's limb. It tackles the problematic aspects of Charcot's hypervascularity and vasodilation from multiple angles, taking into consideration the need to "prime" a less than ideal wound, which ultimately should result in fewer wound complications and revisions.

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Part III
Ischemic Foot

Chapter 17
Introduction to the Ischaemic Foot: Limb Salvage Pathway and Algorithm

Michael E. Edmonds, Bauer E. Sumpio, Daina Walton, and Nina L. Petrova

17.1 Rationale for Modern Management

Recently, there has been a change in the approach to the ischaemic foot, including the diabetic ischaemic foot. Previously specific attention was paid to the clinical entity of the critically ischaemic foot in which there was a marked reduction in perfusion leading to imminent death of tissues and gangrene unless it was revascularised.

Recent attention to less severely ischaemic but nevertheless threatened limbs has been epitomised in the Global Vascular Guidelines, which have recently proposed the term Chronic Limb Threatening Ischaemia to include a broad heterogeneous group of patients with varying degrees of ischaemia ranging from the severe ischaemia (i.e. the previous critical ischaemia) to the mild or moderate ischaemia which can often delay wound healing and increase amputation risk [1].

This is exemplified by the recent WIfI classification of peripheral arterial disease [2]. This grades ischaemia from severe ischaemia WIfI grade 3, which demands revascularisation to the less severe grades of ischaemia (WIfI ischaemia grades 1 and 2) which may selectively benefit from revascularisation, if the wounds of such limbs fail to progress (or regress) despite appropriate limb care (infection control and wound care) after 4–6 weeks treatment. In diabetes, WIfI ischaemia grade 1 and 2 refers to the neuroischaemic foot which is often complicated by ulceration and infection and WIfI ischaemia grade 3 to the critically ischaemic foot.

As well as directing attention to ischaemia, the WIfI classification encourages the clinician to assess the extent of any wound or gangrene and the degree of infection,

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which leads to an objective classification of the threatened limb based on the extent of the wound, ischaemia, and infection [2]. Limbs are then grouped into four stages based on estimated risk for limb loss. Multiple studies have validated WIfI as a predictor of increased major amputation rates, length of stay, and re-interventions [3–5].

The Global Vascular Guidelines also propose the adoption of the Global Limb Anatomic Staging System (GLASS) which provides a matrix to assess two levels (femoral-popliteal and tibial) regarding arterial vasculature with the aim of restoring a single arterial pathway to the foot. Restoration of straight line flow to the foot is a primary goal of revascularisation, particularly in patients with tissue loss. GLASS assesses the distribution and the severity of the varying lesions in the leg and grades them according to the chances of success with endovascular treatment [6].

17.2 Management of the Diabetic Ischaemic Foot

17.2.1 Step 1. Classification of the Diabetic Ischaemic Foot Into Neuroischaemic, Critically Ischaemic and Acutely Ischaemic Foot

Clinically, it is important to classify the diabetic ischaemic foot into neuroischaemic, critically ischaemic and acutely ischaemic foot based on the clinical presentation (Chap. 18) and haemodynamic parameters (Chaps. 19 and 20) as shown in Fig. 17.1. Special clinical consideration should be given to two other ischaemic presentations, namely the renal ischaemic foot (Chap. 27) and the ischaemic Charcot foot (Chap. 28). The presence of heart failure and the need for dialysis in diabetic patients with ischaemic foot ulcers is associated with a high risk of amputation and mortality [7].

17.2.2 Steps 2 and 3

Step 2 is revascularisation and step 3 is debridement and wound care. However, the order and timing of each depends on the degree of ischaemia, the extent of tissue loss and the aggressiveness of any complicating infection.

17.2.3 Step 2. Revascularisation

In this step, revascularisation is carried out with initial planning through non- invasive assessment (Chap. 19) and digital subtraction, computed tomography (CT) and magnetic resonance (MR) angiography (Chap. 21).

The acutely ischaemic foot needs emergency revascularisation and the critically ischaemic foot needs urgent revascularisation (Fig. 17.1). For the neuroischaemic

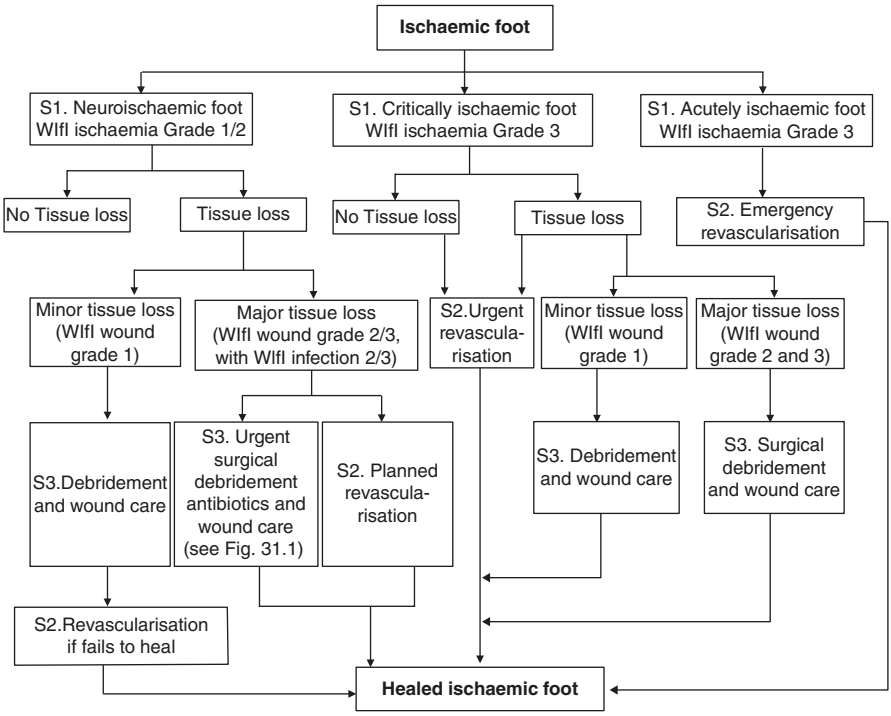

Fig. 17.1 Algorithm for limb salvage pathway of the ischaemic diabetic foot. The WIfI gradings of wound, ischaemia and infection are explained in Chap. 1. The prefixed numbers (S1–3) refer to the intervention steps described in the text

foot, revascularisation needs to be planned and this depends on the extent of tissue loss and complicating infection (Chaps. 24 and 25).

Revascularisation is carried out by either endovascular techniques (Chaps. 22 and 23) or by open surgical bypass procedures with due regard for the angiosome concept (Chaps. 24, 25 and 26). The relative roles of each are discussed, including the role of the hybrid procedure of endovascular and bypass surgery (Chap. 24).

Recently deep venous arterialization has been described in patients with critical limb ischemia including in those with renal failure and on dialysis (Chap. 27). Various techniques have been used. Percutaneous approaches have been described. Using a dedicated, ultrasound-guided crossing method to create an arteriovenous fistula, a crossing stent is deployed from the artery to the vein to divert flow into the peripheral venous system [8]. Seven patients with critical limb ischaemia and no traditional endovascular or surgical revascularisation options (no-option critical limb ischaemia) were recruited in a pilot study to determine the safety of percutaneous deep venous arterialization. Complete wound healing was achieved in 5 of 7 patients at 12 months with a median healing time of 4.6 months. Five underwent minor amputation of one or more toes, and two underwent major amputations within 12 months giving a 71% limb salvage rate.

Gandini et al. described an endovascular distal plantar vein arterialization: from a subintimal channel in the occluded plantar artery an entry was intentionally pursued into the distal plantar vein. The technique was attempted in 9 consecutive diabetic dialysis patients and was successful in 7 patients [9].

A further study combined three complementary techniques: a surgical bypass on the dorsal or plantar foot veins, a percutaneous technique for valvulectomy of the foot veins with balloon angioplasty, and the embolisation of collaterals to focalise blood distally. The key point was the replacement of a single-step vascular procedure with multiple staged endovascular steps aimed at different pathophysiological targets and the combination of hybrid foot vein arterialisation (HFVA) with a dedicated foot surgical treatment. At a mean follow-up of 10.8 ± 2 months, limb salvage was achieved in 25 (69%) limbs and wound healing in 16 (44%); nine patients had unhealed wounds and eleven (31%) patients underwent a major amputation (2 below the knee and 9 above the knee) [10].

17.2.4 Step 3. Debridement and Wound Care

The nature of debridement and its timing depends on the extent of tissue loss and any complicating infection which is often a feature of the neuroischaemic foot. If there is major tissue loss in the neuroischaemic foot, comprising WIfI wound grade 2 or 3, this is usually caused by WIfI infection grade 2 or 3, and surgical debridement needs to be carried out urgently and antibiotics administered followed by wound care (Chaps. 29, 30 and 31). Revascularisation is required if there is major tissue loss or if there is subsequent poor progress in wound healing (see Fig. 17.1). Minor tissue loss should be treated with sharp debridement either in the clinic or if necessary, operatively followed by wound care.

The critically ischaemic foot needs urgent revascularisation and if there is major tissue loss with or without infection, then surgical operative debridement should be carried out preferably at the same time and antibiotics administered if necessary (see also Fig. 31.1). With minor tissue loss, debridement can be carried out in the clinic or if necessary operatively, pre- or post- revascularisation.

Recently, sucrose octasulphate dressing has been shown to be of benefit in neuroischaemic ulcers. In a randomised, double blind, controlled trial, wound closure occured in 48% of participants who were treated with sucrose octasulphate dressings compared with 30% in the controls (95% CI 5-30; Adjusted odds ratio 2.60, 95% CI 1.43-4.73; p = 0.002) [11].

17.3 Conclusion

The diabetic ischaemic foot can be divided clinically into the neuroischaemic foot, the critically ischaemic foot and the acutely ischaemic foot. The limb salvage pathway comprises revascularisation, debridement and wound care. However, the

ischaemic foot is often associated with infection, particularly the neuroischaemic foot, which needs aggressive antibiotic treatment and also debridement. Furthermore, the recent COMPASS study has shown that in patients with PAD taking Rivaroxiban 2.5 mg twice daily and Aspirin 100 mg daily, the incidence of total vascular amputations was reduced by 58% [12].

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Chapter 18
Presentation of Ischaemic Foot

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18.1 Scenarios of the Diabetic Ischaemic Foot

Peripheral arterial disease has become an increasing cause of ischaemia contributing to diabetic foot disease [1, 2]. The presentation of the ischaemic foot includes the neuroischaemic foot, the critically ischaemic foot and the acutely ischaemic foot. [3, 4]. Infection often complicates the neuroischaemic foot and can lead to a septic vasculitis resulting in necrosis and a "diabetic foot attack." In the critically ischaemic and acutely ischaemic foot, it is ischaemia itself that leads to tissue necrosis and a "diabetic foot attack." Recent guidelines have proposed the term chronic limb threatening ischaemia to take the place of critical ischaemia. This new category will include both the neuroischaemic and the critically ischaemic foot and thus a diverse group of patients with varying degrees of ischaemia that can delay wound healing and increase amputation risk [5]. In the present publication, however, the categories of the neuroischaemic foot and the critically ischaemic foot have been kept separate, as in the context of diabetes, they have distinctive presentations and pathogeneses.

Although not included as a main subdivision of ischaemia, peripheral arterial disease in diabetic patients with renal failure often presents with distinct necrotic lesions not necessarily related to infection but probably due to disease of the small arteries of the foot in the so called renal ischaemic foot. Another presentation of necrosis, particularly to the toes, are emboli to the digital circulation.

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18.2 Neuroischaemic Foot

The neuroischaemic foot is characterised both by ischaemia from stenosis or occlusion of the leg and foot arteries and also by neuropathy which predisposes to ulceration [3]. The degree of ischaemia is mild to moderate. The perfusion in the neuroischaemic foot is usually sufficient to maintain the tissues intact in the absence of minor trauma and ulceration but cannot be increased adequately to heal an ulcer or to control a complicating infection.

Tissue loss and infection are common at presentation. Claudication and rest pain may be absent because of peripheral neuropathy [3]. Ulceration in the neuroischaemic foot usually develops on the margins of the foot over a bony prominence. The classical sign of pre-ulceration in the neuroischaemic foot is a red mark on the skin, which can be difficult to detect in dark skin. It is often triggered by tight shoes or a slip-on style shoe leading to frictional forces on the vulnerable margins of the foot. This leads to the formation of a bulla or blister. The bulla can develop into a shallow ulcer with a base of sparse pale granulations or yellowish closely adherent slough. Pressure over bony prominences directly leads to partial thickness ulceration and, in the absence of relief, full thickness ulceration with exposed tendon and bone.

Ulcers, tissue loss and necrosis mostly occur on the forefoot, particularly on the medial (Fig. 18.1) and lateral aspect (Fig. 18.2) but the commonest sites are the apices and the margins of the toes (Fig. 18.3). If toe nails are allowed to become overly thick, they transmit pressure onto the nail bed leading to ulcers developing beneath the toe nails.

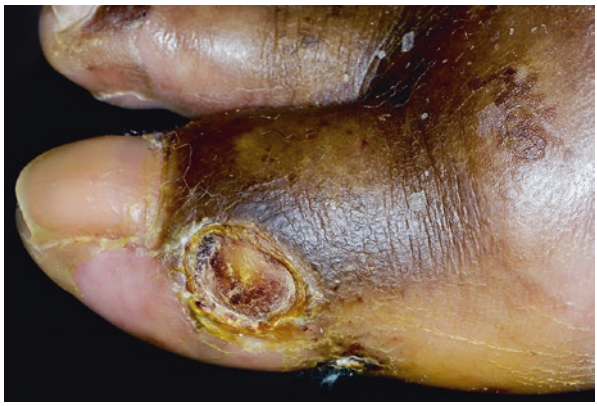

Fig. 18.1 Ischaemic ulcer on medial aspect of 1st toe

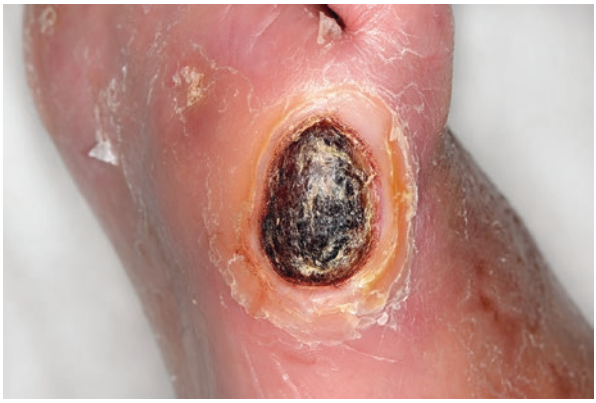

Fig. 18.2 Necrotic ulcer over lateral aspect of 5th metatarsal head

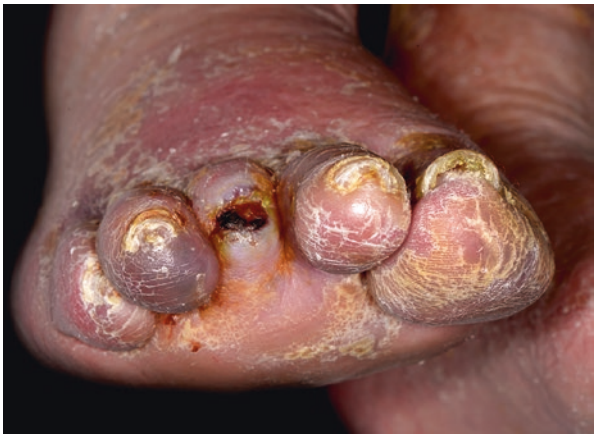

Fig. 18.3 Necrosis of tip of 4th toe, and previous partial amputation of 3rd toe

18.3 Critically Ischaemic Foot

Peripheral arterial disease usually advances steadily in the diabetic patient, and eventually results in very low levels of arterial perfusion. The severity of reduction in limb perfusion leads to borderline viability as the ischaemia is so severe that it threatens the integrity of the tissues, namely the situation of 'critical ischaemia.' The final reduction in blood supply is usually caused by a thrombosis (or embolism) complicating the existing atherosclerotic disease [6].

Pain may be present in the foot although this depends on the degree of ischaemia and also neuropathy. This pain is relieved by lowering the foot e.g. by hanging it over the side of bed. A classical sign of critical ischaemia is that the foot is pale on

elevation and becomes red on dependency which is called a positive Buerger's test (Fig. 18.4). The pink painful red "sunset foot" with taut shiny skin is typical of critical ischaemia. The critically ischaemic foot will progress eventually to develop localised areas of ulceration and necrosis. Toes may become cyanosed and will progress to necrosis unless the foot is revascularised (Fig. 18.5).

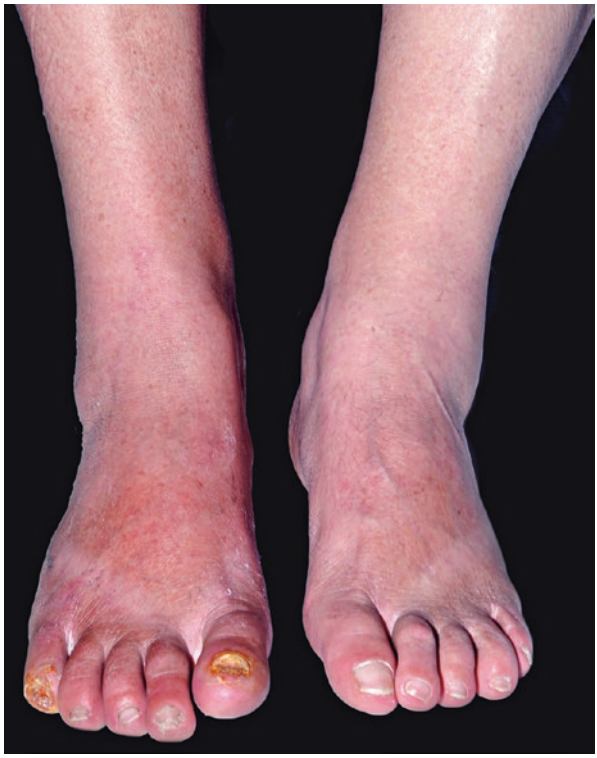

Fig. 18.4 Critically ischaemic right foot showing rubor on dependency

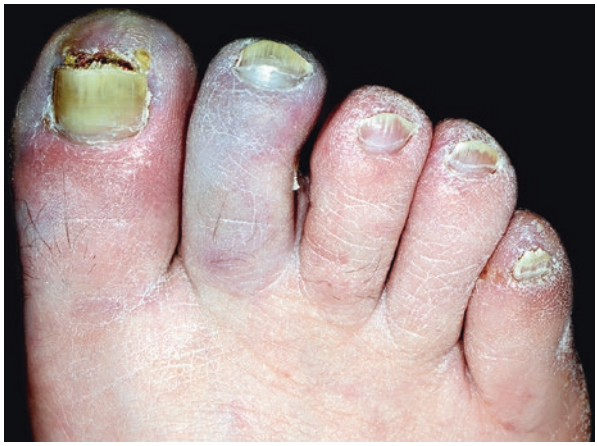

Fig. 18.5 Critically ischaemic foot with cyanosis of 1st and 2nd toes

18.4 Acutely Ischaemic Foot

Acute ischaemia is usually caused either by sudden thrombosis complicating an atherosclerotic stenosis in the superficial femoral or popliteal artery or by emboli from proximal atherosclerotic plaques in the aorta, iliac, femoral or popliteal arteries. Emboli may also originate from the heart in atrial fibrillation or after myocardial infarction. Acute ischaemia presents as a sudden onset of severe and constant pain in the leg associated with pallor of the foot, quickly followed by its mottling and slatey grey discolouration. The severity of pain will depend on the degree of neuropathy. The lack of perfusion causes numbness, paraesthesiae and eventually paralysis and the foot becomes extremely cold. However, the diabetic patient may not suffer severe paraesthesiae because of concomitant sensory neuropathy, which reduces the severity of ischaemic pain and may thus delay presentation. In addition to foot pallor, a purple blue discolouration of the toes leading on to necrosis of the toes is also seen in acute ischaemia. The presence of fixed mottling of the skin and tenderness of the muscles indicate that the limb is probably irreversibly ischaemic.

18.5 Renal Ischaemic Foot

Diabetic patients with end stage renal failure often have heavily calcified narrowed arteries below the knee and the ankle [7]. These patients classically present with spontaneous dry necrosis of the toes (Fig. 18.6) [8]. Digital necrosis may be precipitated by trauma and can spread to involve the mid-foot and hind foot (Fig. 18.7). Superadded infection is common.

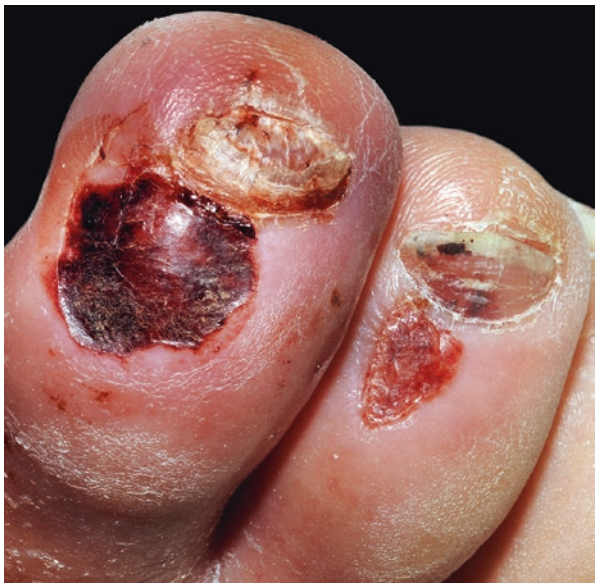

Fig. 18.6 Localised digital necrosis in renal ischaemic foot

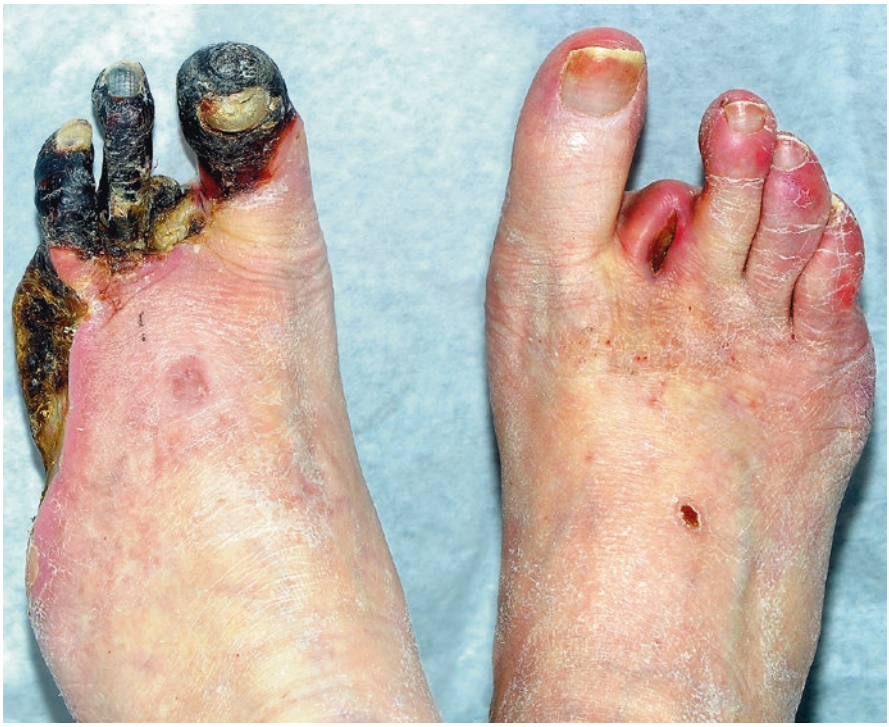

Fig. 18.7 Digital necrosis and previous minor amputation in a renal ischaemic left foot

18.6 Embolism to the Toes

Another cause of necrosis, particularly to the toes, is embolism to the digital circulation often originating from atherosclerotic plaques in the aorta and leg arteries [8]. Occasionally, emboli are dislodged from arterial plaques during angioplasty. The initial sign may be bluish or purple discolouration which is quite well demarcated but which quickly proceeds to necrosis (Fig. 18.8). If the necrotic area escapes infection, it will dry out and mummify. Microemboli present with painful petechial lesions in the foot that do not blanch on pressure.

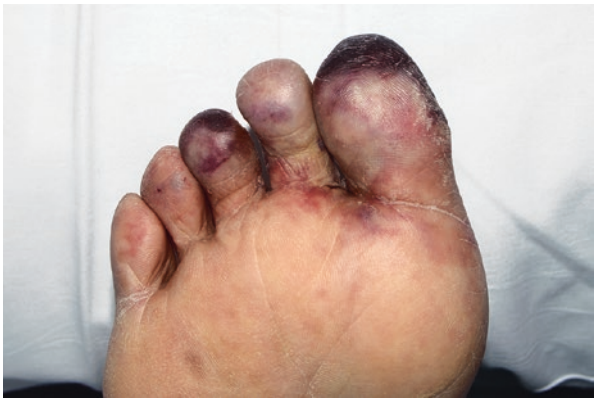

Fig. 18.8 Necrosis of tips of 1st and 3rd toes and discolouration of 2nd toe from emboli to the toes

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Chapter 19
Ischaemic Foot: Noninvasive Assessment Including Surveillance of Peripheral Arterial Grafts

Chris Adusei Manu, Domenico Valenti, and Benjamin J. Freedman

19.1 Introduction

Peripheral artery disease (PAD) is more common in patients with diabetes and around half of patients with a diabetic foot ulcer have co-existing PAD [1–3]. Patients presenting with diabetes foot ulceration have a high risk of major amputation and more than 50% mortality rate at 5 years. However, the mortality rate is even higher, at 70%, when patients have PAD, characterized by atherosclerotic occlusive disease of the lower extremities. Although much is known regarding PAD in the general population, the assessment and management of PAD in those with diabetes is less well understood. The diabetic foot is different because three great pathologies come together in the diabetic foot; neuropathy, ischaemia and infection. PAD is often more subtle in its presentation in patients with diabetes than in those without diabetes. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in diabetic patients the lesions are more likely to be more diffuse and distal. Importantly, PAD in individuals with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback. Patients with PAD and diabetes experience worse lower-extremity function than those with PAD alone [4]. Also, diabetic patients, who have been identified with PAD, are more prone to sudden ischemia of arterial thrombosis [5], or may have a pivotal event leading to neuroischaemic ulceration or infection and the risk of amputation. By identifying a patient with subclinical disease and instituting

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preventative measures, it may be possible to avoid limb-threatening ischemia. The aim of this chapter is to give an overview of some of the common non-invasive modalities for the assessment of native PAD and also the patency of arterial grafts in the lower limb.

19.2 Modalities of Assessment

19.2.1 Medical History

A detailed clinical history can form a very important component of the peripheral vascular assessment by eliciting possible indicators of signs and symptoms of peripheral vascular disease. A good history needs to include enquiries about previous foot ulceration or amputations as well as the existence of other microvascular and macrovascular complications, such as in Table 19.1, including the existence of retinopathy, nephropathy and other cardiovascular diseases. The existence of cardiovascular risk factors should be explored, including the use of tobacco and duration of cigarette smoking. The patient with diabetes may have neuropathy and a very distal disease which may result in suppression of some of the vascular symptoms summarised in Table 19.1. Thus, for example the classical history of claudication and rest pain may be less common in patients with diabetes and advanced neuropathy. However, a patient may remark on more subtle symptoms, such as leg fatigue and slow walking velocity, which may be missed or simply attributed to getting older.

Table 19.1 Key aspects of non-invasive assessment via a clinical history

Past clinical history of:
• Amputation
• Angioplasty
• Vascular surgery
• Smoking
• Charcot foot
Existence of other diabetes complications:
• Retinopathy
• Nephropathy
• Cardiovascular complications (IHD, hypertension, stroke)
• Neuropathy
Vascular symptoms:
• Rest pain
• Claudication
• Cold feet or coolness of feet

IHD (Ischaemic Heart Disease)
Table 19.1: Illustrates some of the key aspects patients' history that needs to be extracted in a detailed clinical history when assessing for the existence of possible peripheral vascular impairment

19.2.2 Clinical Examination

A good clinical examination should comprise of a thorough inspection, followed by palpation and manoeuvres where indicated. The patients' feet and legs should be fully exposed and examined in a room with good lighting. On inspection one needs to look for possible signs of vascular impairment; loss of hair, thinning of skin, muscle wasting especially between metatarsals, skin discolouration, thickened and brittle nails. In the presence of severe ischaemia, there may be evidence of tissue loss and digital gangrene (Figure 19.1). The clinical examination of the vascular supply should include palpation of the femoral, popliteal, posterior tibial and dorsalis pedis pulses and should be characterized as either "present" or "absent" [6]. Other manoeuvres can be used as part of the clinical examination, such as the use of the capillary refill time, and assessment for blanching on elevation of the limb and a subsequent rubor on dependency which would indicate critical ischaemia. A comprehensive examination of the foot should also include assessment of the appropriateness of the footwear to make sure that it is not causing rubbing, erythema, blister, or callus formation on the foot. As it is well documented that there may be significant PAD even in patients with palpable foot pulses, other non-invasive measures of peripheral circulation are needed to complement the clinical examination when assessing the degree of decreased peripheral circulation [7, 8].

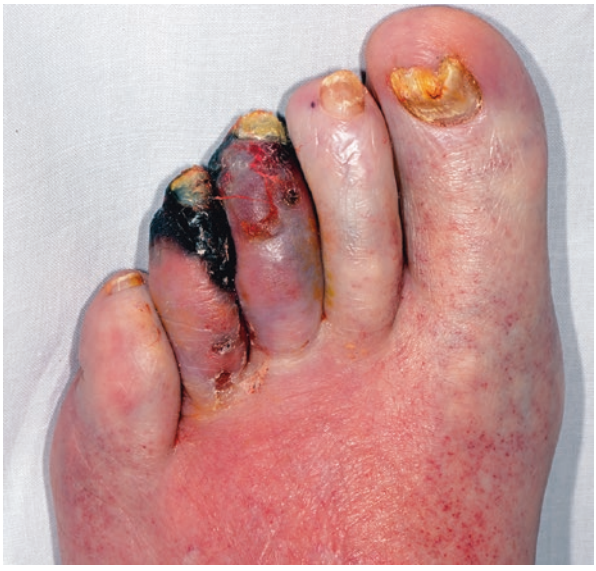

Fig. 19.1 Critically ischaemic foot with dry digital necrosis and brittle nails

19.2.3 Ankle Brachial Index (ABI)

Arterial pressure measurements in lower extremities were first described by Naumann in 1930 [9]. In 1950, Winsor first used ABI measurements in patients with peripheral arterial disease [10]. The ABI is well established as a simple and easily reproducible method of diagnosing vascular insufficiency in the lower limbs. Blood pressure at the ankle (dorsalis pedis or posterior tibial arteries) is measured using a standard Doppler ultrasonic probe, or a laser Doppler in more modern equipment, to measure return of flow at the distal extremity. The ABI is obtained by dividing the higher ankle systolic pressure by the brachial systolic pressure. An ABPI >0.9 to <1.3 is presumed to be normal. ABI <0.8 is usually associated with claudication but this may not necessarily be the case in patients with diabetes and neuropathy. An ABI of <0.4 is commonly associated with ischemic rest pain and tissue necrosis (Table 19.2). The ABI may therefore be part of the annual comprehensive foot exam in these patient subgroups. Although the ABI is used to indicate adequacy of peripheral blood flow in patients without diabetes, it is less reliable in diabetic patients because calcification of the media of the distal arteries [11, 12]. The calcification makes the vessels relatively non-compressible, resulting in an artificially high systolic pressure in the ankle or supra-systolic ankle pressures. The effect of calcification of the artery leading to falsely elevated ABI is obvious when ABI is >1.3. However this phenomenon is more challenging to recognise in patients with moderate stenoses which lead to pressure loss in the arterial system. This is obscured by the stiffening of the arteries leading to an ABI reading in the normal range, thus leading the observer into a false negative interpretation. This error can be reduced if the ABI is not interpreted in isolation but alongside a subjective assessment of Doppler waveform quality.

Table 19.2 Interpretation of ABPI

ABI range	Interpretation
0.91–1.30	Presumed normal
0.70–0.90	Mild obstruction of PAD
0.40–0.69	Moderate obstruction of PAD
<0.40	Severe obstruction PAD
>1.30	Poorly compressible falsely high

The ABI is presumed to be normal between if 0.91–1.30, and more likely to be influenced by calcification when readings are more than 1.3, however it should be noted that in the cohort of patients with diabetes and medial calcification even those with reading between the presumed normal range of 0.91–1.30 may still have a degree of PAD

19.2.4 Doppler Ultrasound Scans

This test uses ultrasound to look at the blood flow in the arteries and veins in the legs and foot. It uses high frequency sound waves (ultrasound) to measure the amount of blood flow through the blood vessels, and in expert hands can give very good anatomical illustration of the flow in the leg, as illustrated in Fig. 19.2.

This can help to diagnose and treat a variety of conditions, including impaired circulation. It is a risk-free and pain-free procedure that requires little preparation, but is very operator dependent. The Doppler ultrasound can estimate how fast blood flows by measuring the rate of change in its pitch (frequency), demonstrating if the flow is normal as in a triphasic, or biphasic waveform or is reduced as in a monophasic as illustrated in the sample tracing in Fig. 19.2. During the procedure of

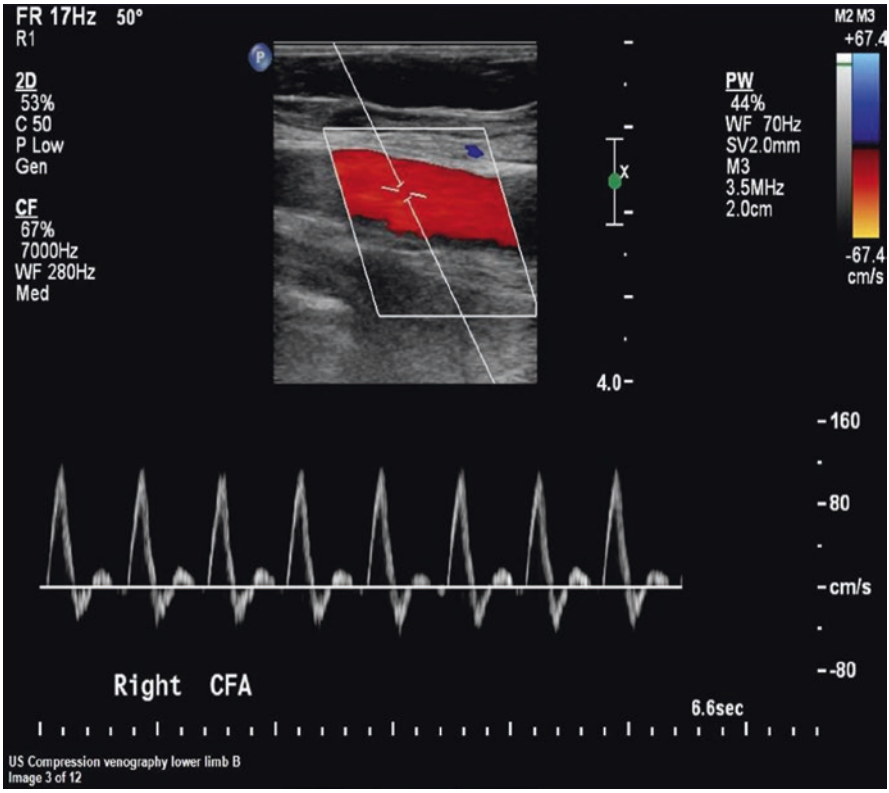

Fig. 19.2 Doppler spectrum normal appearances of a peripheral artery showing colour flow and spectral Doppler information with its characteristic triphasic Doppler waveform

Doppler ultrasound, a hand-held transducer is held against the skin over the area of the body being examined, and then it is moved it from one adjacent area to another. As such, it may be limited or restricted by subjects who have painful ulceration in the areas of examination or interest. Recently, tibial waveform analysis has been shown to be the best screening tool to exclude peripheral arterial disease [13]. Thus, Doppler ultrasound can therefore be a useful non-invasive assessment of peripheral blood flow, as well as helping to plan for interventions.

A normal ABI alongside a normal triphasic Doppler waveform is reassuring whereas a normal ABI with reduced velocity, monophasic Doppler waveform indicates further evaluation is required. When the ABI is >1.30, other modalities of assessment, such as toe brachial index (TBI) and transcutaneous partial oxygen pressure ($TcPO_2$) are recommended.

19.2.5 Toe Brachial Index (TBI)

Toe digital arteries are perceived to be less likely to be calcified so toe occlusive pressure measurements seem to be more reliable and more reflective of pressure within the digital artery. Therefore, the toe brachial index (TBI) is deemed to be a more valuable indicator of foot perfusion in patients with diabetes [11, 12]. In a recent study, TBI was found to be useful for selecting those needing diagnostic testing [13]. It may however, be more challenging to perform in patients with diabetes and clawed toes, when standard hand held Doppler is used, but with the appropriate equipment such as the laser Doppler, it can be done much more easily and reliably, as illustrated in Fig. 19.3. Guidelines by the International Working Group on the Diabetic Foot, propose that the presence of PAD is unlikely if the TBPI is ≥0.75 [14]. A toe pressure of ≥30 mmHg. is associated with an increased pre-test probability of healing by at least 25% but when the toe pressure is < 30 mmHg, urgent

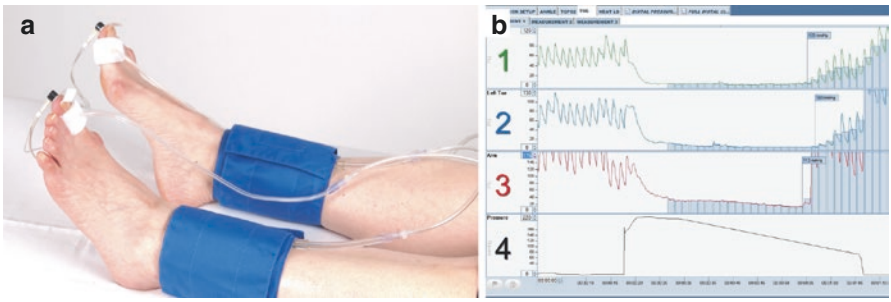

Fig. 19.3 Illustrating the measurement of TBI with laser: (**a**) Illustrating the placement of pressure cuff and laser Doppler probe on toes and pressure cuff on ankle. (**b**) Illustrates an example of a toe pressure measurement. Panels 1, 2 and 3 indicate blood flow in right toe, left toe and arm respectively. Blood flow is occluded by the rise in pressure in the cuff which is shown in panel 4. As the pressure in the cuff falls, there is a return of flow as depicted in panels 1, 2 and 3. The cuff pressure at the return of flow indicates the systolic toe pressure (Image provided courtesy of Perimed AB)

vascular imaging and revascularisation should be carried out. It is nevertheless important to note that toe pressures may also be falsely elevated by the same factors that affect ABI (i.e. possible digital calcification), although perhaps not to the same extent as it affects the ABI. The measurements of toe pressure may therefore be complemented by other measurements of the distal circulation such as $TcPO_2$ and laser Doppler flowmetry.

19.2.6 Transcutaneous Partial Oxygen Pressure

Transcutaneous partial pressure oxygen ($TcPO_2$) measures the local oxygen released from the skin through the capillaries, and is therefore accepted to be reflective of the metabolic state of the lower limb at the area of the measurement. It is particularly useful for prediction of wound healing, assisting in determination of possible safe amputation level and also in assessing patients for suitability for hyperbaric oxygen therapy. Transcutaneous oximetry is also recommended as a means to quantify the severity of ischemia and to stratify the prognosis in patients with severe ischaemia as well as being useful to diagnose PAD in patients with calcified arteries and loss of toes. However, it needs to be acknowledged that it is a bedside technique that ought to be performed in a standardised manner by trained healthcare professionals. Figure 19.4 illustrates the concept of the technique and sample tracings. Readings of

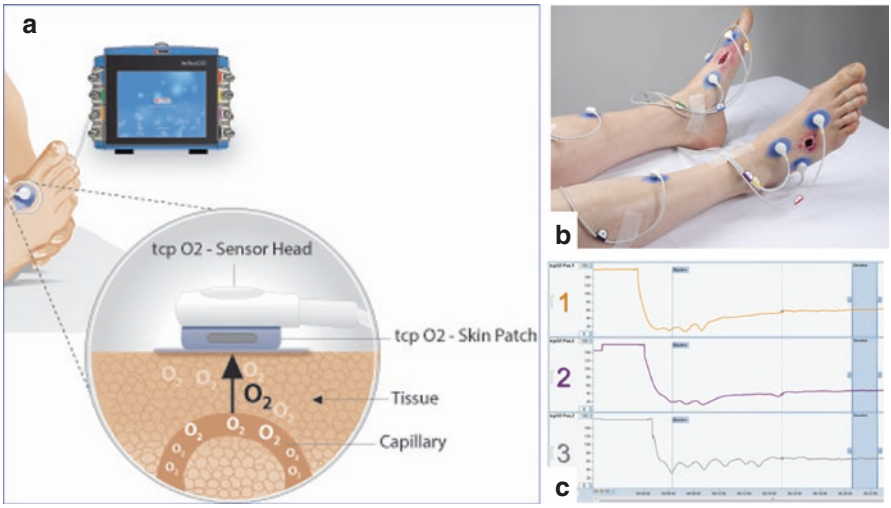

Fig. 19.4 Illustrating the measurement of forefoot transcutaneous partial pressure of oxygen. (**a**) This illustrates the measurement of pressure via the sensor which quantifies the excess tissue space oxygen which has diffused from the capillary bed into the interstitial space and has not been consumed in cellular metabolism. (**b**) Positioning of the sensor 1, 2 and 3 around a wound on the foot is illustrated to give readings as depicted in **(c)** showing initially the calibration curve and then the gradual increase in $TcPO_2$ until a study state is reached after about 15–20 min and this level is taken as the transcutaneous partial pressure of oxygen (Image provided courtesy of Perimed AB)

>40 mmHg are deemed to be associated with good ulcer healing, whereas readings of less than 25 mmHg are associated with PAD and poor wound healing and readings of 25–40 mmHg are deemed to be moderate PAD [14]. There is also the possibility of using a reference point such as the chest or forearm and also to measure the responsiveness to oxygen inhalation, in patients with low $TcPO_2$ pressures.

19.2.7 Pulse Wave Velocity (PWV)

Pulse Wave Velocity (PWV) is a measurement of arterial stiffness, or the rate at which pressure waves move down the blood vessel. It has been established as a highly reliable prognostic parameter for cardiovascular morbidity and mortality in a variety of adult populations including older adults, as well as patients with end-stage renal disease, diabetes and hypertension. PWV can be collected by using two pressure catheters placed a known distance from one another, referred to as the Pulse Wave Distance. The time it takes the pressure wave to go from the upstream pressure catheter to the downstream pressure catheter provides the Pulse Transit Time (PTT). PWV can then be calculated by dividing the distance by the transit time and this provides a measure of cardiovascular health.

19.2.8 Skin Perfusion Pressure (SPP)

Skin Perfusion Pressure (SPP), is presumed to be reflective of the local pressure in the microcirculation, with regards to the area being measured. It has been successfully employed in the determination of amputation level, in particular when considering patients for major amputations. It is similar to the concept of capillary refill time, with the application of pressure and measuring return of flow. The actual procedure is similar to that of an ankle pressure measurement, with the difference being that of the type of probe which is used to detect the return of flow, as illustrated in Fig. 19.5. The probe is positioned underneath the pressure cuff, which then detects the change in pressure at the area as it is compressed and decompressed. There is an increased pre-test probability of healing by at least 25%, with a skin perfusion pressure ≥40 mmHg [15].

19.2.9 Heat Provocation Test

The heat provocation test can be used to determine the viability of tissue and the degree of microcirculatory impairment, as illustrated in Fig. 19.6. The increase in blood perfusion as a response to local heating is thought to indicate the reserve capacity and the endothelial function of underlying tissues. These can be important parameters for predicting healing and determining amputation level and can be used in combination with other modalities of non-invasive assessment of the peripheral vascular system.

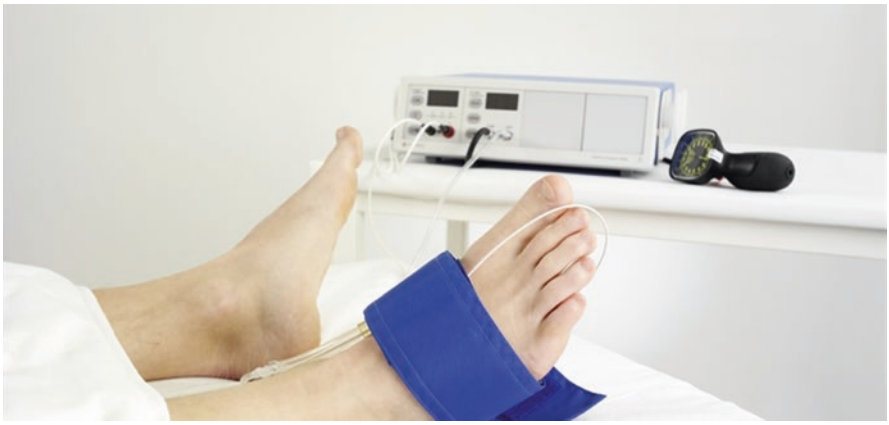

Fig. 19.5 Measurement of skin perfusion pressure. The measurement procedure is similar to an ankle pressure, with the difference that the probe which detects the return of flow is positioned underneath the pressure cuff (Image provided courtesy of Perimed AB)

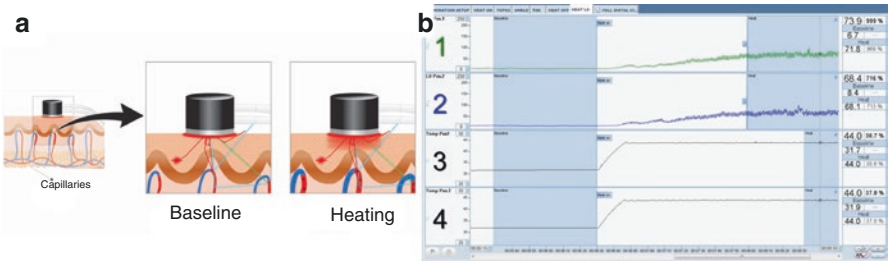

Fig. 19.6 Illustration of the heat provocation Test. (**a**) Illustrating the concept of capillary bed flow at baseline and increase in blood flow with heating using a combined laser Doppler and heat probe. (**b**) The tissue is heated and panels 1 and 2 show increase in blood flow on right and left dorsum respectively and 3 and 4 illustrate the rise in temperature reflecting the heating of the electrodes to 44°. The perfusion change from before to after the local heating is a measure of the tissue reserve capacity (Image provided courtesy of Perimed AB)

19.2.10 Duplex Ultrasound Scanning

Ultrasound imaging of the lower limb arteries has now become the mainstay of non-invasive investigation with respect to defining the anatomical location, severity and extent of obstructive lesions. Combining grey scale images with colour flow Doppler and spectral Doppler waveform analysis in real time allows accurate detection of stenotic and occlusive lesions of the entire lower limb from abdominal aorta down to digital artery level. Figure 19.2 demonstrates normal appearances of a peripheral artery showing colour flow and spectral Doppler information with its characteristic triphasic Doppler waveform. While it is recognised that ultrasound is operator dependent, in skilled hands, information can be sufficiently reliable for planning further intervention for both interventional radiology and open surgical techniques.

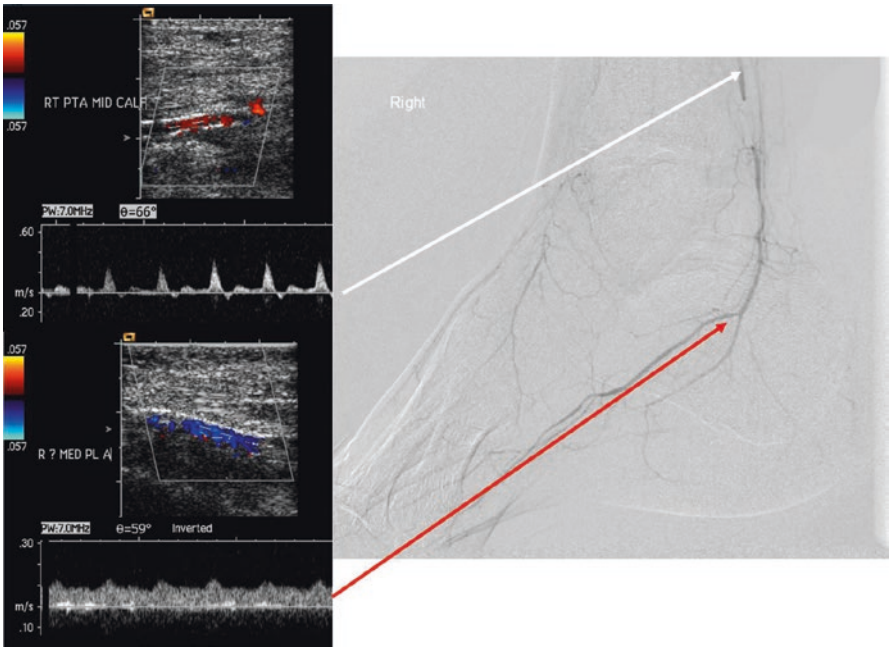

Fig. 19.7 Example of waveforms above and below very calcified lesion allowing diagnosis of haemodynamically significant lesion despite that area not being well visualised. White arrow indicates triphasic waveform above the lesion and red arrow indicates monophasic waveform below the lesion

There are challenges when performing duplex scans both general and specific to the diabetic population. Imaging of the abdominal aorta and iliac arteries can be limited as bowel gas may obscure images. Medial calcification of the arteries also obscures the lumen so detail may be lost but good understanding of haemodynamics allows the observer to make interpretations based on detected flow above and below the obscured segments. Figure 19.7 shows example of waveforms above and below a very calcified lesion allowing diagnosis of a haemodynamically significant lesion despite that area not being well visualised.

19.2.10.1 Advantages of Duplex Ultrasound

The main advantages of ultrasound over other imaging modalities are well documented, namely those of cost compared to CT and MR imaging, general availability and its non-invasive nature without need for nephrotoxic contrast agents. There are specific advantages for the diabetic population some of which are less well recognised. It is increasingly necessary for surgical bypasses to be placed to very distal arteries including arteries below ankle level. Many of these potential bypass recipient sites fail to be properly identified on the gold standard imaging techniques. Figure 19.8a demonstrates an example of a clear picture of a normal dorsalis pedis artery. Figure 19.8b also demonstrates a widely patent dorsalis pedis artery even though it has very poor flow.

Ultrasound can be especially effective for patients requiring "ultra-distal" bypass. Using modern small footprint, very high frequency ultrasound transducers, the

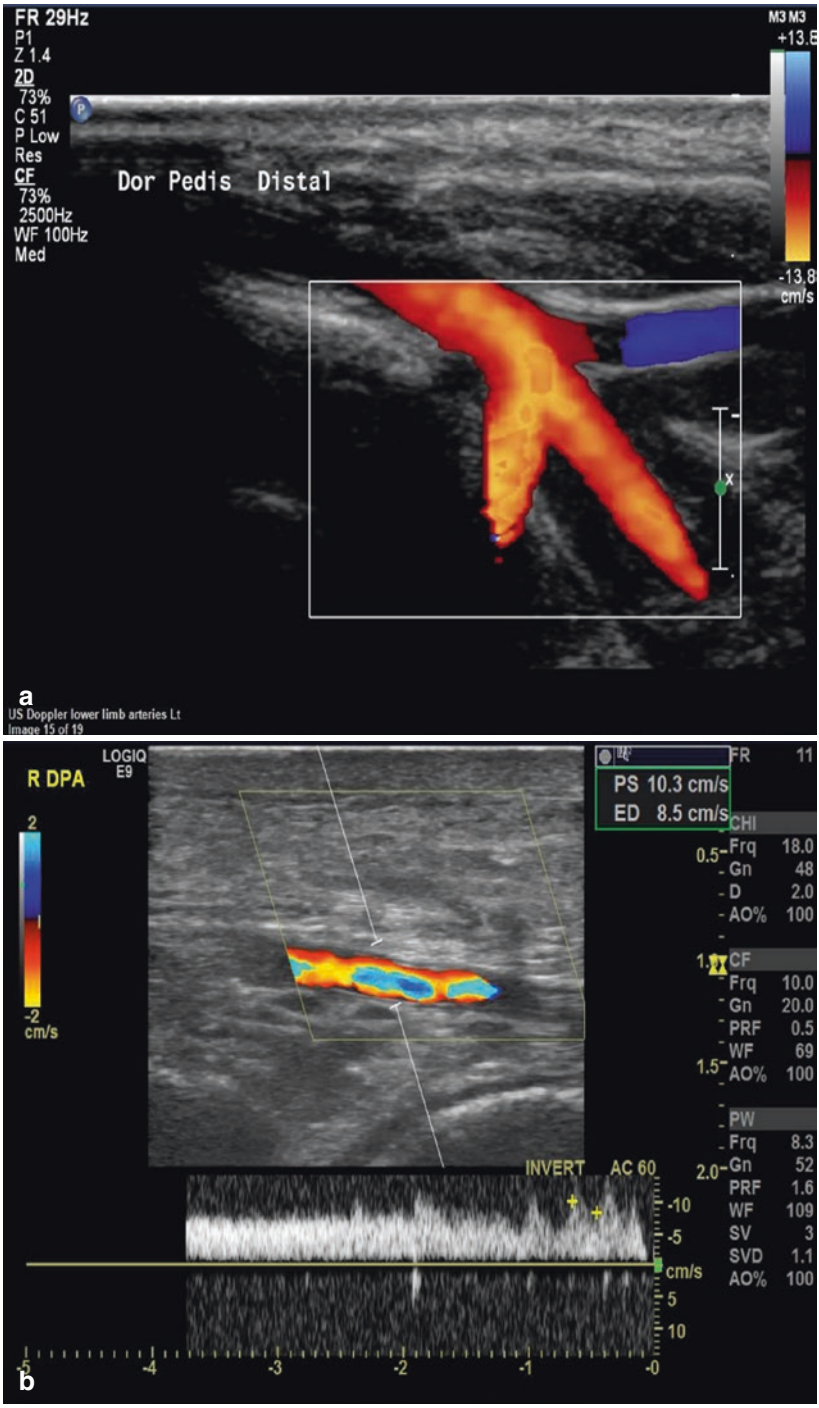

Fig. 19.8 (**a**) Normal dorsalis pedis artery and branches. (**b**) Dorsalis pedis with very poor flow but widely patent

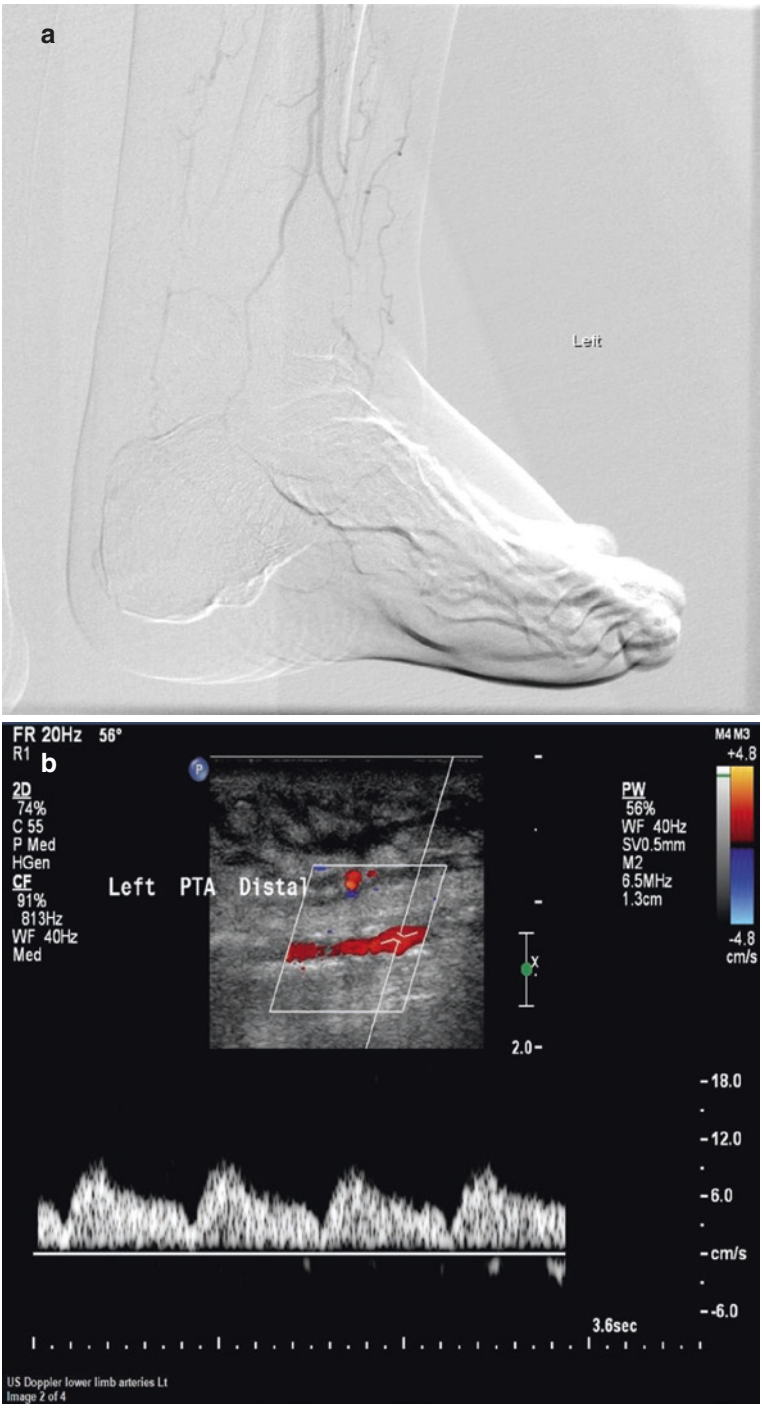

Fig. 19.9 (**a**) Angiography fails to show any by-passable recipient artery. (**b**) Duplex scan shows a patent below ankle posterior tibial artery which went on to receive a successful distal bypass

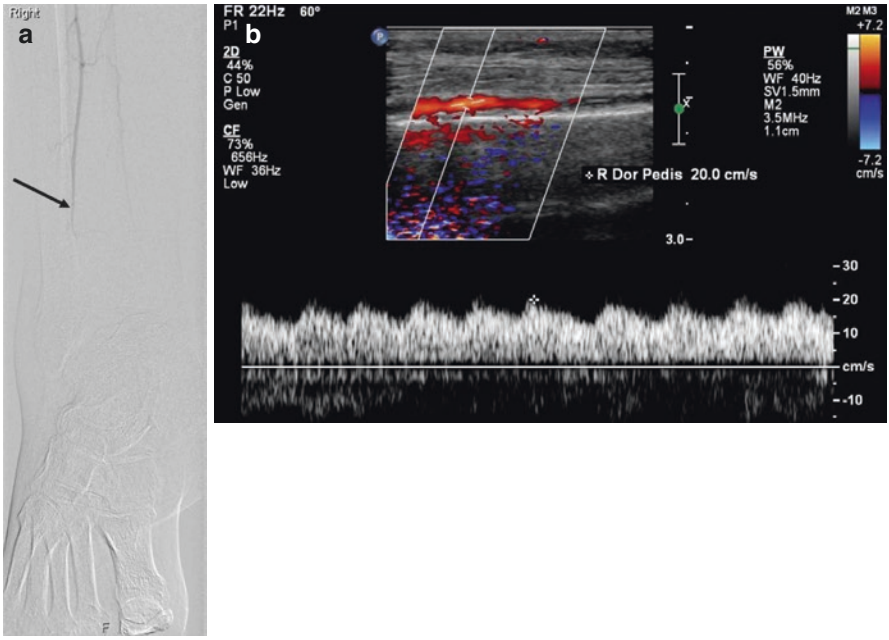

Fig. 19.10 (**a**) Angiography shows no arterial run off to the foot (arrow) (**b**) Duplex shows a patent dorsalis pedis artery

arteries of the foot can be well visualised due to their superficial nature at this level. Figure 19.9 demonstrates an example of a patient offered below knee amputation due to un-reconstructable disease at another centre. Angiography failed to show any by-passable recipient artery but duplex scan was able to demonstrate a patent below ankle artery which went on to have successful distal bypass. Similarly, Fig. 19.10 shows a further example of a patient with seemingly no arterial run off to the foot but duplex shows a patent dorsalis pedis artery.

For patients with co-morbidities such as renal failure which are increasingly common in the patient with diabetes, the nephrotoxic nature of contrast used in conventional angiography cannot be ignored. Bypass planning can in many patients be performed using a duplex only approach. As treatment strategies for managing patients with disease of the very distal arteries have developed, such as angioplasty of pedal arteries and foot arch arteries as well as very distal bypass, the diagnosis of previously unrecognised disease with ultrasound has become more important. There is a subset of patients with normal Doppler waveform appearances to the ankle level, whose foot ulcerations may have been previously dismissed as purely neuropathic or pressure point, yet they have evidence of severe stenotic lesions only below ankle level. Figure 19.11 demonstrates an example of a patient with large foot ulceration and significant arterial stenosis only below ankle level.

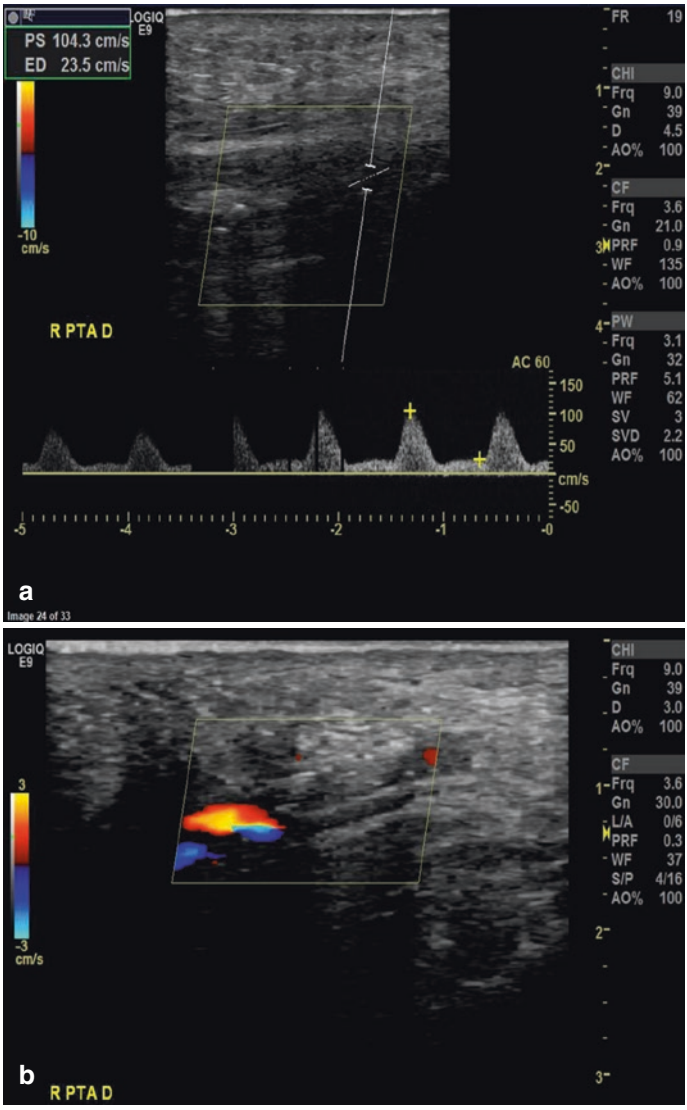

Fig. 19.11 Significant arterial stenosis only below ankle level. (**a**) Good velocity flow in posterior tibial artery to above ankle. (**b**) Localised occlusive disease of posterior tibial artery at malleolar level. (**c**) Very damped flow waveform below ankle. (**d**) Angiogram confirms duplex findings; posterior tibial artery below ankle not seen (arrow). (**e**) Balloon dilatation of below ankle posterior tibial artery (arrow). (**f**) Post angioplasty showing improved flow in posterior tibial artery (arrow)

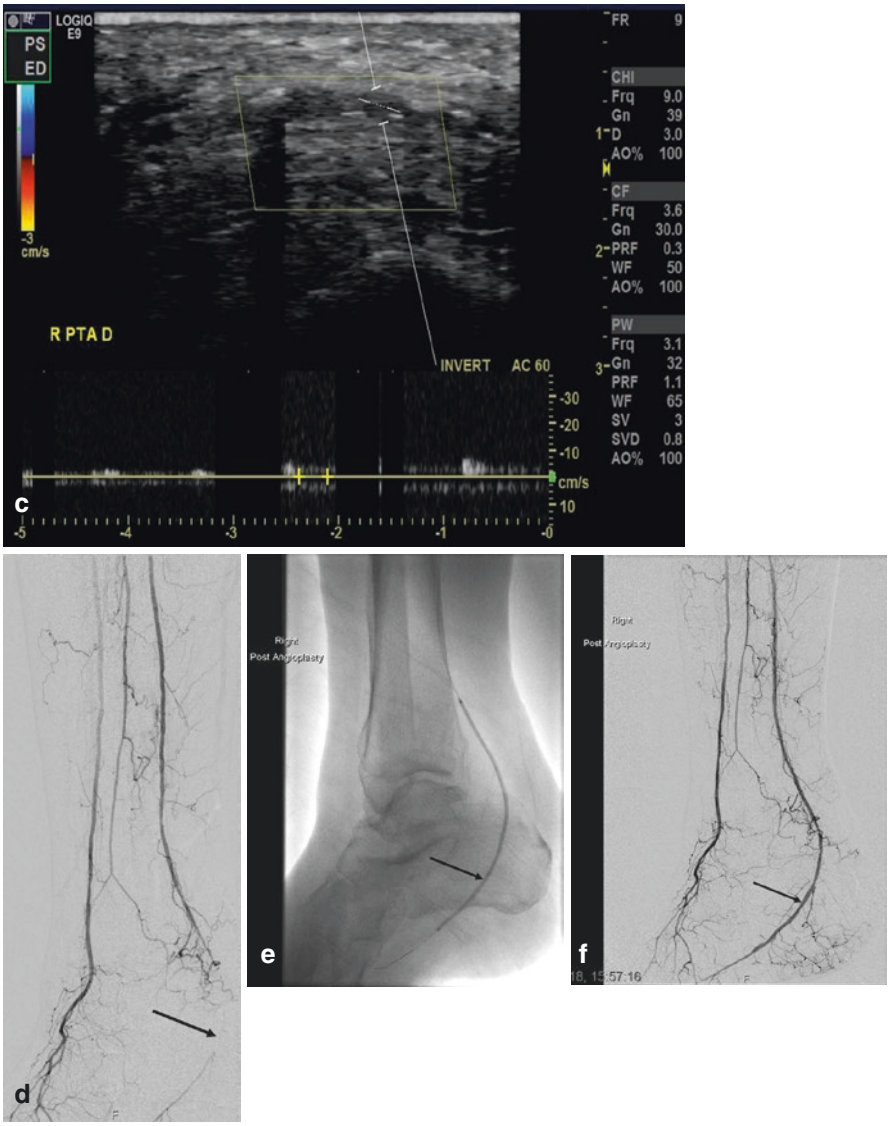

Fig. 19.11 (continued)

Ultrasound images do not have the same readily appreciable appearance as an angiogram or CTA. It has been a challenge in many institutions to ensure vascular surgeons trust the reliability of ultrasound. Supporting the scan images with a diagrammatic outline of the findings improves the confidence in ultrasound reports and in some cases reduces the need for confirmatory alternative imaging. Figure 19.12 gives an example.

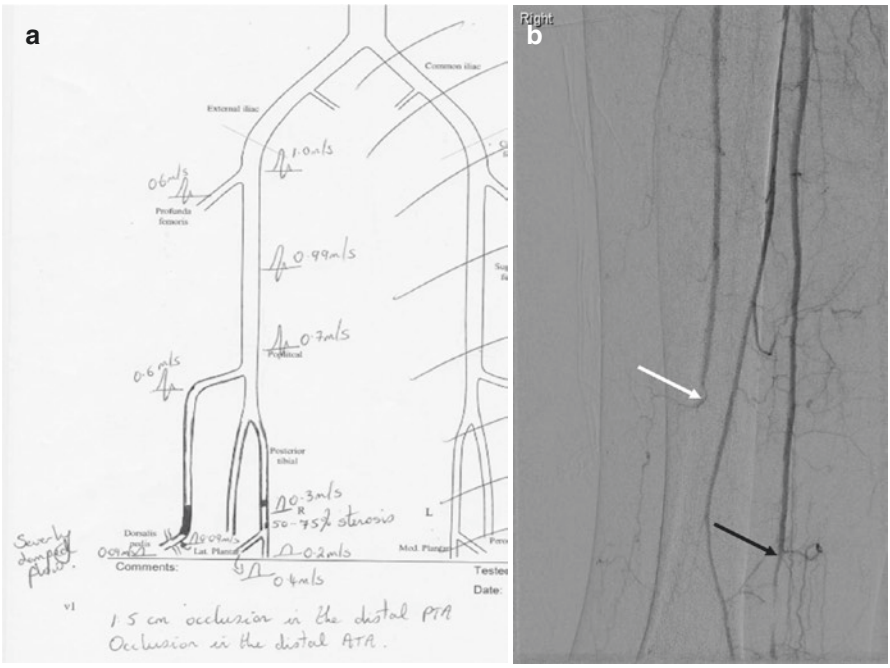

Fig. 19.12 (**a**) Example of duplex scan diagram report of the right calf arteries showing occlusions of anterior and posterior tibial arteries and patent peroneal artery. (**b**) Subsequent angiogram showing occlusions of anterior tibial (white arrow) and posterior tibial (black arrow)

19.3 Duplex Ultrasound and Surveillance of Grafts

Duplex ultrasound is valuable in the surveillance of patients with lower limb vein bypass grafts in order to pre-emptively treat patients with lesions likely to lead to graft failure.

Grafts may fail for the following reasons:

- Technical errors including intimal flaps, twisted or kinked grafts,. These usually are manifest within 30 days of the procedure.
- Intimal hyperplasia (vein grafts), affecting the conduit and anastomoses. These usually occur from 30 days to 24 months.
- Late failures after 24 months are due to the progression of disease in native arteries leading to inadequate inflow or outflow.

The practice of graft surveillance has been somewhat controversial. A prospective randomized controlled trial performed by Lundell et al. demonstrated a

significant benefit with intensive duplex ultrasound surveillance [16]. Assisted primary and secondary patency rates at 3 years were 78% and 82% in surveyed grafts compared with 53% and 56% in non-surveyed bypasses. However, Davies et al. reported the results of the Vein Graft Surveillance Randomised Trial (VGST), in which 594 bypasses were randomised to a DUS surveillance or nonsurveillance protocol. The nonsurveillance group had ABI measurement and clinical examination on the same schedule as the surveillance group. There was no difference in primary patency, assisted primary patency, secondary patency, and limb salvage between the groups [17]. While such randomised controlled trial data do not support routine use of duplex surveillance, this trial was based on a significant majority of patients with femoral popliteal bypasses in a predominantly non diabetic population Although a recent systematic review concluded that the evidence base supporting routine duplex ultrasound surveillance of infrainguinal vein grafts remains dependent on low-quality evidence, nevertheless duplex ultrasound should be incorporated in surveillance protocols of lower extremity vein grafts that can be individualized on the basis of the setting and resources [18]. At King's College Hospital, the protocol determines that once the ulceration is healed, patient's follow up is led by scientific staff without surgical input. However, urgent review by surgical teams is initiated from the duplex laboratory if significant lesions are found on the ultrasound.

Haemodynamic features of a successful infrainguinal bypass graft include an ABI >0.9 or an increase in ABI of at least 0.15. A focal increase in Peak Systolic Velocity (PSV) can be used to calculate a velocity ratio (Vr), defined as the PSV at the site of a stenosis divided by the PSV in a normal vessel segment proximal to the stenosis. Increased risk for graft thrombosis is indicated by a focal increase in PSV to 180–300 cm/s and a Vr of 2.0–3.5.The highest risk for graft thrombosis is indicated by a focal increase in PSV to >300 cm/s, Vr > 3.5, graft flow peak velocity <45 cm/s, and drop in ABI >0.15. Thus, a peak velocity within the graft <0.45 m/s is a widely used criterion for prediction of graft failure [19]. However, patients with very distal bypass grafts have successful healing and long term graft patency with lower average velocity. Severe stenosis being present with serial reduction in flow velocity seems to be the more useful predictor of impending failure but this is an area where further research is required to better define diagnostic criteria. Figure 19.13 gives an example of a patient with a below knee popliteal to below ankle level bypass graft with reducing velocity on serial scans and significant stenosis requiring angioplasty but mean graft velocity was always above the usual threshold requiring intervention.

Recent Guidelines on follow-up after vascular surgery arterial procedures have been produced by the Society for Vascular Surgery [20]. Based on the high prevalence of abnormalities detected by duplex ultrasound as well as the relatively low associated cost and risks, clinical examination, ABI, and duplex ultrasound for

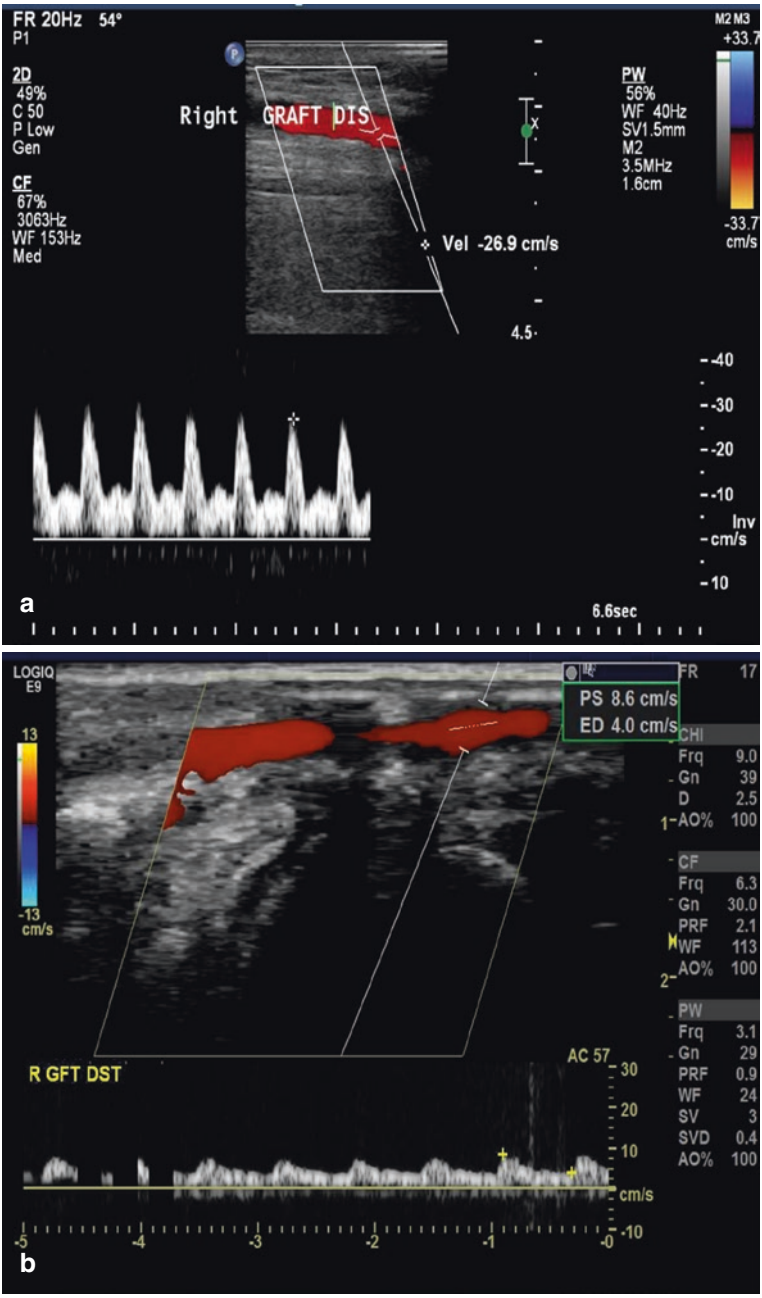

Fig. 19.13 Example of a patient with a below knee popliteal to below ankle level bypass graft with reducing velocity on serial scans and significant stenosis requiring angioplasty but mean graft velocity was always above the usual threshold requiring intervention. (**a**) Surveillance >2 years with flow below 0.45 m/s the usual threshold given for an at-risk graft but foot lesions were healed and no severe stenosis was found on ultrasound so routine surveillance. (**b**) Then subsequent surveillance shows drop in velocity and associated change in waveform due to progressive inflow stenosis (**c**) Angiogram showing inflow stenosis of popliteal artery (arrow)

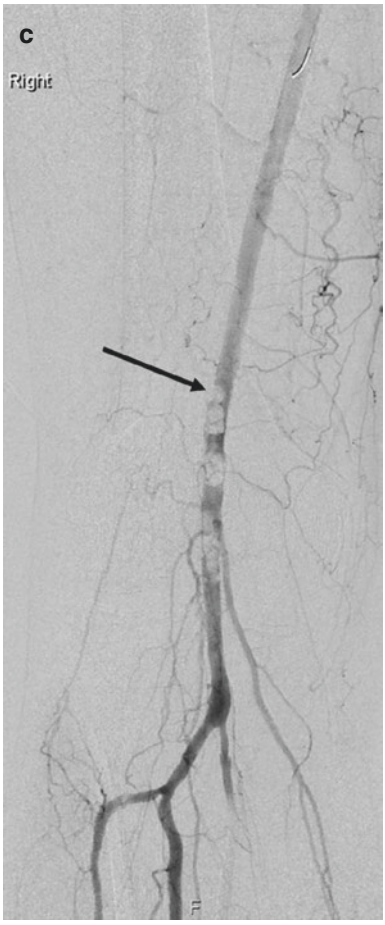

Fig. 19.13 (continued)

infrainguinal vein graft surveillance is recommended. This should include an early postoperative baseline evaluation and follow-up at 3, 6, and 12 months and at least annually thereafter. More frequent surveillance may be considered when uncorrected abnormalities are identified on duplex ultrasound or when alternative vein conduits (other than great saphenous vein) are used.

After endovascular therapy (EVT) the guidelines suggested clinical examination, ABI, and duplex ultrasound within the first month after femoropopliteal artery EVT to provide a post-treatment baseline and to evaluate for residual stenosis. Continued surveillance at 3 months and then every 6 months was indicated for patients with interventions using stents because of the potential increased difficulty of treating an occlusive vs. stenotic in-stent lesion and also for patients undergoing angioplasty or atherectomy for critical ischemia because of increased risk of recurrent critical ischemia should the intervention fail.

These guidelines also proposed clinical examination, ABI, and duplex ultrasound within the first month after tibial artery EVT to provide a post-treatment baseline and to evaluate for residual stenosis. Continued surveillance at 3 months and then every 6 months should be planned. Those patients with a deteriorating clinical vascular examination, return of rest pain, non-healing wounds, or new tissue loss should undergo repeated duplex ultrasound.

19.4 Conclusion: Advantage and Disadvantages of Non- Invasive Vascular Tests

The advantages and disadvantages of the various non- invasive bed side tests have been described and are summarised in Table 19.3. From a practical point of view the toe brachial index and the Doppler tibial waveform are useful bed side investigations, particularly as screening tests, to rule out peripheral arterial disease. The assessment and management of peripheral arterial disease in patients with diabetes is difficult but noninvasive tests are extremely useful and have replaced the role of invasive angiography as a diagnostic investigation.

Table 19.3 Summary of the advantages and disadvantages of discussed modalities of assessment

Modality	Advantages	Disadvantages
Medical History	• Achievable at no equipment cost	• Dependent on skills of clinician • Reliant on patients knowledge and engagement
Clinical Examination	• Achievable at no equipment cost	• Dependent on the clinical skills of the examiner • Signs may be masked by neuropathy
Ankle pressures (ABI)	• Well established with mortality data and outcome	• Falsely normal test in patients with calcification
Toe pressures (TBI)	• Less influenced by calcification compared to ABI	• Can be anatomically challenging to perform without appropriate equipment
Doppler Ultrasound Scans	• Ability to give a good anatomical picture in an experienced hands	• Operator dependent
Transcutaneous oxygen ($TcPO_2$)	• Ability to give an assessment of the end tissue perfusion	• May be influenced by oedema, skin impedance
Pulse Wave Velocity (PWV)	• Has good correlation data with cardiovascular outcomes and mortality	• May be more indicative of central vascular stiffness
Skin Perfusion Pressure (SPP)	• Easy and quick with the correct equipment	• May require a standardised or controlled environment
Heat Provocation Test	• Ability to give local perfusion state and vasculature reserve	• May require a standardised or controlled environment

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Chapter 20
Newer Techniques for Assessment of Foot Perfusion

Brandon J. Sumpio, Samuel M. Miller, Erik Benitez, and Bauer E. Sumpio

20.1 Introduction

The most important factor for determining the healing potential of a pedal wound is the degree of perfusion to the affected foot segment. The classic pathway for assessment involves history taking, physical examination, and review of both physiological markers and anatomical imaging obtained through non-invasive imaging [1]. However, due to the persistent rate of limb loss despite revascularization via the "best vessel" approach, there has been increasing interest in performing targeted reperfusion interventions to improve rates of limb salvage and decrease rates of secondary complications. The angiosome concept, was introduced by Taylor and Palmer more than 25 years ago, and extended to the foot by Attinger [2, 3]. Since then there have been various studies comparing outcomes for both open bypass and endovascular interventions using angiosome-based revascularization (direct) versus nonangiosome-based revascularization (indirect) [4]. As a result there has been increased interest in the development of effective diagnostic and prognostic studies to evaluate and monitor the regional (angiosome) perfusion of the affected extremity as the current modalities only provide a global assessment of the state of perfusion in the affected extremity.

Digital subtraction angiography (DSA) remains the gold standard of all imaging modalities but like computed tomographic angiography (CTA) and magnetic resonance angiography (MRA), it is an anatomic study that provides spatial resolution of arterial

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lesions but primarily assesses the status of large and medium caliber blood vessels. With the growing interests in targeted revascularization for regional areas of lower limb ischemia, new modalities are now evaluating micro-perfusion in the lower extremity guided by the angiosome model. The ideal imaging modality should be applicable to use in both planning a direct-targeted intervention as well as surveillance of the perfusion in the angiosome after the index procedure. Second, this imaging modality should be able to produce a clearly delineated wound topography as well as targets for angiosome directed interventions. Lastly, the imaging modality should be dynamic, safe, fast and easily repeatable in both the intervention and surveillance settings.

Although measurement of ankle brachial index (ABI) and pulse volume recording (PVR) [5] are widely used as a sensitive evaluation of lower limb perfusion, they provide only a global assessment. There are currently a number of physiologic and imaging modalities that attempt to provide information on regional perfusion of the foot, such as transcutaneous oximetry (TcPO2) and laser Doppler flowmetry (LDF) (Table 20.1). There are also a few newer modalities have not been sufficiently investigated in detail in patients but have promising results in animal models. These include hyperspectral imaging (HSI), which utilizes scanning spectroscopy to construct spatial maps for tissue oxygenation using visual light, as well as single photon emission computed tomography (SPECT) imaging that utilizes a combination of high sensitivity radiotracer based imaging with high resolution CT scan imaging obtaining both functional and structural information to better visualize perfusion of ischemic tissues. The adaption of the angiosome model as well as utilizing perfusion-

Table 20.1 Targeted perfusion /imaging modalities

Modality	Description	Benefits	Limitations
TcPO2	Physiologic testing to evaluate potential wound healing by measuring the partial pressure of O2 in tissue	Fast, noninvasive, cost effective Office/clinic application	The accepted level of TcPO2 that indicates tissue healing remains controversial.
LDF	Uses light penetration and absorption to evaluate microcirculatory perfusion	Fast, noninvasive, cost effective	Cannot provide absolute perfusion values, must combine with other modalities
HSI	Scanning spectroscopy to display tissue perfusion at a microvascular level. Measures oxyhemoglobin and deoxyhemoglobin, along with surface temp	Noninvasive Can be used for surveillance imaging post revascularization procedure	No large scale studies have been undertaken to verify the reliability of measurements in patient with PAD
ICGA	Traditional angiography with injection of intravascular contrast agents to visualize the vasculature and areas of tissue perfusion	Can be used to monitor perfusion closely Can perform on the spot interventions	Nephrotoxic contrast agents Costly & time consuming Invasive Study requiring direct arterial puncture for access
SPECT	Employ small amounts of radioactive substances that are injected into a vein and used with special cameras to produce images of the lower extremity vasculature and angiogenesis	Noninvasive Can be used for surveillance imaging post revascularization procedure	No large scale studies have been undertaken to verify the reliability of measurements in patient with PAD

based imaging studies allows the vascular specialists to refine their understanding of the disease process in CLI while enhancing therapeutic modalities, clinical decision-making, and improving outcomes after revascularization interventions.

20.2 Transcutaneous Oxygen Monitoring

Transcutaneous oxygen monitoring, more specifically, transcutaneous partial pressure of oxygen (TcPO2) measurement, provides information regarding local tissue perfusion and skin oxygenation (Fig. 20.1). It is an older noninvasive modality that has been studied for a variety of medical applications since the 1980s. Platinum oxygen electrodes are placed on the chest wall and legs or feet. One can use either the absolute value of the oxygen tension at the foot, or the ratio of the foot value to chest wall value. A normal value at the foot is 60 mmHg and a normal chest/foot ratio is greater than or equal to 0.9. This technology has been studied since 1982 [6], as a noninvasive assessment of the healing potential of lower extremity ulcers or amputation. This was the paper that demonstrated the utility of TcPO2 in patients with severe PAD and CLI before and after undergoing revascularizations as well as assessing amputation healing potential.

The use of TcPO2 in evaluating lower extremity perfusion after angioplasty has been extensively reported [7–9]. In one study, after revascularization of 43 diabetic patients with ischemic foot ulcers TcPO2 progressively improved in the successfully revascularized group. TcPO2 greater than 30 mmHg was seen in 38.5% of patients 1 week after percutaneous transluminal angioplasty and reached its peak of 75% postop week four [7]. Pardo et al. reported in a prospective study that after angioplasty, although both the ABI and the TcPO2 significantly increased, the ABI could not be measured in 25.4% of pre-treatment and in 17.91% post-treatment patients, while TcPO2 could be measured in all patients [8]. This was confirmed in diabetic patients with non-healing ischemic ulceration of the lower extremity who also underwent percutaneous transluminal angioplasty [9].

The utility of TcPO2 to assess amputation healing levels has been extensively studied [6]. Andrews et al., conducted a retrospective observational study of patients that underwent partial foot amputation and reported that a TcPO2 value of ≥38 mm Hg had a sensitivity and specificity of 71% for predicting healing or failure [10]. Misuri et al. similarly evaluated patients undergoing amputation due to CLI and found that 15/17 patients with successful amputations had a TcPO2 value greater than 20 mm Hg, while 11/13 failed amputations had a TcPO2 of 20 mmHg or less. The findings were statistically significant with a sensitivity of 88.2% and specificity 84.6% in predicting success or failure by this modality [11]. In a systemic review and meta-analysis [12] to determine the validity of TcPO2 as a predictor of lower limb amputation healing, there was an inverse relationship between decreasing TcPO2 values and increasing rate of amputation healing failure. However, the independent predictive value could not be precisely determined.

TcPO2 is valuable because it allows the clinician to closely evaluate the microcirculation and tissue perfusion in specific segments of the foot post revascularization.

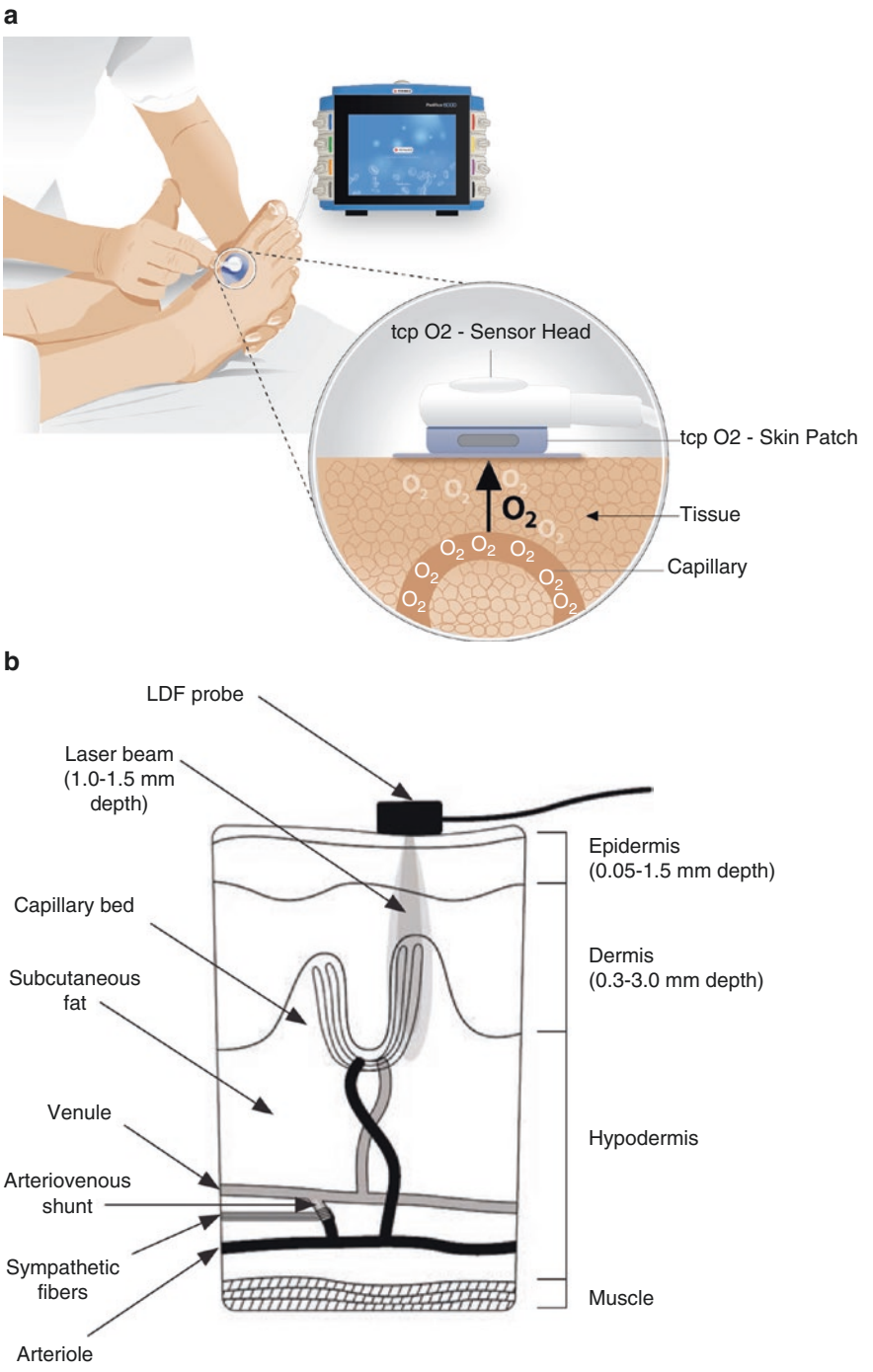

Fig. 20.1 (**a**) Schematic representation of transcutaneous oximetry. Platinum oxygen electrode heats the underlying tissue to create a local hyperemia, which intensifies the blood perfusion, increasing the oxygen pressure. In addition, the heat will dissolve the lipid structure of the dead, keratinized cells in the epidermal layer making the skin permeable to gas diffusion. Image provided courtesy of Perimed AB (**b**) Schematic representation of laser doppler flowmetry

It also serves as a supplement to the clinical exam in predicting the likelihood of wound failure in patients requiring amputation. Although the level of TcPO2 that predicts wound healing remains controversial, it is generally accepted that wounds are likely to heal if oxygen tension is greater than 40 mmHg (in the absence of diabetes, infection, and tissue edema). Patients with values of <20 mmHg are severely ischemic and will likely require either revascularization or amputation for lower extremity ulceration. However, as stated [12], a sufficiently powered study that incorporates multi-variable analysis is needed to further identify its use in clinical practice. Although there is a correlation with decreasing TcPO2 values and increasing need for re-amputation, no study has definitively shown that this modality should solely be used in the selection of amputation sites in patients failing revascularization. Local edema, skin temperature, emotional state (sympathetic vasoconstriction), inflammation, and pharmacologic agents limit the accuracy of the test. In a study that evaluated the predictive value of wound healing by measuring the TcPO2 in surgical wounds pre and post operatively [13], variances in TcPO2 values were noted and attributed to changes in oxygen delivery, metabolism, and diffusion after surgery—hyperemia, edema due to inflammatory response [14, 15], as well as trauma to the microvasculature of the wound site. The increase in the metabolic demand of the wound site tissue in comparison to normal tissue was also contributory.

20.3 Laser Doppler Flowmetry

The laser doppler measures the total local microcirculatory blood perfusion and encompasses the capillaries, arterioles, venules, and shunting vessels [16]. A laser light is emitted that is then scattered and partially absorbed as it penetrates the tissue (Figure 20.1b). Moving blood cells results in a change in wavelength (doppler shift) and the magnitude and frequency distribution of these changes related to the tissue perfusion in the targeted region. A signal proportional to the tissue perfusion at each measurement point is calculated expressed as relative perfusion units, the laser doppler flow (LDF). A color-coded perfusion image can also be generated [17].

Laser doppler can identify different regions of perfusion in lower extremities ulcers. For example, investigators [17] have measured the average LDF and the number of capillaries/mm^2 in defined regions of the skin in patients with foot ulcers. In the non granulation tissue area (ulcer area without healing), low LDF is combined with very low capillary density. In the granulation tissue area (wound healing) the highest LDF of all three areas and an intermediate capillary density is measured. In adjacent skin area (with the healing process nearly completed and no granulation tissue), an intermediate laser Doppler area flux is associated with the highest capillary density of all three areas.

Clinicians [18] have also compared the ABI obtained with traditional continuous wave Doppler (CWD) versus LDF in patients with PAD/CLI. They reported a comparable correlation between both ABI-CWD and ABI-LDF with relation to claudication distance. LDF was not limited by the technical skill of the user, and was faster and simpler. Another study [19] compared both TcPO2 and LDF of patients with symptomatic PAD and CLI that underwent revascularization. In healthy subjects peak LDF is usually observed 20–30 s following restoration of flow while in

claudicants peak LDF may be delayed for over 60 s. When supine healthy subjects assume the sitting position LDF at the toe is normally reduced by between 30 and 50%, while LDF in a leg threatened by severe ischemia increases by as much as threefold during leg dependency. Peak LDF is preferred over resting LDF, as there is greater variability in the latter's reproducibility. A peak LDF delay in excess of 100 s correlates with increased risk of failing revascularization or amputation wound healing. Time to peak LDF following a period of ischemic occlusion is closely related to total limb vascular resistance as well as vascular ischemia.

20.4 Hyperspectral Imaging

HSI utilizes scanning spectroscopy to construct spatial maps for tissue oxygenation using wavelengths (between 500 and 660 nanometers, nm) of visual light (Fig. 20.2a). These wavelengths penetrate to 1–2 mm below the skin to the

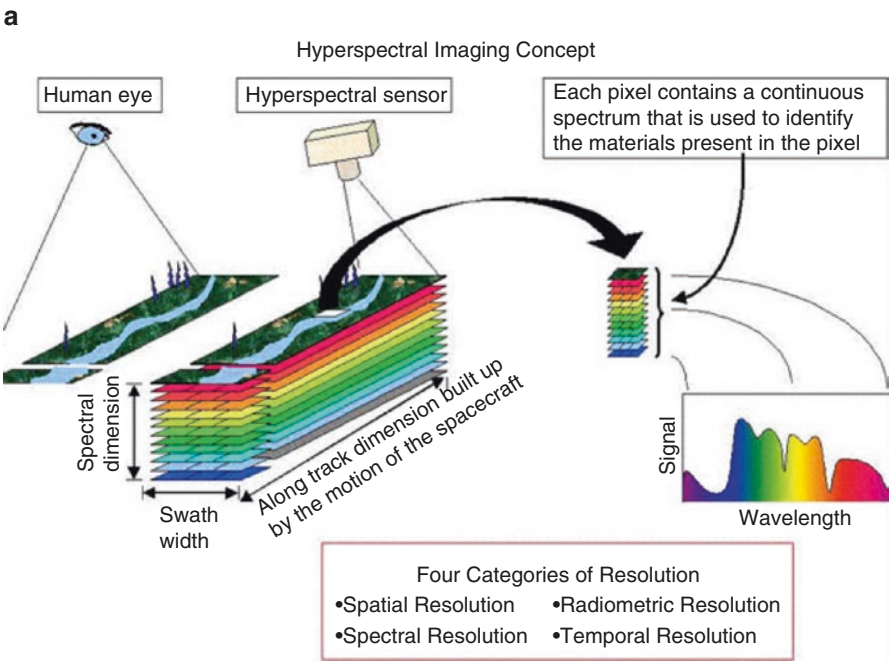

Fig. 20.2 (**a**) HSI can noninvasively measure oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb). Wavelengths of visual light are collected from each pixel in an image and broken down by a spectral separator to generate a diffuse reflectance spectrum. Deoxyhemoglobin features a single absorption peak around 550 nm while oxyhemoglobin exhibits absorption peaks around 540 and 580 nm. These wavelengths of light penetrate 2 mm below the skin and thus obtain information from the subpapillary plexus. The hemoglobin calculation algorithm is calibrated for different skin pigmentations. (**b**) (Top) Visual imaging of both PAD and Non-PAD patients. (Center) Integrated oxyhemoglobin-deoxyhemoglobin (Oxy-Deoxy) hyperspectral imaging of both PAD and Non-PAD patients. (Bottom) Deoxyhemoglobin (Deoxy) hyperspectral imaging of both PAD and Non-PAD patients. The foot with PAD has substantially decreased oxyhemoglobin and deoxyhemoglobin values throughout the angiosome [20]

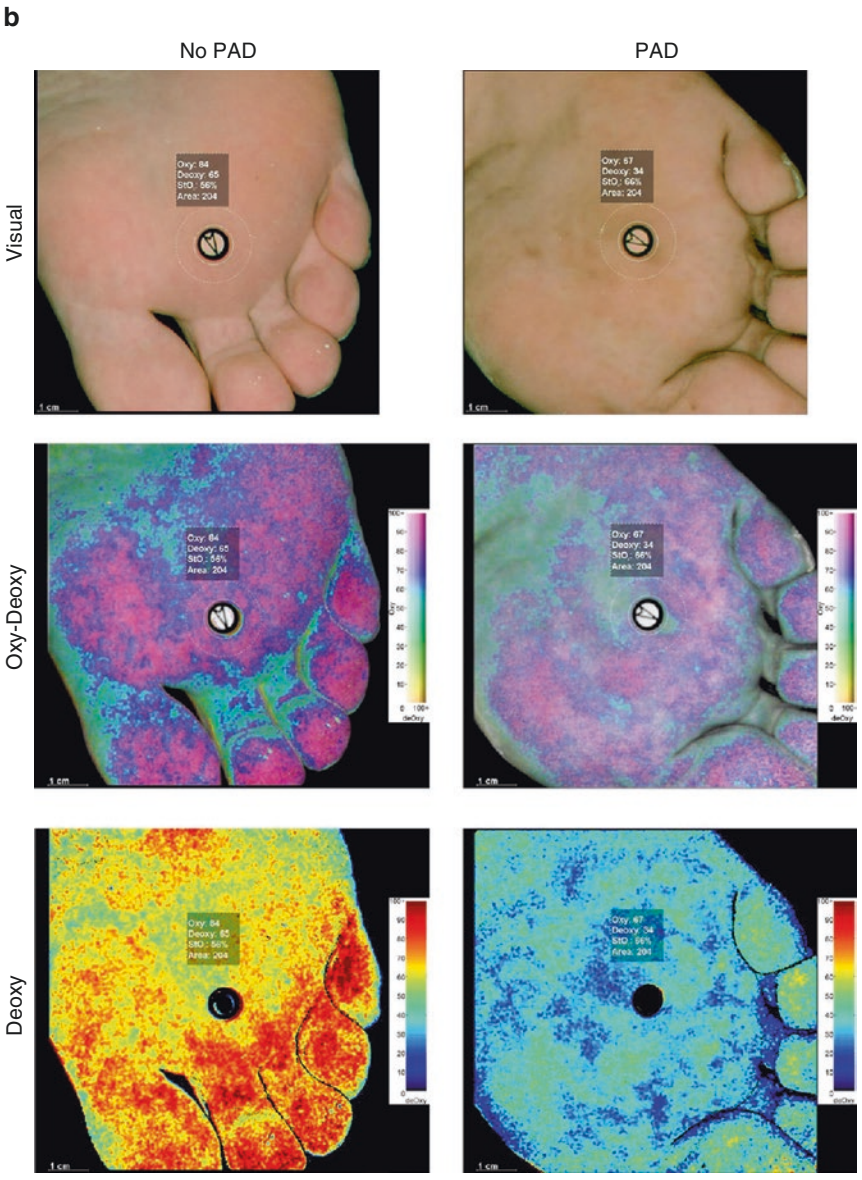

Fig. 20.2 (continued)

subpapillary plexus. The subcutaneous arteries form a network in the subpapillary plexus and supply the skin with blood. By combining digital imaging with conventional spectroscopy, targeted wavelengths for the absorption peaks for oxyhemoglobin and deoxyhemoglobin can be identified and measured.

Chin et al. [20], reported differences in the tissue oxygenation of patients with PAD along angiosome regions of the foot. They identified significant differences in deoxyhemoglobin at the plantar angiosomes, which encompasses the plantar meta-

tarsal, plantar arch, and plantar heel. The level of deoxyhemoglobin in these angiosomes was found to be decreased in patients with PAD compared to non-PAD patients. Nouvong et al. [21] performed a prospective study, demonstrating that HSI is predictive of ulcer healing in diabetic patients with foot ulcers (Fig. 20.2b). They reported higher oxyhemoglobin levels in the 85% of diabetic foot ulcers that healed vs. the 64% that did not heal. They concluded that HSI offers high sensitivity (86%) and specificity (88%) in determining healing potential.

Compared to ABI and PVR, HSI can deliver a finer assessment of perfusion in specific anatomic areas. This is accomplished through its anatomic oxygenation maps in contrast to the gross oxygenation used in ABIs. Its noninvasive nature is a major asset, as no patient contact is necessary to image the target area. The use of visual wavelengths of light can further protect patients from exposure to ionizing radiation. Anatomic maps can be rendered in other modalities such as indocyanine green (ICG) angiography and SPECT imaging (see below); however, HSI avoids the use of intravenous contrast agents which often require more highly trained personnel, elaborate examination areas, and supply storage facilities. Unfortunately, HSI may still remain vulnerable to weaknesses faced by other skin perfusion detectors such as TcPO2 and LDF. Inflammatory reactions, such as those induced by infection, could cloud the interpretation of measurements in with local hyperemia exists. Target area positioning will also need to be standardized as the study by Chin et al. [20] suggested detectable changes to the venoarteriolar reflex with ischemia. Nonetheless, the study by Novuong et al. [21] does demonstrate the feasibility of HSI to identify changes in skin microcirculation in diabetic patients. The long term and large population validity of HSI no doubt requires more extensive testing, yet as a diagnostic and prognostic tool, it certainly has important potential advantages. HSI has demonstrated an ability to show real-time perfusion of the angiosome for preoperative planning. This technology can potentially evaluate the level of reperfusion after an intervention to monitor success or failure after index procedure.

20.5 Indocyanine Green Angiography

ICG is inert, water soluble, nonradioactive, and relatively nontoxic contrast agent—approved by the U.S. FDA in 1959. ICG toxicity is low, but it does contain sodium iodide so caution should be exercised in patients with history of iodine allergies [22]. ICG is rapidly bound to plasma albumin prior to undergoing hepatic metabolism, and has a relatively short half-life of 3–5 min; as such it can be utilized safely in patients with renal insufficiency. When ICG absorbs light it fluoresces at a wavelength between 750–880 nm. In comparison to hemoglobin, that absorbs light at 650 nm, and water that absorbs light at greater than 900 nm there is an optical window where the fluorescent activity of ICG could be observed and is near-infrared light range. The technique of ICG angiography uses a low-power laser coupled with a charge-coupled device camera to sequence ICG perfusion at the surface of the

skin. The intensity of fluorescence is proportional to the rate of perfusion in the affected tissue. The areas of fluorescence intensity can be viewed in gray scale with whiter imaging indicating higher intensity, or as a heat map where red indicates high intensity and blue indicate low intensity (Fig. 20.3a). Multiple data points can be analyzed, including the starting fluorescent intensity upon initiation of the ICG angiography study (starting intensity), the magnitude of intensity increase from baseline to peak intensity (ingress), the rate of intensity increase from baseline to peak intensity over time (ingress rate), the area under the curve of intensity over time (curve integral), the intensity at the end of the study (end intensity), the magnitude of intensity decrease from peak intensity to the end of the study (egress), and the rate of intensity decrease from peak intensity to the end of the study (egress rate) (Fig. 20.3b).

The clinical utility of ICG angiography has been explored in PAD and CLI patients for the diagnostic evaluation and planning of angiosome-based direct revascularization. Many investigators utilize the SPY system (Novadaq, Bonita Springs, Florida) to perform their imaging. For example, Braun et al. [23], studied patients being revascularized with post procedural ICG angiography and demonstrated the increasing perfusion of the affected angiosome after targeted intervention. Braun et al. [24], studied patients that underwent revascularizations for CLI and tissue loss and reported a statistically significant correlation ($P < 0.05$) between ABI and degree of ingress as well as ingress rate for both pre and post interventions. The parameters of ingress as well as ingress rate appeared to correlate with improved perfusion after revascularization, and is objective data that are quantifiable and easily obtained when evaluating perfusion.

The use of ICG angiography as an adjunct to distal pressure measurements in patients with symptomatic PAD and CLI, utilizing the Photodynamic Eye System (Hamamatsu K.K., Japan) has also been evaluated [25]. The intensity of fluorescence was then plotted on a time-intensity curve with the severity of ischemia defined as the duration between the rising point and half the value of maximum brightness (T1/2). There was a comparison of fluorescent intensity at the 10-second mark (PDE10) with TcPO2 at those sites to evaluate for possible correlation in CLI. Terasaki et al. [25] evaluated total of 34 patients, 16 with ulceration or tissue loss (Fontaine class IV), 11 with claudication (Fontaine class II), and 7 with rest pain (Fontaine class III). They found that the median T1/2 in Fontaine II patients was 23 s, Fontaine III was 41 s, and Fontaine IV was 17 s. The highest correlation was demonstrated between PDE10 and TcPO2: in Fontaine class IV patients with PDE10 value of 28 (calculated from ROC curve) used to identify tissues with TcPO2 < 30 mmHg. The calculated sensitivity and specificity were 100% and 86.6% respectively. A potential confounder of median T1/2 as an objective parameter is that conditions within the foot (inflammation and hemodynamic status) could falsely elevate the value. Other factors such as body habitus and penetration of light into target tissue can further skew the value of T1/2.

Igari et al. [26] also evaluated the use of ICG angiography with the Photodynamic Eye during DSA in patients with PAD and CLI, pre and post revascularization. The foot was divided into regions of interest and the magnitude of intensity from ICG

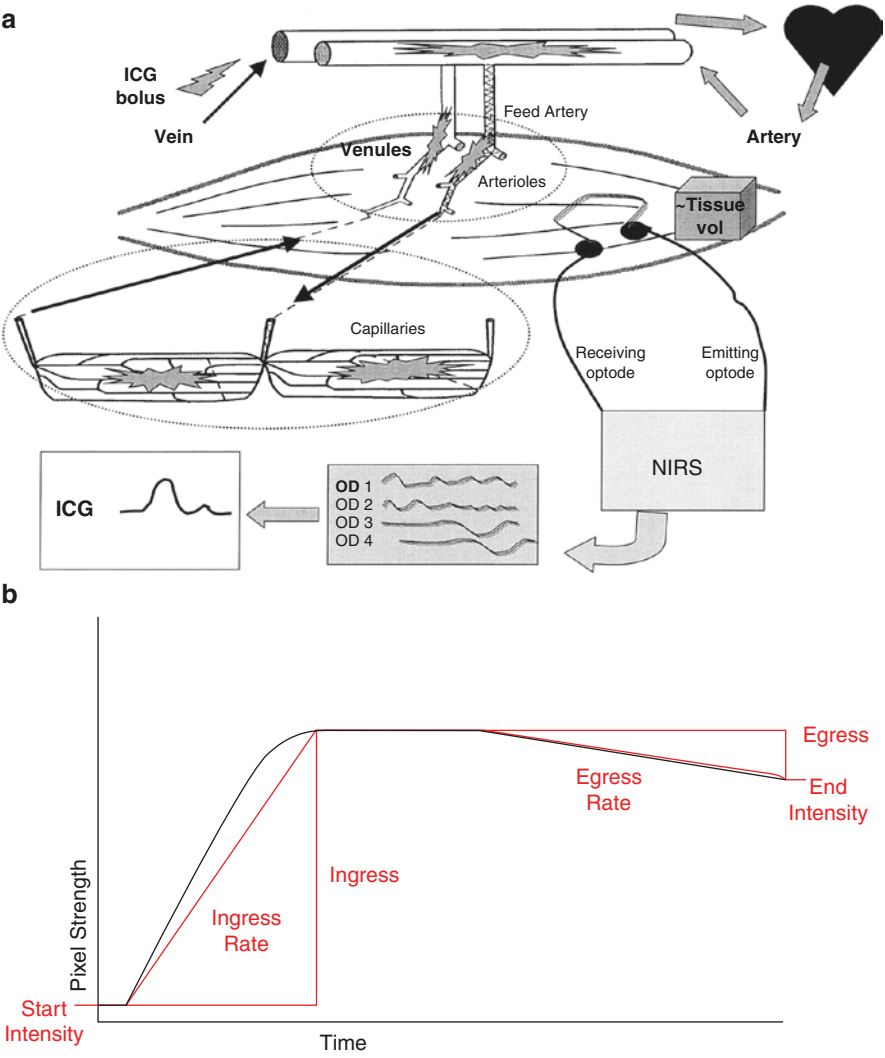

Fig. 20.3 (**a**) Schematic representation of the Near Infrared Spectroscopy (NIRS) measurements of indocyanine green (ICG) in tissue after venous bolus infusion. From top left, an ICG bolus is injected into the venous circulation; it passes through the heart and lungs and into the arterial circulation and into the microcirculation. The NIRS optodes positioned over the tissue detect the ICG at several wavelengths, and, by use of specific extinction coefficients in a matrix operation, the ICG curve is isolated. The dotted circles represent the vessels from which the NIRS signal is detected. *vol* Volume; OD 1–4, wavelengths 775, 813, 850, and 913 nm, respectively (*OD* optical density) [32]. (**b**) Indocyanine green angiography (ICGA) parameter definitions. Multiple objective data points are obtained and analyzed for potential application to objectively and reproducibly assess perfusion and, in the future, to potentially predict healing [23]. These data points included the starting fluorescent intensity upon initiation of the ICGA study (starting intensity), the magnitude of intensity increase from baseline to peak intensity (ingress), the rate of intensity increase from baseline to peak intensity over time (ingress rate), the area under the curve of intensity over time (curve integral), the intensity at the end of the study (end intensity), the magnitude of intensity decrease from peak intensity to the end of the study (egress), and the rate of intensity decrease from peak intensity to the end of the study (egress rate)

onset to maximum intensity (Imax), the time from ICG onset to maximum intensity (Tmax), the slope of the intensity increase from ICG onset to maximum intensity (S), the time elapsed from the fluorescence onset to half the maximum intensity (T1/2), and the fluorescent intensity measured 10 s after the onset of fluorescence (PDE10) were recorded. The investigators observed significant differences between regions and as well as between the pre- and post interventional ICG angiography tests.

However, as noted in previous studies, the intensity of ICG does depend on the distance from the camera to the skin, the patient's skin color, and the ambient light in the testing room. Thus, the intensity of ICG may not be a good parameter for assessing tissue perfusion using ICG angiography. Instead the study indicates that parameters based on the time after ICG injection may be the best markers of perfusion.

Because the prognosis of ischemic vascular disease is directly related to the functional perfusion level, rather than merely a vascular structure, functional perfusion imaging is superior to structural vascular imaging in guiding targeted therapy via the angiosome model. Thus, ICG angiography has been a focus of interest based on its convenience and effectiveness for imaging the vasculature. This test allows for a quantitative estimation of tissue perfusion and real time assessment of perfusion after a revascularization procedure. Furthermore, ICG angiography tests are useful as minimally invasive tools for determining the tissue viability in patients who lack toe pulses due to ulceration or amputation of the toes, and in patients with an abnormal ABI due to medial calcification. Further research must be done to establish a standard technique, as there was variation between equipment and practices in each of the aforementioned studies. A comparison between intensity of signal and initial detection of fluorescence must be performed to determine which parameter most accurately depicts perfusion in the lower extremity.

20.6 Spect Scans

Nuclear imagers have been using radioisotopes to assess myocardial perfusion for years. However, only recently have these same clinical tools been translated into assessing perfusion in patients with PAD. Recent advancements in the field of positron emission tomography and SPECT technology have allowed for the targeting and imaging of more specific cellular processes. SPECT imaging can visualize perfusion and the process of angiogenesis in affected ischemic tissue by providing a combination of high sensitivity radiotracer based imaging with high resolution CT scan imaging. This allows for both functional and structural information to more effectively evaluate the disease process and supplement clinical judgment. SPECT followed by CT scanning provides clinicians with a noninvasive tool to determine areas of high and low tracer uptake. The tracers are general perfusion markers such as Myoview (99mTc), commercial radiolabeled perfusion molecules or can be specifically labeled to only target certain membrane peptides or areas of low pH [27].

Using perfusion markers on patients with PAD or CLI potentially allows clinicians to assess changes in perfusion along the length of the lower extremities without an invasive procedure such as angiography. Furthermore nuclear technology is the only diagnostic tools that offer clinicians the ability to look at the lower extremity in a three dimensional manner (Fig. 20.4a). SPECT scans of the lower extremities using technetium perfusion tracers can be used before and after intervention to help assess the degree of tissue perfusion and to determine the success of the intervention (Fig. 20.4b) [28, 29]. By applying the angiosome model to SPECT data analysis, it allows vascular specialists to quickly and effectively determine the effect of the revascularization. The advantage of this testing over the current clinical tests is its focus on tissue blood perfusion. If the clinicians are primarily interested in increasing blood flow to the area of an ulcer, SPECT scanning can tell them instantly if the intervention actually increased blood flow to that area (Fig. 20.5).

Nuclear Imaging offers clinicians a new and improved way to detect and assess patients with PAD. However, these advancements come at a large cost. SPECT machines are not only extremely expensive, costing several million dollars; they also require a team of trained nuclear technicians to run each scan. Furthermore, hospitals need a way to produce the radioactive isotopes every day, as many of them have short half-lives: 6 h for SPECT and around thirty minutes for PET. While many

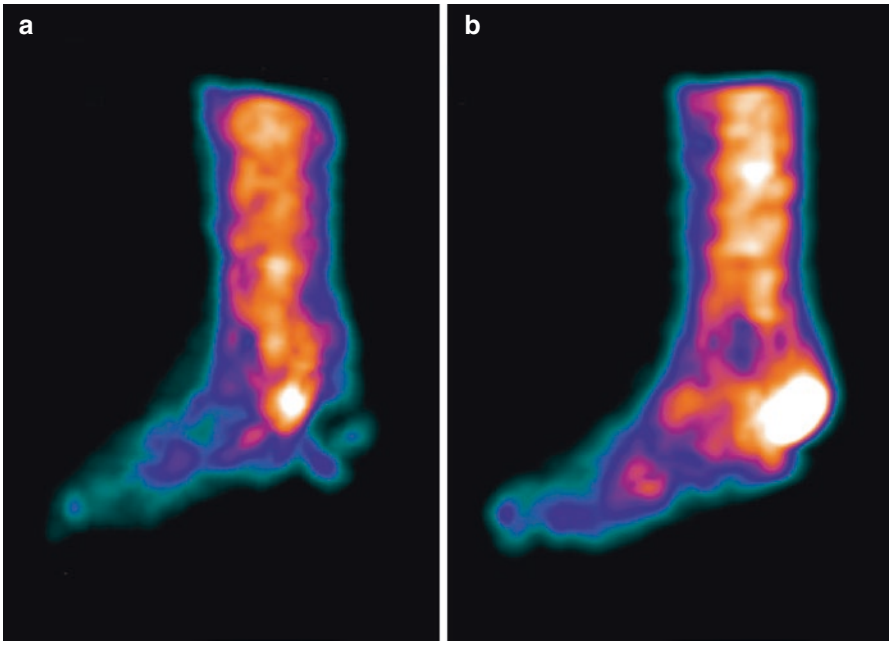

Fig. 20.4 Sagittal view of 99mTc-tetrofosmin SPECT imaging in a patient with nonhealing heel ulcer before (**a**) and after (**b**) lower extremity revascularization and wound debridement shows increased tracer uptake in the heel and distal foot

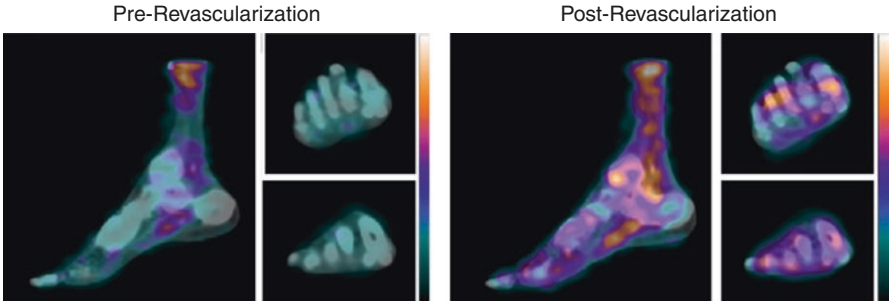

Fig. 20.5 A diabetic patient underwent single-photon emission computed tomography (SPECT)/CT perfusion imaging of the feet before and after revascularization. CT images were segmented into angiosomes and relative radiotracer uptake was quantified

large hospital systems already have nuclear labs used for cardiac imaging, smaller hospitals may not be able to afford these machines. Main drawbacks would be exposure to ionizing radiation and cost of maintaining nuclear technicians and producing radioisotopes for daily testing, limiting this option for availability at smaller hospitals.

20.7 Conclusion

With the knowledge that the prognosis of PAD and CLI is closely correlated to the functional perfusion level of the affected extremity rather than the macro-vascular structure [30, 31], regional foot perfusion imaging may predict wound healing success in addition to becoming a dependable surveillance tool. The clinical evaluation of the angiosome model will only be truly realized if a proper imaging system is in place that is noninvasive, fast, and safe and can easily delineate wound topography to guide directed revascularization therapy. Some of these modalities, such as SPECT/PET, have wide and varied future applications like delivery of targeted drug therapy using nanoprobes. Many of these imaging systems are in the infancy for their clinical application would further require long term and large population trials to ensure efficacy as well as to develop future protocols. With increasing interest and continued refinement in our understanding of PAD/CLI, the field of vascular surgery moves towards achieving a significant reduction in persistent ulceration and a decreasing the rate of complications after revascularization for our patients. To accomplish this we must be willing to adopt new paradigms and techniques in the treatment of this complex disease process. The implementation of these newer modalities as part of our routine clinical evaluation appears increasingly closer as each individual technology is optimized and we understand how to better utilize them effectively in conjunction with clinical judgment.

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Chapter 21
Computed Tomography and Magnetic Resonance Angiography

C. Jason Wilkins and Priyan Tantrige

21.1 Introduction

Diabetes is a major risk factor for the development of peripheral arterial disease (PAD) often coexisting with peripheral neuropathy with a mixed clinical presentation. Disease severity is categorised clinically using recognised grading systems such as the Rutherford classification. Grades 4–6 represent increasing degrees of ischaemia with tissue loss and ulceration presenting as end stage processes possibly leading to amputation. PAD detection and treatment ideally enables maximal treatment prior to this point with prevention of ulceration and amputation the goal.

The presence of superadded infection in a neuro-ischaemic foot represents a clinical emergency with prompt recognition and urgent referral for revascularisation in addition to medical and wound care therapy being mandatory for successful treatment outcomes. The International Working Group on the Diabetic Foot recommended in 2015 that all patients with diabetes and ulceration should be examined for PAD and 'bedside' non-invasive tests such as ankle or Toe Brachial Index (TBI) or pedal Doppler arterial waveform assessment could reliably exclude the presence of macrovascular PAD although no single modality has been shown to be optimal. A further recommendation was made for urgent vascular imaging and revascularisation in any patient with a foot ulcer with toe pressure < 30 mmHg or no improvement after 6 weeks of conservative therapy. Clearly ulcer progression or the presence of infection would mandate a more aggressive approach.

Multidisciplinary decision making allows surgical or endovascular revascularisation (or a hybrid combined procedure) to be performed depending on local expertise and patient factors. Key to this process is prompt and accurate diagnostic imaging of the entire vascular tree from aorta to the toes to enable accurate planning and appropriate intervention. High quality diagnostic imaging results in decreased

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contrast and radiation dose, helps decide on endovascular vs. surgical approaches and enables accurate pre-procedural planning.

The characteristic vascular calcification seen in diabetic PAD limits the sensitivity of duplex ultrasound (DUS) and computed tomography angiography (CTA). Of the multiple co-morbidities associated with diabetes, obesity limits reliability of DUS and patients may require bariatric compatible CT, magnetic resonance (MR) and angiography suites. Furthermore complicating features such as infection, ulcers and gangrene may render DUS technically impossible. Implanted cardiac devices may not be MR compatible. Other implants such as joint prostheses and stents cause artefact with resultant image degradation on both CT and MR. Additionally the cumulative effect of ionising radiation exposure from CTA and catheter digital subtraction angiography (DSA), often over many years for various investigations, needs to be borne in mind and minimised.

Additionally the multisystem nature of the disease may contra-indicate certain modalities requiring flexibility in the imaging approach. Renal impairment must be considered when using iodinated contrast with CT or DSA due to contrast related nephrotoxicity (CRN). Similarly contrast enhanced MR angiography may be inadvisable due to the risk of nephrogenic systemic fibrosis.

Thus the ischaemic diabetic foot poses a number of challenges to service planning. The patient might require routine or emergency imaging, and the availability of MRA, DUS and DSA may be limited outside routine working hours. Out of hours CTA is more widely available but image interpretation by experts may not be immediate.

21.2 Imaging Modalities and Strategies

Within the UK, in common with many other countries, DUS is often recommended as the first choice imaging modality (National Institute for Health and Clinical Excellence (NICE) Clinical Guideline 147). Duplex is generally widely and rapidly available during routine working hours and there are no side effects. There is a relatively low cost but at the expense of a relatively lengthy examination time (30—45 min for one leg). However, although able to accurately characterise iliac and SFA disease, its sensitivity and specificity to quantify below knee and foot disease, where the bulk of the lesions are present in the diabetic patient, can be unreliable. Extensive calcification and body habitus along with tissue breakdown are among the factors preventing diagnostic quality imaging. Additionally in many centres DUS would generally be considered inadequate for planning open surgery, especially for ultradistal bypass. Emerging and evolving techniques such as contrast-enhanced ultrasound may offer improved diagnostic outcomes. DUS is discussed more fully elsewhere (Chap. 19).

Our institutional strategy is to utilise the local sonographic expertise for all patients and progress to CTA or MRA only in those patients where doubt remains regarding the treatment options. Thus if iliac and SFA disease are adequately char-

acterised with a high degree of confidence and there is reasonable characterisation of below the knee (BTK) disease then, if angioplasty is considered appropriate for first line revascularisation therapy, we will progress directly to angiography with a planned approach either retrograde or antegrade depending on disease distribution.

DSA is the usual 'gold standard' for PAD assessment but due to its invasive nature and cost along with radiation exposure and the requirement for, sometimes in large doses, intra-arterial iodinated contrast (alternative carbon dioxide contrast DSA is not widely available) DSA is now rarely used as a diagnostic modality. The strength of DSA lies in the simultaneous diagnosis, treatment and evaluation of technical treatment outcome along with its minimally invasive approach. There is however an absolute requirement to be confident in the diagnostic imaging in order to adequately plan and perform what is often a complex endovascular procedure in these challenging patients.

The alternatives for further diagnostic imaging are CTA or MRA. Both have been shown to be accurate and specific in vascular territories above the knee but imaging below the knee is more demanding and each modality has individual strengths and weaknesses. The distal limit of endovascular and surgical PAD therapies has extended significantly over the last decade and the requirement for accurate diagnostic imaging of diseased, very distal, foot vessels in diabetic patients for interventional planning is a real challenge.

21.3 CT Angiography

CTA is a density based imaging process with excellent spatial resolution but poor soft tissue resolution. Thus administration of intravascular iodinated contrast is necessary to raise the density of flowing blood within the vasculature (and soft tissues in proportion to perfusion and clearance) in order to obtain adequate luminal densities for imaging evaluation. The timing of scan acquisition in relation to the intravascular contrast bolus reaching the area of interest is important to obtain good imaging. The technical issues surrounding CTA technique are beyond the scope of this article and are well reviewed elsewhere [1, 2].

The iodinated contrast enhanced CT angiogram is a readily available and rapidly acquired study which can provide an "easy to interpret" familiar roadmap from the aorta to the foot. Most emergency patients presenting with an ischaemic limb may be rapidly assessed in this way. Minimal, usually relatively automated, post-processing is often sufficient for diagnosis.

The only absolute contraindication is seen in patients with iodine allergy due to the risk of anaphylaxis. Relative contraindications include renal impairment due to the relatively large iodinated contrast dose required (75—150 mL intravenously). Patients with an estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2 appear safe from contrast related nephrotoxicity (CRN). Between 30–45 mL/min/1.73 m^2 there is intermediate risk and other factors should be considered such as age and coexistent illness. Diabetes is an independent risk factor. Those with an

eGFR <30 mL/min/1.73 m^2 are at high risk and preventative strategies are usually employed which include cessation of nephrotoxic medication e.g. non-steroidal anti-inflammatory drugs, hydration and use of various pharmacological agents such as N-acetylcysteine. Current evidence suggests that efficacy is doubtful for anything other than adequate hydration and use of as low a contrast dose as possible. Iso-osmolar contrast may also confer a benefit [3].

Using alternative imaging modalities may be appropriate in some patients. A process should be in place for close renal function monitoring in patients at risk and supportive therapy instituted if CRN occurs. CRN has been shown to prolong hospital stay and causes significant morbidity and mortality.

As an additional consideration in diabetic patients with poor renal function, care is required post contrast administration in patients taking metformin due to a theoretical risk of lactic acidosis. The medication should be discontinued for 48 h post procedure and reinstated once renal function is shown to have remained or returned to normal.

A routine CT angiogram rapidly acquires a large volume of data with a helical acquisition thickness of 0.625 mm on a small field of view (for high spatial resolution), At our institution 80–100 mL of iodixanol (Visipaque, a non-ionic iso-osmolar iodinated contrast agent 300 mg/mL) is injected into a peripheral vein at 5 mL/s. The scan is usually triggered using a bolus tracking technique in the abdominal aorta. Bolus tracking utilises repetitive static single slice scans with a region of interest centred over the inferior abdominal aorta. As the injected contrast reaches this region the measured attenuation value within the region of interest increases and the arterial phase scan is 'triggered' at a preset attenuation value or manually by the technician assessing the enhancement curve. This allows optimal timing for peak opacification of the lower limb and aorto-iliac vasculature.

However there is often differential flow through diseased regions of the vascular tree. The accuracy of CTA relies on contrast density and therefore is blood flow rate dependent. The routine scan protocol does not allow for highly variable and asymmetric distal flow rate either in run-off or collateral vessels beyond occlusive disease. Delayed opacification can be overcome by performing a second repeat below the knee scan immediately following the first using the same contrast bolus. This must be pre-planned. This however will carry an additional radiation burden and often, venous enhancement, and this results in consequent degradation of the image. Depending on the protocol, radiation exposure of approximately 12 mSv (as against a typical background radiation annual dose of 3 mSv) can be expected from a typical CTA [4].

Multi-planar (MPR) and volume rendered (VR) reformats as well as the base data and thin axial reformats are generally sent to the picture archiving computer system (PACS). The data can be reconstructed on the viewing station into maximum-intensity projection (MIP) images and the vessels interrogated using vessel analysis software. These image-viewing techniques give a readily recognisable and familiar appearance to the dataset allowing simple interpretation (Fig. 21.1). However care is required with image interpretation as artefact can be easily introduced. CT images are essentially density maps in 3 dimensions. Heavily calcified crural ves-

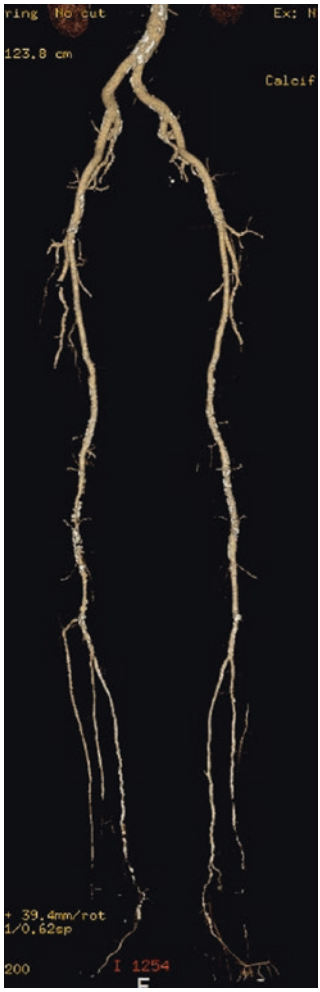

Fig. 21.1 Volume rendered (VR) projection of a full computed tomographic angiography (CTA) dataset following bone removal showing the aorto-iliac segments to the feet in one easily assessable image. These image reconstructions can be rotated and examined from any angle. Vascular calcification has not been removed

sels may thus appear completely patent on VR images for example when in fact there is complete calcific occlusion (Fig. 21.2). Additionally the bone removal algorithm relies on CT attenuation/density and given the similarity of bone and calcified enhanced tibial vessels, along with the proximity of crural arteries to the bone, inadvertent below the knee vessel processing artefact may 'remove' vessels resulting in spurious occlusions and misinterpretation. Accuracy using conventional bone removal algorithms has been shown to drop significantly in the below knee segment due to calcification [5].

Thus CTA interpretation must always include the axial source images both to allow assessment of surrounding soft tissue structures and to prevent misinterpretation of artefact introduced by post-processing (Fig. 21.3). Accuracy of interpreta-

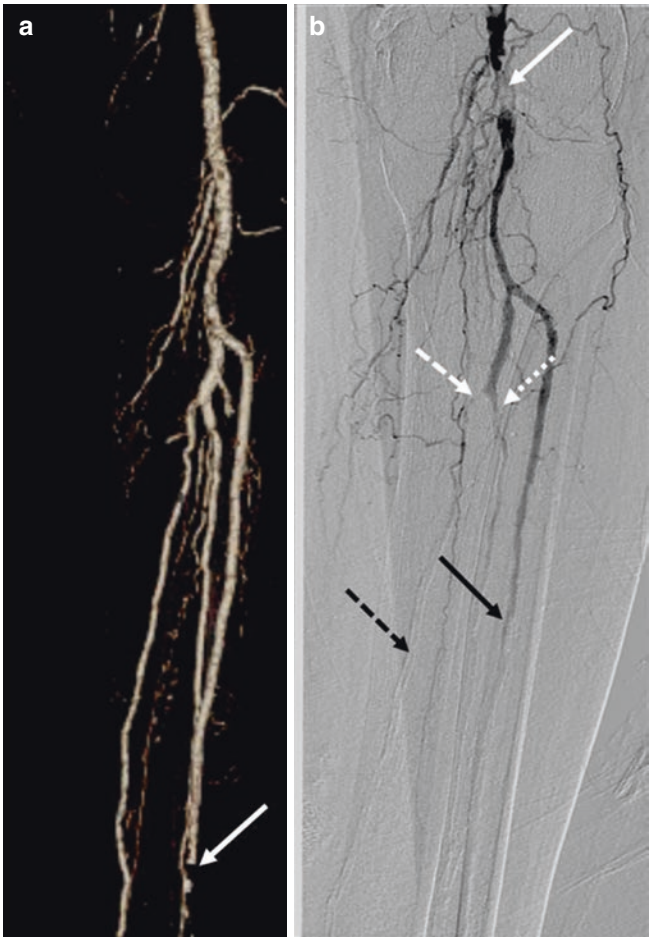

Fig. 21.2 (**a**) Volume rendered (VR) CTA reconstruction of the above knee to ankle segment. There is an occlusion of the distal ATA (arrow) but apparent patency of the remaining vessels. There are several collateral vessels noted however. (**b**) Digital subtraction angiography at the same level in the same patient demonstrates total popliteal artery occlusion (white arrow) with collateral reconstitution and occlusive disease of the posterior tibial (broken white arrow), peroneal (dotted white arrow) and more distal anterior tibial arteries (black arrow). Even on the subtracted image, the 'tramline' calcification in the posterior tibial artery is clearly visible (broken black arrow). The CTA is density based imaging and the VR post processing cannot separate contrast from calcification giving a spurious appearance of vessel patency

tion is significantly improved with the use of axial source images in addition to CT reconstructions [6].

Beam hardening within small heavily calcified vessels as often seen in diabetic patients is a significant issue. This results in 'blooming' and streak artefact (Fig. 21.4) and on conventional soft tissue window settings, wall calcification and contrast within the lumen may be indistinguishable. Additional specific window

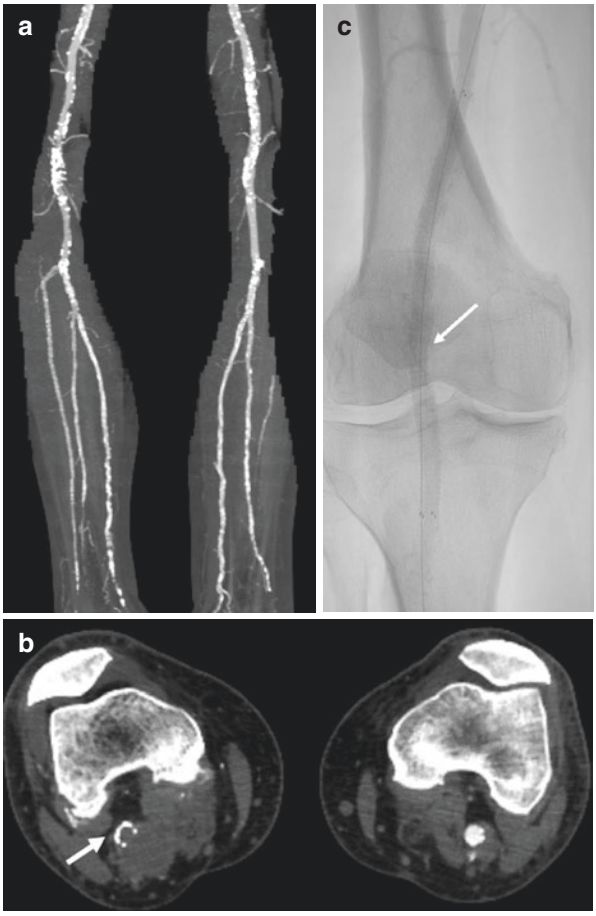

Fig. 21.3 (**a**) CTA Maximum intensity projection (MIP) imaging through the knee reveals calcified vessels but no definite above knee disease. Occlusive and calcified distal crural disease is noted. (**b**) An unenhanced axial source image revealing a large popliteal aneurysm on the right (arrow)—inspection of source images and soft surroundings are essential to correct interpretation—this is especially true when luminal imaging or display techniques are used for viewing the data. In this patient although there is diabetic vasculopathy, embolism from the popliteal aneurysm was the clinical issue requiring a different treatment approach. (**c**) Post treatment angiography showing recanalization of the popliteal artery occlusion (arrow) and insertion of a covered stent for popliteal artery aneurysm. Luminal imaging only could have resulted in inappropriate balloon angioplasty with possible disastrous consequences from distal embolisation

settings must be used to allow proper interpretation. Generally the vessels are read at a higher window level of perhaps 200–300 and a window width of 1000–1500 (roughly equivalent to 'bone interpretation' windows). This extends the grey scale and allows separation of high density structures which would otherwise all appear completely 'white' on a more restricted window width (Fig. 21.5). Special image

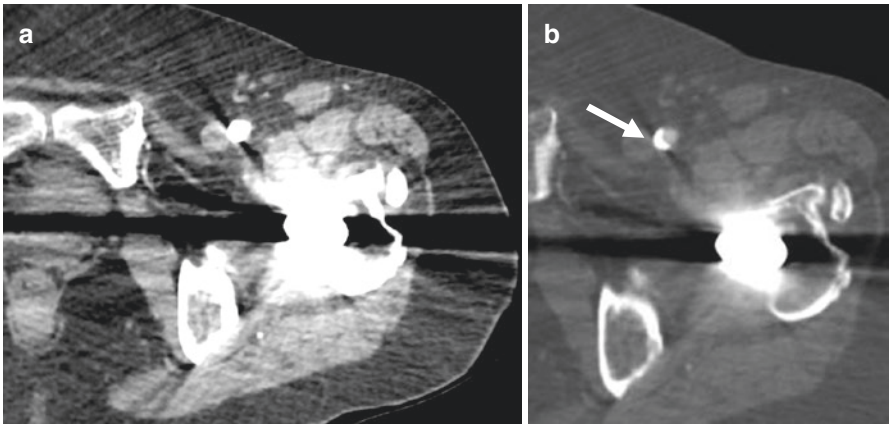

Fig. 21.4 (**a**) CT angiography at the common femoral artery (CFA) level in the presence of a total hip replacement. Significant streak artefact due to beam hardening secondary to the metallic prosthesis is noted extending through the imaged CFA. At standard soft tissue window settings, the CFA appears widely patent with no disease. (**b**) Widening the window level to extend the grey scale increases the detail visible within the CFA and allows visualisation of medial calcified plaque (arrow) which is denser than contrast/blood mixture and also reduces the severity of streak artefact from the hip replacement

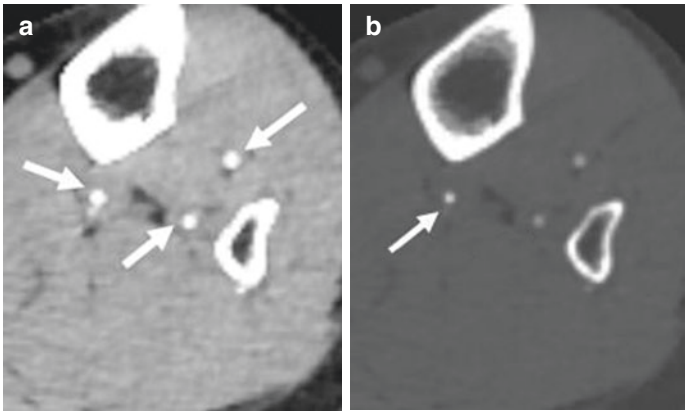

Fig. 21.5 Axial reconstructions through the proximal crural vessels. (**a**) Standard soft tissue windows suggests that all three vessels (arrows) are widely patent. Above a certain density all structures appear of equal brightness. This includes contrast, calcium and bone. Blooming artefact causes apparent enlargement of the vessel and obscures luminal detail. (**b**) A raised window level of around 300 and a window width of about 1500 shows that the posterior tibial artery (arrow) is in fact occluded with dense calcification which is clearly visible with the correct windowing technique when compared to the adjacent contrast filled vessels

reconstruction techniques using a different sharp 'kernel also reduce artefact but at the expense of image noise.

Dual energy CTA (DE-CTA) is a newer, not widely used, technique where there is simultaneous acquisition using two different tubes at voltages e.g. 80 and 140 kV. A subtraction technique is used which may improve the luminal evaluation compared to standard single tube CTA. One study showed better luminal evaluation using this technique due to improved bone and calcified plaque post processing outcomes but this was only seen in vessels above 5 mm diameter. Below the knee in smaller calf vessels with circumferential calcification the benefit was lost [5, 7] and a further study showed that despite the benefit of improved bone and plaque removal on DE-CTA images, diagnostic specificity was impeded by calcification and imaging artefacts [8].

CT angiography provides an overview of the vasculature and plays an invaluable role in acute limb ischaemia. CTA clearly has a role in the assessment of aorto-iliac and SFA disease in the patient where sonography is non-diagnostic. A systematic review looking at 20 studies using DSA as the gold standard showed a sensitivity and specificity of 96% and 98% respectively for the aorto-iliac segment for detection of a >50% stenosis. Data showing efficacy below the knee is less well established (although the same analysis showed sensitivity and specificity of 95% and 91% respectively) [9]. More modern 64 or 256 slice scanners may offer improved results with sensitivities and specificities between 90 and 100% [10, 11]. This is not uniform across studies with a further study showing accuracy of only 73.3% in the infra-popliteal segment associated with degree of calcification along with a sensitivity of only 62.7% for collateral vessel assessment compared to DSA [12].

Thus interpretation of CTA in the diabetic population with multilevel disease and extensive below knee calcification requires great care. The use of CTA for BTK disease should be based on local expertise and availability of other imaging modalities. Careful technique including image post processing and manipulation will result in improved results. DE-CTA where available, may also be of benefit in some situations.

21.4 MR Angiography

MR angiography provides luminal imaging similar to DSA, does not use ionising radiation and can also be performed without intravenous contrast using newer techniques. Specific to the diabetic foot, MRI is not degraded by calcification (which essentially gives virtually no signal), and additional sequences can be acquired to examine associated complications such as suspected soft tissue infection and osteomyelitis. As long as 15 years ago, contrast enhanced MRA was shown to be capable of depicting distal crural and pedal vascular anatomy [13].

Contraindications to MRI include non-MR compatible patient devices such as pacemakers as well as implanted paramagnetic material liable to displacement or excessive heating during the scan. Patient suitability can usually be confirmed

using a screening questionnaire, plain radiography for loose metallic objects such as eye shrapnel, or occasionally a short test MR sequence where there is uncertainty. Metallic implants such as surgical clips, stents and joint prostheses are not generally a contraindication to MRI after 6 weeks post implantation. However, they cause adjacent artefact, of which the extent depends on the material and the structure.

Currently the majority of MRA for peripheral vascular disease is performed following contrast administration. Alternative non-contrast techniques such as time of flight and phase contrast imaging do exist but are not ideally suited to the extremities. Here there are small vessels, flow reversal post occlusions, large areas to cover and problems with patient movement during the long acquisition times needed to provide adequate spatial resolution and signal to noise ratios using these techniques. Newer non-contrast techniques are becoming more widely available, which show considerable promise and these are discussed below.

21.5 Contrast Enhanced Magnetic Resonance Angiography (CE MRA)

Contrast is used to increase the signal to noise ratio as MRA and MRI in general, even with more powerful modern magnets and radiofrequency (RF) gradients, is always a trade off between scan time (number of acquisitions) and the spatial resolution and signal to noise ratio. The signal strength from normal tissue following an RF pulse and a single acquisition is very low so multiple pulses and acquisitions are obtained and added together to create the final image. For vascular imaging, short scan times are essential and patient movement results in artefact whenever subtraction techniques are used.

MR contrast is distinct from iodinated CTA or angiography contrast and essentially utilises a paramagnetic substance to alter the magnetic characteristics of blood and soft tissue, dependent on the contrast concentration within them. An ideal angiographic substance would remain in the vascular compartment until the imaging is completed and then be rapidly excreted. The commonest agent used for this purpose is gadolinium which is chelated with various compounds to provide a safe preparation for intravenous injection. This family of contrast agents are known as gadolinium-based contrast agents or GBCAs. Broadly speaking they are divided into linear compounds and cyclic compounds. The latter appear to be more stable and result in less deposition of free gadolinium within tissues.

Although gadolinium preparations are shown to be safe in the short term in 2006 an association between GBCAs and nephrogenic systemic fibrosis (NSF)—a systemic fibrosing disease, causing painful skin thickening and other symptoms, found only in renal failure patients exposed to GBCAs was shown to exist. This was thought to relate to retention of contrast in patients with poor renal excretion and consequent increased tissue deposition of free gadolinium. The linear chelates seemed related to NSF and were stopped from use in chronic renal failure patients resulting in virtual eradication of NSF. However, more recent work has suggested

that there is dose dependent deposition of gadolinium in brain and skin even in patients with normal renal function [14, 15].

The possible effects of this are as yet unknown although the latest FDA update in 2017 found no evidence of harm. Thus although CE MRA is very commonly used and, with modern cyclic GBCAs, no evidence of harm currently exists there is resurgent interest in possible contrast free alternative imaging strategies.

Gadolinium works by causing a shortening of T1 relaxation time and thus increases T1 signal allowing T1 weighted imaging to be performed with an adequate spatial resolution in a reasonable time frame.

The routine CE MRA sequences are T1 weighted gradient echo 3-D (T1 GE), with as small a field of view as possible to encompass the area of interest. A high dose of GBCA is administered and injected at 2–4 mL/s through a venous cannula to give optimal concentration in the arterial phase. In a similar manner to CTA, the scan is triggered when contrast reaches the region of interest (using a region of interest placed on a large vessel at the site of interest and performing repetitive short scan sequences to follow the arrival of the contrast bolus as a rise in signal intensity) or, alternatively, timed by using a small test bolus to identify the necessary time delay from contrast injection to the arrival of contrast at the region of interest.

The lower limb is typically scanned in four stations: pelvis, groin to knee, knee to foot and feet. Control unenhanced sequences are initially performed at each station as a subtraction mask in a similar manner to DSA. The sequences are usually acquired in the coronal plane as a slab volume and 3-D maximum intensity projection images (MIPs) are sent to PACS for assessment along with source images. The MIPs give a similar type of image to CTA/angiography but it is important to note that they represent luminal contrast only. Figure 21.6 illustrates a typical CE MRA of the vascular tree from the para-renal aorta to the feet.

CE MRA is very effective with various studies quoting sensitivity and specificities for stenotic/occlusive disease in the 90% range. However the majority of studies are in whole limbs and below knee disease especially in diabetes is not as well researched. A meta-analysis of CE MRA studies in 2013 found only 3 studies with 83 patients in total, looking at performance in BTK disease in diabetics. The pooled sensitivity was 86% and sensitivity was 93% in this challenging vascular segment [16]. Some authors have compared CE MRA directly to DSA in diabetic PAD and found excellent agreement in assessment of vessel patency and stenosis with the added benefit of evaluation of soft tissue and bone involvement in infective processes [17] and others have shown CE MRA to be better than DSA in evaluation of distal pedal vessels for bypass planning [18].

Limitations however do exist. Using the standard single bolus technique and station timings such as above the problem of venous contamination is often present as the bolus outruns the imaging. Fig. 21.7 shows venous contamination rendering assessment of distal native vessels beyond a bypass graft difficult. Various strategies are used to overcome this. There is no radiation cost to repeat scanning so a small contrast bolus can be given first and the feet/distal calves can be imaged first followed by a second injection and imaging of the remainder of the vascular tree. Alternatively, often used at our institution, Duplex can provide adequate

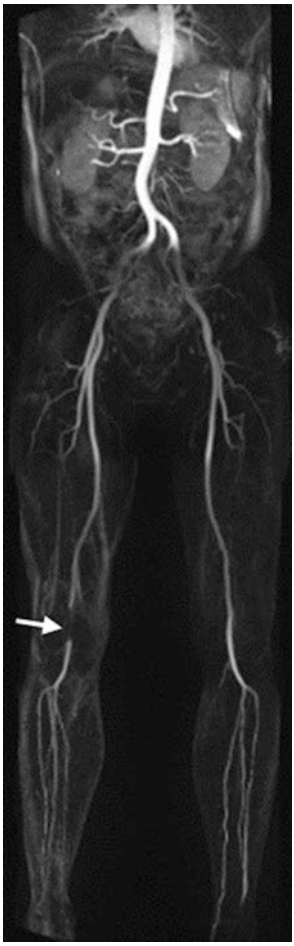

Fig. 21.6 Contrast enhanced magnetic resonance angiography (CE MRA) 3 D subtracted angiographic maximum intensity projection (MIP) from the inferior thoracic aorta to the feet. This illustrates the angiographic coverage now available with modern MRI scanners. The imaging presents only luminal contrast with soft tissue subtraction and is akin to 'traditional' digital subtraction angiography in this respect. The signal drop out at common femoral level is due to the coronal slab acquisition being positioned slightly too posterior with partial exclusion of the arterial signal noted here as an edge of slab phenomenon. Slower flow on the right is noted beyond a popliteal artery occlusion (arrow) with poorer opacification of the crural vessels on this side

imaging to the knee or proximal calf so focussed 'time resolved' CE MRA can be performed with a small field of view including only the foot and distal calf. This gives excellent spatial resolution and allows arterial assessment without venous contamination regardless of the bolus timing/scan time relationship. A bolus of GBCA is given and repetitive short sequence scans only of the region of interest are performed from the arrival of the arterial bolus through to the venous phase [19]. Any of these individual sequences can then be used as a subtraction mask and venous contamination can be 'removed' and late filling collaterals/native vessels can be more fully assessed (Fig. 21.8). The stacked images can be used to assess flow in much the same way as a DSA.

Artefact in MR imaging is still an issue since any local inhomogeneities of the magnetic field e.g. from skin tattoos, surgical clips or joint replacements may render images uninterpretable. Imaging within stents is still possible depending on stent material and orientation. Nitinol/cobalt stents for example create less artefact com-

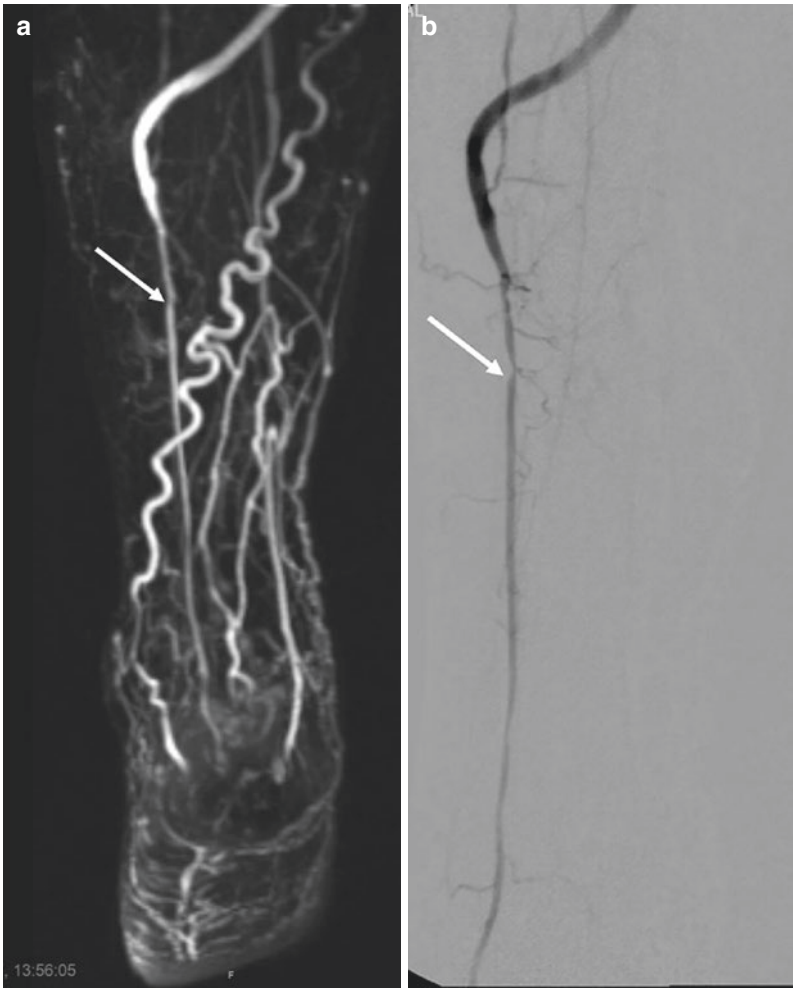

Fig. 21.7 (**a**) MRA of a popliteal to anterior tibial artery bypass graft. There is graft patency and a stenosis in the proximal run off vessel (arrow) along with distal foot disease. Due to the timing of the scan acquisition significant venous artefact makes assessment of the remainder of the vasculature difficult. (**b**) The angiogram confirms the patent graft with a focal native artery stenosis (arrow). No other definite patent artery is seen

pared to stainless steel which creates a local signal void. Stents oriented parallel to the main magnetic field (e.g. SFA, crural rather than perpendicular e.g. renal arteries) are also less susceptible. However within the crural vasculature stent insertion is relatively uncommon. As the CE MRA technique relies on a coronally oriented slab shaped volume acquisition, it is possible to inadvertently exclude anterior or posterior vessel segments if they are not included in the slab resulting in apparent occlusion. Near the edge of the slab, vessels may have spurious edge effect stenosis-like

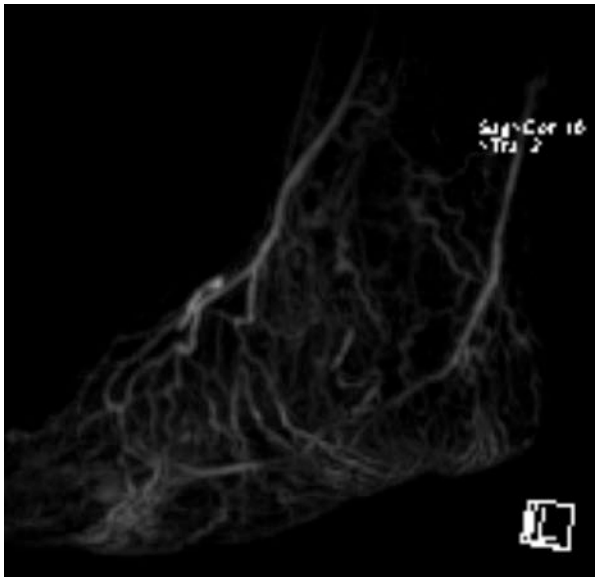

Fig. 21.8 Post contrast dedicated time resolved CE MRA of the foot. The MIP shows a patent dorsalis pedis and distal ATA with a patent distal posterior tibial artery but an incomplete arch. Popliteal to ATA bypass was planned and performed on the basis of the MRA and prior Duplex showing no above knee stenosis of note (not shown)

appearances (Fig. 21.6). The common femoral artery shows signal drop out due to its anterior location near the edge of the imaging volume. Interrogation of the source images will prevent incorrect diagnosis and will also give additional information on surrounding soft tissues.

21.6 Non-Contrast Techniques

Newer unenhanced MR angiography sequences with use of flow-sensitive dephasing (FSD)–prepared steady-state free precession (SSFP), and ECG gating use a subtractive approach similar to CE MRA but without contrast [20]. They rely on blood signal differences in arteries and veins in systole and diastole. Essentially arterial signal is only present in diastole with venous signal present in both phases. Thus the systolic venous mask can be subtracted from the diastolic acquisition to eliminate the diastolic venous signal. Several studies have shown adequate angiographic imaging using these techniques but images may be degraded by signal contamination from deep veins and soft tissues [21].

A further development of this technique known as Quiescent Interval Single Shot, or QISS, is outlined below and seems to offer promising results compared to standard 3D turbo spin echo (TSE) based flow/subtraction methods [22]. The technique relies on saturation pulses to annul the background signal, with a further pulse, inferior to the slice of interest, to eradicate venous flow signal. Following these pulses there is an interval (the quiescent interval), which allows arterial blood with unsaturated spins to flow into the slice and generate signal on sampling. An

axial slice is sampled and then automatically stacked with adjacent slices to produce a volume of data. This axial acquisition technique negates the possibility of accidental exclusion of anatomical segments of artery as seen with coronal slab CE MRA techniques. Studies at 1.5 and 3 T have shown results comparable to CTA /CE MRA and DSA [23–25]. Importantly the calcific artefacts and difficulty in stenosis evaluation seen with CTA are less problematic with QISS, as expected from the differing imaging techniques.

QISS-MRA still suffers from specific artefacts and may have a lower rate of assessable segments compared to conventional CE MRA [26] as well having the inherent limitations of MRI in some patients. The technique also requires adequate fat-suppression which may be difficult to achieve in the feet. This requirement also makes the sequences more sensitive to magnetic susceptibility artefact. As venous flow is magnetically saturated, reversed or in plane arterial flow may not be well visualised, resulting in artefactual occlusions and overestimation of occlusion length (Fig. 21.9).

With the improved shorter imaging times now available, no requirement for GBCA administration and demonstrable diagnostic equivalence QISS-MRA (or similar further evolved non-contrasted enhanced MRA techniques) may become the first choice investigation of the foot arteries in patients with diabetes. However, due to the inherent limitations of access to MRI due to patient factors e.g. implants, patient size and claustrophobia, along with cost and resource availability, CTA and Duplex are likely to always be required.

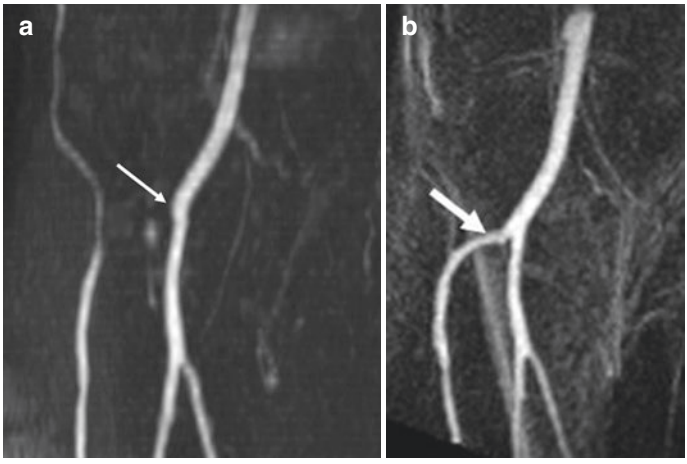

Fig. 21.9 (**a**) Non contrast magnetic resonance quiescent interval technique (QISS-MRA) and (**b**) contrast enhanced MR angiography (CE MRA) in the same patient. (**a**) The proximal anterior tibial artery appears occluded (arrow) on the QISS sequence due to artefact likely due to horizontal/upwards orientation resulting in loss of arterial signal as flow is insufficient to fill the vessel with unsaturated spins due to the in plane orientation. (**b**) The artery is shown to be widely patent on the CE MRA acquisition (arrow) There is however evidence of motion artefact on the CE MRA with the subtraction mask and acquisition mismatch causing blurring at soft tissue/bone interfaces and of the vessel outlines

21.7 Conclusion

The choice of vascular imaging modality for assessment of the diabetic foot depends on local expertise and equipment availability as well as patient variables. Duplex ultrasound should be attempted in all patients first to minimise possible risks of MR, intravascular contrast agents (either iodinated or gadolinium based) and ionising radiation exposure.

MRA should be ideally considered as the first alternative for below knee disease as it is less susceptible to calcium artefact than CT (a major limitation of CTA in the diabetic lower limb). MRA has been shown to be more sensitive for identifying suitable vessels for ultra-distal bypass than catheter angiography, although it does not offer simultaneous therapeutic opportunity. However CTA is cheap and widely available and with careful post processing should still be considered where other modalities have been inconclusive, are contraindicated or are not available and is especially useful in the aorto-iliac and SFA segments. Dual energy CTA may become more widespread and may improve diagnostic quality below the knee.

Unenhanced non-contrast MRA sequences may eventually supersede CE MRA as the first investigation following duplex ultrasound. However with current sequences, limitations still exist with respect to artefact, diagnostic quality and stenosis length which are important for procedural planning and decision making.

What is certain is that for the diabetic foot with critical ischaemia, especially where there is superadded infection, multidisciplinary management and decision making within a dedicated team must be based on prompt high quality diagnostic imaging. This is required in order to guide optimal revascularisation strategies to prevent amputation and ensure limb salvage.

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Chapter 22
Ischaemic Foot: Endovascular Intervention in the Distal Arteries of the Leg and Foot

Riad Alchanan and Dean Y. Huang

22.1 Introduction

Diabetic patients with critical limb ischaemia (CLI) usually have significant multilevel arterial diseases. One of the features of diabetic patients with CLI is the predominance of diffuse obstructive lesions in the distal, sub-popliteal arteries [1–3], either in isolation or concomitantly with more proximal femoro-popliteal disease, and often with compromised outflow in pedal arteries. The combination of severe arterial occlusion in the small, distal arteries with the increased blood flow requirement, necessary to achieve the healing of skin lesions or surgical incisions, makes this population particularly challenging to treat, requiring coordinated care with multidisciplinary approach [4].

The optimal revascularisation strategy for this population of patients aims to restore a direct arterial inflow from principal circulatory pathways of the foot, achieving a complete below-the-ankle revascularization [5]. Diabetic patients with CLI have a high rate of comorbidities, which increase surgical risks. The introduction of endovascular procedures in the routine of vascular surgery allowed for the expansion of therapeutic options in the diverse areas of vascular disease. Endovascular revascularization has now been widely accepted as a first line choice to treat diabetic patients with CLI [6–8]. This strategy is based on the superior perioperative safety of results compared to surgery. Results are at least equivalent to that of surgery in terms of efficacy and limb salvage rate [9–12]. Recent studies support the role of endovascular therapy in diabetic patients with CLI caused by below-the knee (BTK) and below-the-ankle (BTA) arterial occlusive disease, as percutaneous

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angioplasty for BTK and BTA vascular disease has shown to be feasible and safe in this setting [13–18], achieving successful revascularization, necessary for limb salvage and ulcer healing, and avoiding amputations. In addition to the traditional approach, alternative techniques such as pedal-plantar loop technique and retrograde percutaneous access have been shown to be beneficial in further increasing intervention success rates [19–21].

The aim of the current article is to summarize the principles of endovascular revascularisation and currently available advanced techniques to treat lesions within distal arteries of the leg and foot.

22.2 Vascular Anatomy

In the normal anatomy, the anterior tibial artery (ATA) gives rise to the anterior circulation of the foot, and the posterior tibial artery (PTA) to the posterior circulation of the foot. Both tibial arteries, together with the peroneal artery (PA), supply different regions of the foot and ankle. In the anterior circulation, the ATA continues to the dorsum of the foot as the dorsalis pedis artery at the ankle level. As an anatomic variation of the foot, the dorsalis pedis artery may be absent in 6–12% of cases. Running laterally to medially along the dorsal aspect of the foot to the first metatarsal space, the dorsalis pedis artery gives off the medial malleolar, lateral malleolar, medial tarsal, lateral tarsal, and arcuate arteries. The arcuate artery, which usually arises at the level of the tarsal-metatarsal joint and travels laterally, in turn gives rise to small dorsal digital arteries supplying the second, third, and fourth toes. At the level of the first metatarsal space, just distal to the origin of the first dorsal metatarsal artery, which mainly supplies the first toe, the dorsalis pedis artery curves in the plantar direction; this arterial segment, named the deep perforating artery, communicates with the lateral plantar artery from the posterior circulation [22]. The posterior circulation of the foot, which is supplied by the posterior tibial artery consists of three main arteries—the medial plantar, lateral plantar, and medial calcaneal arteries. The medial plantar branch feeds the medial plantar instep, and a lateral plantar branch supplies the lateral forefoot, plantar midfoot, and entire plantar forefoot. In some cases, the lateral plantar artery, through plantar arch, is the predominant artery for the first toe. The calcaneal branch supplies the medial ankle and plantar heel. The peroneal artery supplies the lateral ankle and plantar heel via the calcaneal branch and the anterior upper ankle via an anterior branch.

22.3 Anatomic Consideration for Revascularisation

Graziani et al. [23] demonstrated through angiographies of 417 diabetic patients with 2893 ischemic trophic lesions that vascular obstructive disease involved the iliac arterial system in 1% of patients, but was present in 74% of patients at the sub-popliteal

level. 66% of leg lesions were obstructive and 50% were over 10 cm in length. All three arterial systems were involved in 28% of patients whereas in 55%, at least one distal artery remained patent (Fig. 22.1). The predominance of diffuse obstructive lesions in the distal, sub-popliteal arteries makes diabetic vasculopathy particularly challenging to treat (Fig. 22.1). There seems to be sufficient evidence to suggest that the establishment of at least one straight-line flow to the foot on angiographic interpretation basis (Fig. 22.2) could be the primary strategy for infra-popliteal intervention [24] but the optimal revascularisation strategy ideal should aim to achieve a complete direct revascularization of the leg arterial system below-the-knee. In 2010, Peregrin et al. [25] showed that diabetic patients with CLI had a 1 year limb salvage rate of 56% if direct patency was not obtained in at least one vessel and 73%, 80% and 83% if 1, 2 or 3 vessels became patent following revascularisation.

It has been shown that pedal arch classification is a predictor of wound healing [26]. This finding suggests that clinically driven, more distal revascularization to establish a patent pedal arch is vital to facilitate complete wound healing in terms of endovascular strategy. In a series of 42 cases involving below-the-ankle angioplasty, technical success was achieved in 88%, and the reported 2-year limb salvage rate was 81.9% [16]. Simultaneous above the ankle angioplasty in this series would have

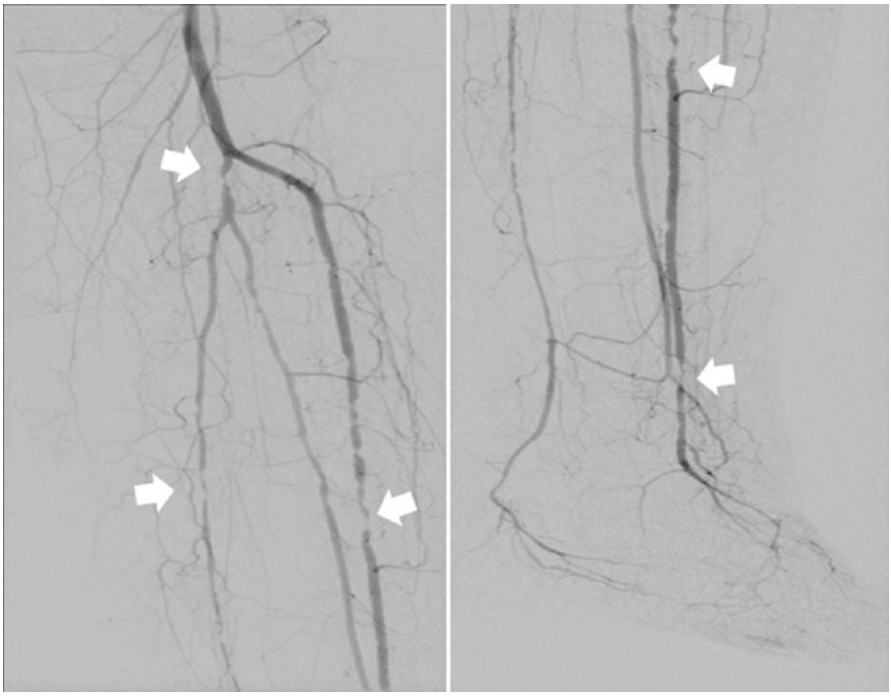

Fig. 22.1 An infra-popliteal angiogram of a diabetic patient with CLI demonstrating the typical pattern of multi-focal obstructive lesion (white arrows) in the distal sub-popliteal levels involving anterior and posterior tibial arteries

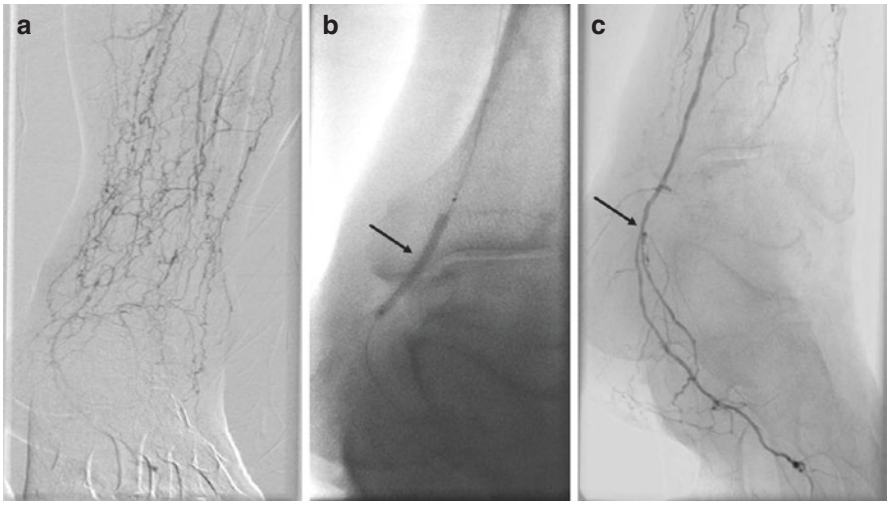

Fig. 22.2 Revascularization procedure of the posterior vascular pathway to the foot. (**a**) pre-treatment angiogram demonstrating occlusion of all calf vessels at the ankle level with an extensive collateral network with no direct straight-line flow into the foot. (**b**) Balloon angioplasty (arrow) recanalization of the posterior tibial artery. and the plantar artery was performed (**c**) Completion angiogram demonstrates establishment of straight-line flow into the foot (arrow) via the recanalized distal posterior tibial and plantar arteries

contributed to the clinical outcome but the report nonetheless reflects the feasibility and benefit of below the ankle endovascular intervention. Nakama et al. [27] further investigated the clinical impact of additional pedal artery angioplasty in patients with CLI attributed to pedal artery occlusion with insufficient 'wound blushing' after conventional above-the-ankle percutaneous revascularization. Additional dorsalis pedis angioplasty resulted in higher wound healing rate (93% vs. 60%, p = 0.050) and shorter time to wound healing (p = 0.050). The study concluded that additional pedal artery angioplasty might improve clinical outcomes (especially speed and extent of wound healing) in patients with CLI attributed to infra-popliteal and pedal artery disease and this aggressive strategy may be a salvage procedure for patients with CLI. With improved technology, it is now possible to treat even the very distal arterial lesions which might improve clinical success in selected cases. Manzi et al. [28] performed endovascular recanalization of digital branches in 24/1054 CLI patients (2.3%) and reported the technique is feasible and safe and may provide additional support to avoid amputation and healing of distal wounds on the toes.

22.4 Endovascular Devices for Endovascular Intervention in the Distal Arteries of the Leg and Foot

As current endovascular treatment with plain balloon angioplasty for patients with CLI and BTK lesions are associated with a low primary patency, high risk of restenosis and associated repeat intervention rate, there has been an evolution of newer

technologies and adjunctive endovascular devices including atherectomy, cryoplasty, cutting balloons and laser [29–32]. Most experience has been published in patency-enhancing drug coating for balloons and stents More recently, review of the randomised controlled trials comparing paclitaxel-coated balloons or stents with standard balloon angioplasty or uncoated stents demonstrated a higher mortality in patients treated with paclitaxel products. These results are preliminary and the trials involved mainly claudicants and involved exclusively femoropopliteal lesions and not BTK lesions. However, current societal recommendation on the drug-eluting devices states in majority of patients undergoing lower limb recanallization, alternative to drug eluting devices should be used until more information is available. [33, 34].

22.4.1 Drug-Coated Balloons (DCB)

Drug-coated balloons impregnated with paclitaxel are available in a wide range of lengths and diameters. Liistro et al. [35] published a randomized, open-label, single-center study (Debate-BTK study) which compared the effect of a drug coated balloon with an uncoated balloon in 132 diabetic patients with CLI and a long occlusion (13.0 ± 8.0 cm) of the infra-popliteal vessels. Restenosis occurred in 20 of 74 lesions (27%) in the drug-eluting balloon group compared with 55 of 74 lesions (74%) in the PTA group ($P < 0.001$); target lesion revascularization, in 12 (18%) vs. 29 (43%; $P = 0.002$); and target vessel occlusion, in 12 (17%) vs. 41 (55%; $P < 0.001$). Twelve-month major adverse events occurred less frequently in the DCB (31%) than in the PTA (51%) group, driven mainly by a reduction in target lesion restenosis (TLR) and better ulcer healing. However, there was no difference in the rates of amputation, limb salvage, or mortality between the groups. These encouraging results have not, however, been confirmed in a subsequent multicenter, randomized IN-PACT DEEP study [36], in which low 12-month TLR rates had been observed in both the DCB and standard PTA arms without a statistically significant difference between the groups. A safety signal was activated and the INPACT-DEEP study was stopped prematurely as a result of a high amputation rate of 8.8% in the DCB group vs. 3.6% of the PTA group ($p = 0.08$) which were observed at 12 months . No definitive reason has been provided to explain the lack of efficacy and safety outcomes, but it has been hypothesized that potential disease and device and/or procedure-specific factors might have contributed to the observed outcomes [37]. Subsequently, the BIOLUX P-II study [38] was published comparing the Passeo-18 LUX DCB vs. standard angioplasty for infra-popliteal lesions (lesion length 11.4 ± 8.7 cm). Low and comparable restenosis rates at 6 months of follow-up were observed in both groups (DCB 17.1% vs. PTA 26.1%, $p = 0.298$), indicating no clear benefit of the drug coating in DCB group. Steiner et al. [39] reported in the 220 BTK interventions (144 [69.3%] of patients were diabetic patients). In 19 (8.6%) patients, angioplasty was extended into the pedal arch. This retrospective analysis of a real-world, single-center experience treating BTK peripheral arterial disease with the Lutonix 014 DCB found no unanticipated device events. However, the retrospective nature and lack of the control arm are major limitations of this study.

The use of DCB is not technically complex and it may yet play an important role as a possible solution for re-stenosis in the BTK, but it is not possible at present to propose the first line use of DCB technology in treating BTK disease in diabetic patients with CLI. It is also worth noting that DCB study data in general are strictly device specific. Different DCBs by various manufacturers exhibit substantial disparities with respect to paclitaxel concentrations and excipients, which potentially influence biological effects and subsequent anti-restenotic properties in the vessel wall [40].

22.4.2 Drug-Eluting Stents (DES)

The usefulness of PTA is frequently limited by elastic recoil and high rates of flow–limiting dissection and stent placement may improve radiological and clinical results in such cases (Fig. 22.3). However, stenting may also stimulate neointimal hyperplasia which results in re-stenosis. Primary bare metal stent (BMS) implantation showed no advantage over PTA. Randomized trials of DESs have demonstrated a potential role regarding vascular restenosis, target lesion revascularisation, wound healing, and rate of amputations [41–44]. However, it is worth noting that in these trials the lesions selected were shorter lesions with less calcifications and may not reflect "real world" diabetic BTK lesions. In the IDEAS trial [45],

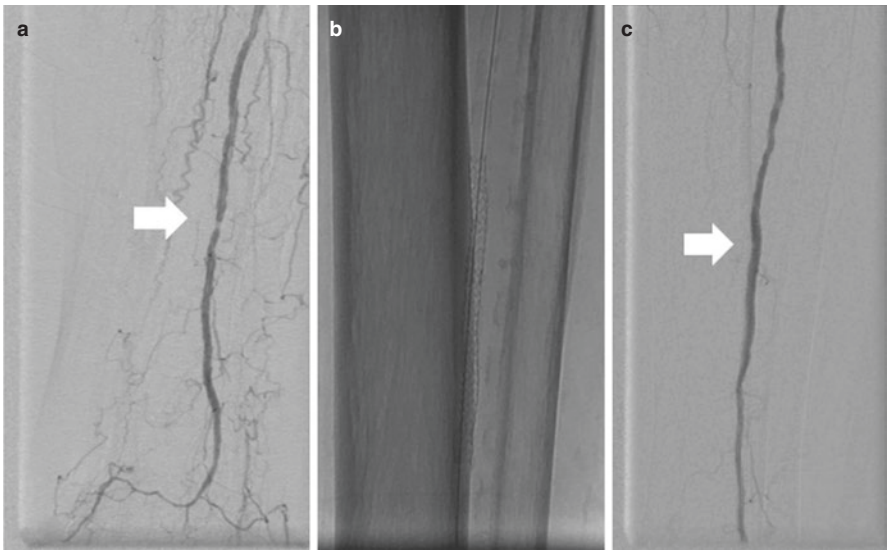

Fig. 22.3 Placement of a DES. (**a**) Angiogram of the peroneal artery demonstrates persistent elastic recoil of a focal stenosis (white arrow) following previous balloon angioplasty. (**b**) A DES was deployed across the stenosis. (**c**) Completion angiogram demonstrating patency across the stenosis (white arrow)

DES proved their superiority vs. PCB in long BTK lesions (107 ± 40.1 mm) but this is a single-center study with a relatively small number of patients and overall follow-up was limited to 6 months. Spiliopoulos et al. [46] reported 214 diabetic patients with CLI and BTK disease (679 lesions) treated with DES in a period of ten years. Survival rates at 1, 5, and 10 years were 90.8%, 55.5%, and 36.2% and amputation-free survival was 94.9%, 90.4% and 90.4%, respectively,. Although a valid control group was not available to provide a comparison with other techniques, DESs proved their potential role in the very demanding field of diabetic CLI revascularization in this retrospective analysis. DES trials have yet to show enough clinical or economic benefit for primary DES stenting in diabetic patients with long lesions but it would be interesting to try to determine if a specific subgroup of diabetic patients with CLI could benefit from use of DES. Further quality trials assessing long-term clinically relevant outcomes [47] and safety may lead to a change in future practice.

22.5 Operator Factor in Endovascular Intervention in the Distal Arteries of the Leg and Foot

Although often the latest advance in technology will grab the headlines, it is worth remembering that endovascular technique is a specialized technique that regardless of tools used, well trained, experienced, and dedicated operators are expected to offer the best outcomes.

Variation among practice patterns and specialists has been evaluated in many areas of medicine. Medicare data show that endovascular lower-extremity revascularization by less experienced operators results in more transfusion and intensive care unit (ICU) use, longer hospital stay, more repeat revascularization procedures or amputations, and higher costs compared with procedures performed by interventional radiologists [48].

22.6 Conventional Techniques of Endovascular Intervention in the Distal Arteries of the Leg and Foot

Antegrade access remains the first-choice approach for the treatment of BTK and BTA lesions as it allows excellent guide-ability of the guidewire and good push-ability of the catheter balloons through long complex atheromatous, often occluded, BTK lesions [49]. Retrograde contralateral femoral ‘crossover’ across the aortic bifurcation is used if there is associated iliac disease or in the presence of morbid obesity and proximal iliac or common or proximal superficial femoral disease.

The first line technique remains the transluminal crossing method [50]. An introducer (45 cm) can be advanced to the lower popliteal artery providing additional

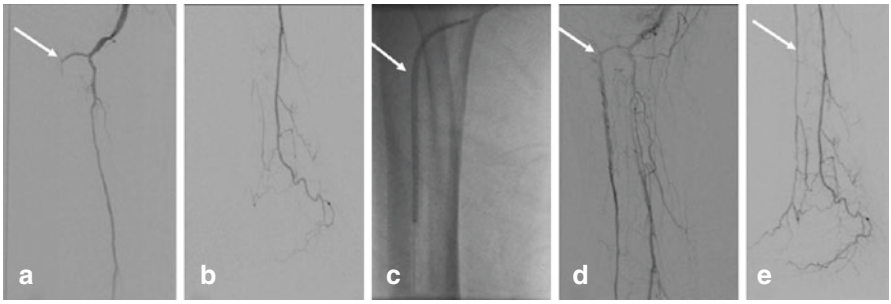

Fig. 22.4 Antegrade approach of crossing of a long anterior tibial artery occlusion. (**a** and **b**) Pre-treatment angiogram demonstrates a full-length occlusion of the anterior tibial artery (arrow). (**c**) A guide wire was successfully navigated through the occlusion intraluminally with a combination of drilling techniques and balloon angioplasty was performed (arrow). (**d** and **e**) Completion angiogram demonstrates restored patency of the anterior tibial artery (arrow)

support. The procedure is started with a drilling motion of the guide-wire, with rotating of the guidewire with alternating clockwise and anticlockwise movements, with gentle push and with a short and low profile coaxial catheter balloon as a support catheter, in the direction of recanalization through areas of lower resistance in the stenosis or occlusion (Fig. 22.4).

On failure of navigating the guidewire through intraluminal path, an attempt can then be made to cross the occlusion using a subintimal approach [51]. In principle, an intentional subintimal plane is initiated proximal to the lesion to bypass the entire diseased area and to exit into a disease–free segment just distal to the lesion. The failure of this technique is mainly due to the guide-wire not being able to re-enter to the true lumen beyond the occlusion, and the failure rate is increased in vessels with significant calcification. Inflation of a balloon next to the assumed re-entry area could be used to traumatically cross the dissection membrane and potentially allow a guidewire to be navigated through into the true lumen.

22.7 Alternative Techniques of Endovascular Intervention in the Distal Arteries of the Leg and Foot

The technical failure rate using the traditional antegrade approach is around 20% with modern devices. Fortunately, the threshold of what can be treated with endovascular procedures is shifting. When conventional techniques fail, a number of alternative techniques can be pursued to restore blood flow to the foot. When applying these advanced techniques, the principle of a ‘step-by-step approach’ should be taken, starting from conventional technique and progress to more advanced techniques if clinically indicated following a balanced assessment of function and degree of collateralization in the vascular territories, as well as consideration of risk of compromising other potential alternative surgical and endovascular options

should advanced endovascular techniques fail. Time and effort should be prioritized to do what is realistic in order not to prolong procedure time and potentially increase risk of complication on attempting unrealistic targets.

22.7.1 Retrograde Pedal Access

This procedure requires combining a conventional ipsilateral femoral approach with direct puncture of the leg vessel distal to the obstruction where it is still patent from rich collateral supply but could not be reached through an antegrade approach in order to cross the occlusion backwards (Fig. 22.5). Various groups have shown good technical and clinical success confirming that a retrograde approach to the vessel leads to high success rate of revascularization when the antegrade approach fails, probably because the distal part of an occlusion generally consists of less fibrotic or calcified tissue, thus allowing an easier passage across the occlusion. Sabri et al. [20] suggested that retrograde pedal access is a viable revascularization technique for achieving limb salvage in patients with CLI in whom antegrade revascularization has failed and surgical bypass is not a viable option. In 124 diabetic patients with CLI (12% of 1035 people treated) in which antegrade recanalization failed,

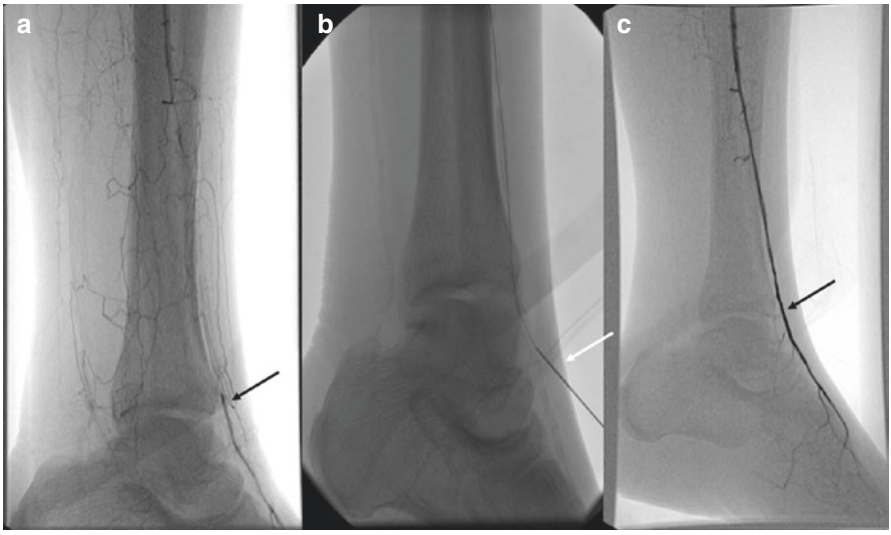

Fig. 22.5 Retrograde pedal access. (**a**) Pre-treatment angiogram demonstrates an occluded distal anterior tibial artery with a patent dorsalis pedis artery (black arrow) which could not be reached via an antegrade approach. (**b**) A direct puncture of the patent distal anterior tibial artery was performed under ultrasound guidance and a guide wire was passed through the occlusion in a retrograde fashion successfully (white arrow). (**c**) Completion angiogram demonstrates restored patency of the distal anterior tibial artery (black arrow) following balloon angioplasty over the guide wire from the ipsilateral femoral approach

Gandini et al. [52] reported a technical success rate of 96% using this dual approach with a limb salvage rate of 83% at 6 months and a 10% mortality rate during clinical follow-up, with 26% repeat procedure and 16% amputation rates. The technical success of this approach using retrograde puncture after antegrade failure is estimated to be around 80% [53, 54]. Access vessel thrombosis has been reported [55], which has created some concerns about the use of pedal arteries as access. However, lower profile, dedicated pedal access sheath and intra-arterial vasodilators can be used to minimize the risk of vasospasm and access site thrombosis.

22.7.2 The Pedal Plantar and "Trans-collateral LOOP" Techniques

The pedal plantar loop technique [19, 52, 56] and the trans-collateral approach [57] consist of using natural anastomosis to optimize pedal flow or to allow access to recanalize a tibial or foot artery via the plantar arcade or a sufficiently well-developed collateral supply. It is based on the technique of successfully advancing a wire followed by a balloon through the plantar arch, or a different anastomosis such as the "deep arch" of the foot which links the medial plantar artery with lateral tarsal branch of the dorsalis pedis artery, recreating a loop or patent communication from the dorsal to the plantar circulation of the foot (or vice versa). The technique can be utilized to optimize pedal flow to achieve a complete below-the-ankle revascularization with the hope of improving perfusion of the forefoot by restoring missing connections in the toes and heels (Fig. 22.6). It can also be used to perform recanalization, crossing through the opposite patent circulatory pathway to obtain a retrograde recanalization of the occluded foot vessel (Fig. 22.7). Manzi et al. described a technical success rate of 85% in 135 patients (10.1% of a population of patients

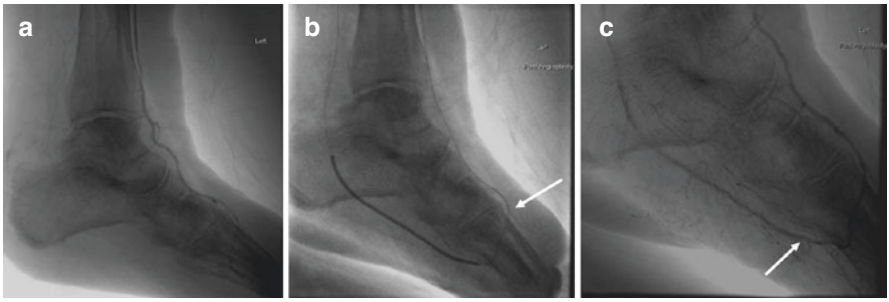

Fig. 22.6 Pedal plantar loop angioplasty. (**a**) Initial angiogram demonstrates poor flow through the pedal arch and an occluded distal posterior tibial artery. (**b**) A guide-wire was negotiated through the pedal plantar arch via an antegrade approach through the anterior tibial artery and balloon angioplasty was performed though the plantar arch to optimize pedal arch flow (arrow). (**c**) Completion angiogram demonstrated improved flow through the pedal plantar arch (arrow) following angioplasty

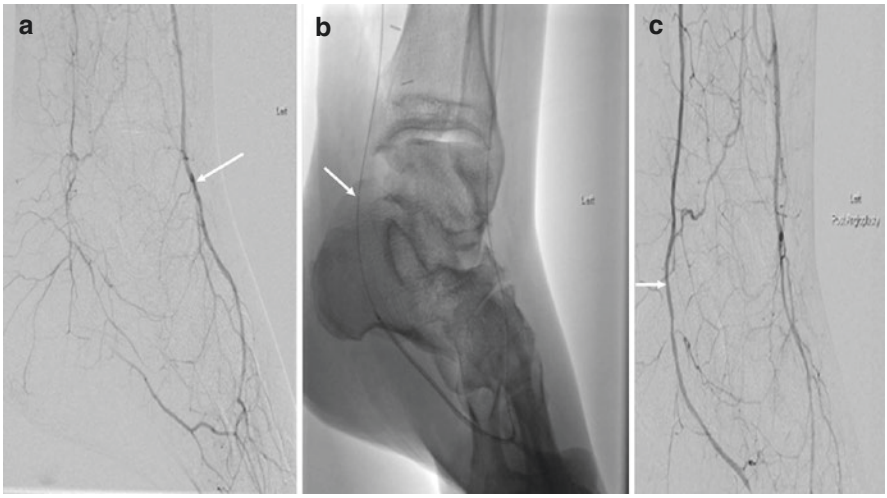

Fig. 22.7 Retrograde recanalization of the distal posterior tibial artery with pedal plantar technique. (**a**) Pre-treatment angiogram demonstrates an occluded distal posterior tibial artery. The anterior tibial artery (arrow) and the pedal plantar arch is patent. (**b**) A retrograde recanalization of the occluded distal posterior tibial artery (arrow) was performed following a successful retrograde crossing of the occlusion through the opposite patent anterior circulatory pathway and the plantar arch. (**c**) Completion angiogram demonstrates restored patency of the distal posterior tibial (arrow) and plantar arteries

treated via an endovascular approach for CLI over a period of 2 years), and clinical improvement in functional status was obtained and maintained after an average of 12 months, with a significant improvement of transcutaneous oxygen tension after 15 days [19].

22.7.3 Metatarsal Angioplasty and Direct Metatarsal Artery Puncture

With the advances in guide wire and catheter technology, it is now possible to perform angioplasty in the very distal, metatarsal arteries to restore direct line flow to non-healing toe ulcers (Fig. 22.8). In addition, Palena and Manzi reported the feasibility to directly puncture the first metatarsal artery or the plantar arcade, following local anesthesia and local administration of antispastic verapamil, to undertake retrograde recanalization of the foot and lower leg arteries. Through this approach, the group reported a technical and clinical success rate of 85% at 6 months in 28 patients, with an associated increase in tcPO2 with 71% of patients alive and not amputated at 6 months [58, 59].

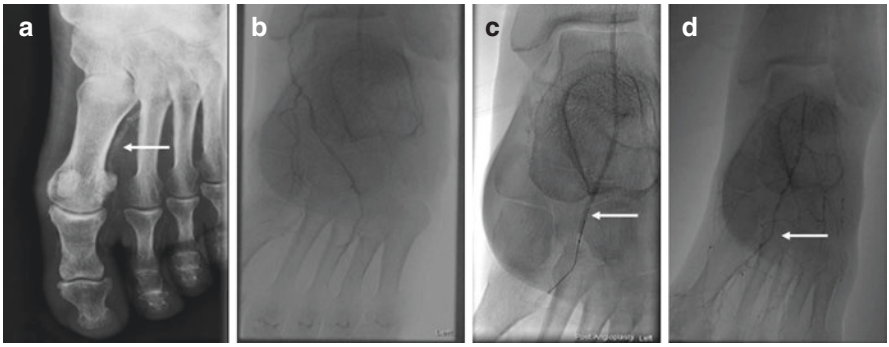

Fig. 22.8 Metatarsal artery angioplasty. (**a**) Radiograph of the right big toe demonstrates a heavily calcified first metatarsal artery (arrow). Clinically, a non-healing ulcer persists at the big toe despite previous successful tibial revascularization. (**b**) Foot angiogram demonstrates an occluded distal dorsalis pedis and first metatarsal arteries. (**c**) Crossing of the distal dorsalis pedis and first metatarsal occlusion was performed successfully and this is followed by balloon angioplasty (arrow) of the dorsalis pedis and first metatarsal arteries. (**d**) Direct vascular flow is restored into the big toe(arrow) where the non-healing ulcer is present

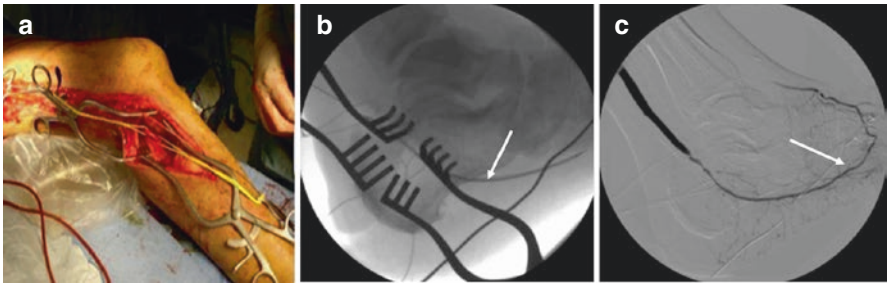

Fig. 22.9 Plantar arch angioplasty through a Critical limb ischemia (CLI):endovascular intervention in distal arteries of leg and foot:hybrid approach. (**a**) An ultra-distal surgical bypass procedure was performed with the distal anastomosis at the common plantar artery. There is, however, poor distal outflow into the lateral plantar artery and foot arch. (**b**) Through access at the distal anastomosis at the time of bypass operation, a guidewire was passed through the plantar arch and balloon angioplasty (arrow) was performed to optimize bypass graft outflow. (**c**) Completion angiogram demonstrates a good graft outflow into the optimized plantar artery and the pedal plantar arch (arrow)

22.7.4 Hybrid Procedures

Another strategy is a hybrid approach, with angioplasty of pedal arteries in the ultra-distal bypass group (Fig. 22.9) [60, 61]. Combined therapy with a hybrid approach simplifies the procedure and allows the one-step treatment of patients with complex vascular disease.

22.8 Conclusion

One of the features of diabetic patients with CLI is the predominance of diffuse obstructive lesions in the distal, sub-popliteal arteries. The range of technical endovascular revascularization possibilities for crural and pedal artery disease has increased considerably. Technical success rate and clinical outcomes for endovascular revascularization techniques are encouraging although this is dependent on the local resources and expertise. The rapid pace of development of various endovascular devices and advanced techniques allow the interventionists to treat increasingly complex and distal patterns of disease. However, a recent meta-analysis has found an increased risk of death at 2 and 5 years after the use of paclitaxel- coated balloons and stents in the femoro-popliteal artery and this is still under discussion at the present time [62]. Revascularization strategy should be individualized through a multidisciplinary process, with a step-by-step technical approach, to facilitate clinically driven, more distal revascularization aiming to establish a patent pedal arch flow, which could be vital to facilitate complete wound healing and achieve limb salvage.

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Chapter 23
Re-Opening Leg Arteries: Approach to Chronic Total Occlusion

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The superficial femoral artery (SFA) is the longest artery in the body and it is prone to the development of atherosclerotic plaque deposition due to repetitive bending, twisting, and trauma with everyday movement. As a result, it is the most commonly affected vessel in patients with symptomatic claudication, and in nearly 50% of patients the atherosclerotic burden is often diffuse and manifests as chronic total occlusion (CTO) [1, 2]. CTO is defined as an arterial segment that has been occluded for greater than or equal to three months [3]. In the absence of prior imaging, stable lesions that prevent contrast from opacifying the distal vessel are also managed as chronic occlusions. CTO lesions are characteristically composed of a proximal and distal fibrocalcific cap, mixed luminal plaque with thrombin and fibrin, and localized inflammation in the vessel wall [4]. In the SFA, the occluded segment can be heavily calcified and span up to 20 cm in length. Microscopically, CTO lesions frequently show neovascularization and the formation of recanalization microchannels that run parallel to the occluded vessel. Revascularization may be surgical or endovascular and choosing the optimal method involves consideration of both patient and anatomical factors [5]. Patient factors include the symptomology at presentation (Rutherford classification [6]), surgical risk, medical comorbidities, and availability of conduit if surgical management is considered. Anatomical considerations include the burden of disease [7], vascular anatomy with regard to inflow and runoff, and the degree of calcification. An early randomized trial comparing bypass surgery or patch endarterectomy with balloon angioplasty in patients with infrainguinal critical limb ischemia (BASIL Trial, 2005) showed less early morbidity with endovascular intervention compared to surgery, but worse long-term outcomes

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with regard to the rate of re-intervention or amputation [8]. However, the study was limited by a low rate of anti-platelet therapy use and 20% of the endovascular procedures were deemed to be immediate technical failures. In 2007 the second Trans-Atlantic Inter-Society Consensus (TASC II) Document on Management of Peripheral Arterial Disease was published and recommended peripheral vascular intervention for lesions less than 5 cm in length (TASC A/B) and surgical bypass for multiple lesions or chronic occlusions greater than 20 cm that include the popliteal artery (TASC C/D) [9]. Subsequently, a randomized prospective study of 86 patients (100 limbs) with TASC A-D occlusive disease of the SFA showed similar rates of patency at 4-years when comparing percutaneous intervention with a self-expanding stent or surgical femoral-popliteal synthetic bypass graft. Over the last decade there have been significant advances in endovascular procedural technique as well as the development of novel guidewires, atherectomy devices, crossing devices, drug coated balloons, and newer generation stents that improve the success rate of percutaneous intervention and long-term patency. As a result endovascular management has become a primary method for revascularization and limb salvage in affected patients. This chapter will focus on the contemporary endovascular management of the lower extremity CTO.

The goal of endovascular intervention is to cross the proximal cap, traverse the occluded segment, and reach the distal re-entry site to establish antegrade flow [10]. This can be technically challenging in a CTO due to the complexity of these lesions and difficulty penetrating the proximal cap. The revascularization strategy is broadly classified into two groups: the "wire-catheter" strategy where a guidewire supported by a microcatheter is used, or use of a specific CTO crossing device. An observational study from the Excellence in Peripheral Artery Disease (XLPAD) database showed improved primary crossing success with use of specialized CTO-crossing devices, but no difference in overall procedural success or duration [3]. Both techniques can utilize a true lumen (intraluminal) or subintimal approach. The intraluminal method is most common and involves utilizing hydrophilic guidewires and low profile support catheters with or without the assistance of atherectomy devices or blunt microdissection to directly penetrate the lesion. Access may be antegrade via the ipsilateral or contralateral SFA, or retrograde via the popliteal or pedal artery depending on the proximity of the lesion.

An initial strategy is to attempt to cross the lesion with a 0.035, 0.018, or 0.014 inch diameter hydrophilic guidewire with a support catheter. This technique relies on tactile feedback as well as the operator's perception of the tortuosity of the vessel and composition of the culprit lesion. Guidewire selection depends on several attributes including diameter of the wire, tip stiffness, torque response, wire stiffness (or rail support), and lubricity. Larger diameter wires are better suited for larger vessels where they can provide support for catheters or crossing devices. The tip stiffness (or tip load) of the wire is the force that is required for the tip of the wire to buckle in response to stress. High tip load guidewires are useful for crossing calcified occlusions but carry a risk of accidental subintimal dissection, whereas "floppy" tips are more flexible and less likely to injure the vessel. Some lesions cannot be crossed via the true lumen and the subintimal method may be used. Subintimal angioplasty was first described by Bolia in 1987 when an accidental popliteal artery dissection

was pursued and used to re-access the true lumen after bypassing a 10 cm occlusion, which was followed by a report of 44 successful cases [11]. Briefly, the subintimal space is accessed with a hydrophilic wire and a wire loop is advanced beyond the occlusion, after which the true lumen is re-entered and balloon dilatation is used to create a disease-free neolumen between the intimal and adventitial layers of the artery. If the wire does not spontaneously perforate into the true lumen distal to the CTO, the support catheter can be advanced to the proximal cap to allow for wire exchange to a smaller-diameter stiff wire that can be used to gain re-entry to the true lumen. In patients with critical limb ischemia the limb salvage rate with subintimal angioplasty at 1 year is between 80–90% but primary patency is only 50–70% [12]. The success rate is lower in patients with intermittent claudication with both initial clinical success rate and one-year patency of 50–60%. Experienced operators may employ complex wiring techniques to cross challenging lesions. Controlled antegrade and retrograde subintimal tracking (CART) involves the placement of an antegrade wire in the true lumen at the proximal cap while a retrograde wire is advanced across the distal cap into the subintimal plane [13]. Balloon inflation via the retrograde track is used to dissect the subintimal space until the retrograde wire can be externalized at the proximal cap. Reverse CART is the same procedure but the antegrade wire is advanced in the subintimal plane and the retrograde wire is placed at the distal cap.

Most operators prefer primary use of a wire-catheter strategy and secondary utilization of specialized crossing catheters for lesions that cannot be crossed with a wire. Crossing devices have been shown to improve both primary and secondary technical success but at the expense of increased economic cost, higher contrast load, and longer procedural and radiation times. These devices use various strategies for tunneling through the CTO, including blunt microdissection, vibrational energy, radiofrequency ablation, and imaging guidance, as described in Table 23.1, [14–20].

In addition to crossing devices, re-entry devices are specialized systems that facilitate true lumen re-entry in patients who undergo subintimal angioplasty. The primary reason for technical failure with a subintimal approach is failure to re-enter the true lumen which occurs in up to 15% of cases. These devices facilitate true lumen re-entry and reduce the risk for distal vessel dissection by providing mechanical or imaging guidance (Table 23.2, [21–25]). The rate of technical success is generally high but there are no head-to-head comparisons of current devices.

Intervention to the infrainguinal arteries can be with a specialized CTO device (as described above), balloon angioplasty, or stent placement. Primary patency of the SFA after balloon angioplasty is only 40–60% after one year, despite an initial technical success rate as high as 95%. Cutting balloons with sub-millimeter atherotomes were initially developed for revascularization of occluded lower extremity saphenous vein grafts, but have been applied to calcified native artery occlusions as well [26]. These specialized balloons help reduce vessel dissection from balloon injury and control plaque fracture to limit distal embolization. Since the SFA lies within the adductor canal stents placed in the vessel are exposed to near continuous forces of flexion, extension, and torsion resulting stent fracture, kinking of the artery along

Table 23.1 Specialized crossing devices for recanalization of infrainguinal CTO

Device	Manufacturer	Technology	Success rate	Trial
Crosser	Bard	High frequency vibration/ atherectomy	41—75%	Gandini et al. (2009) [14]; Khalid et al. (2010) [15]
Frontrunner XP	Cordis	Blunt microdissection		Mossop et al. (2006) [31]
Pantheris/ Ocelot	Avinger	Atherectomy/optical coherence tomography imaging	–	Cawich et al. (2016) (the VISION trial, ongoing) [16]
Safecross	Intraluminal Therapeutics	Radiofrequency ablation	54%—94%	Baim et al. (2004) [17]; Kirvaitis et al. (2007) [32]
TruePath	Boston Scientific	Rotational atherectomy	80%	Bosiers et al. (2014) (the ReOpen Study) [18]
Wildcat	Avinger	Blunt microdissection	89%	Pigott et al. (2012) (the CONNECT trial) [19]
Viance	Covidien/ Medtronic	Blunt microdissection	70—88%	Banerjee et al. (2014) [20]; Sethi et al. (2015) [33]

Table 23.2 Devices to facilitate true lumen re-entry

Device	Manufacturer	Technology	Success rate	Trial
Offroad	Boston Scientific	Positioning balloon with micro-catheter lancet	85%	Schmidt et al. (2014) [21]; Kitrou et al. (2015) [22]
Outback Ltd.	Cordis	Angled guide catheter with nitinol cannula	64—100%	Gandini et al. (2013) [23]
Pioneer	Volcano	Intravascular ultrasound guidance	95–100%	Al-Ameri et al. (2009) [24]; Smith et al. (2011) [25]

the proximal or distal edge of the stent, and a high-rate of in-stent restenosis. Initial trials of first generation endovascular stents showed no significant improvement in technical or clinical outcome compared to balloon angioplasty [27]. However, newer generation stents have reduced the rate of stent fracture as well as restenosis. In 2006 a randomized single-center study of 104 patients showed improved 12-month patency with a nitinol stent compared to angioplasty alone [28]. A subsequent study of the Zilver PTX (Cook Medical) stent (nitinol scaffold with paclitaxel eluting coating) showed superior clinical improvement and greater one year patency with a drug eluting stent compared to bare metal stents [29]. A comparison of infrainguinal interventions (most commonly SFA CTO) in the XLPAD registry showed that stents were most often used in long lesions and resulted in higher rates of limb salvage compared to non-stent interventions (such as atherectomy) [2].

The SFA can be tortuous and occluded by a significant burden of calcified plaque, making both intraluminal or subintimal intervention technically challenging. The operator should be vigilant in addressing complications that may arise such as access site bleeding, vessel perforation, distal embolization, or the occlusion of collateral vessels. Most often these complications can be addressed percutaneously and rarely is there an indication for emergent surgical repair.

After peripheral arterial intervention aggressive risk factor reduction is essential for preventing recurrent occlusive disease. Patients are encouraged to maintain high-intensity statin therapy, discontinue tobacco use, and exercise regularly [30]. Aspirin is recommended for all patients and those who undergo peripheral intervention and most patients receive a brief period (1–3 months) of dual antiplatelet therapy with aspirin and clopidogrel. However, this regimen is extrapolated from trials of coronary stents and there are no randomized controlled trials regarding specific agents or the duration of anti-platelet treatment after peripheral intervention. In patients who undergo drug eluting stent placement dual antiplatelet therapy for two months has been shown to significantly reduce the risk of early thrombosis [29].

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Chapter 24
Surgical Management: Open Surgical Treatment of Infra-Inguinal Occlusive Disease

Hisham Rashid, Raghvinder Gambhir, and Hani Slim

24.1 Infra-Inguinal Occlusive Disease Distribution

Atherosclerotic disease affecting the infra-inguinal arteries differs significantly between diabetic and non-diabetic patients. Femoral-popliteal disease characteristically affects non-diabetic patients causing stenotic and complete occlusive lesions sparing the profunda femoris artery (Fig. 24.1), whereas in diabetic patients the disease is typically infra-popliteal crural disease with sparing of the dorsalis pedis and pedal plantar arteries in some patients but not all (Fig. 24.2). This distribution of the disease with its variance between diabetic and non-diabetic population of patients dictates the different modalities in treatment including open surgery and endovascular techniques. Distal and ultra-distal bypasses are more commonly used to treat diabetic patients with severe tissue loss to try to achieve fast healing (Figs. 24.3 and 24.4). Similarly, crural and pedal arterial arch angioplasty, are generally more commonly performed in diabetic patients, whereas, femoro-popliteal bypass surgery and angioplasty are more common in non-diabetic patients.

24.2 Basil Trial and TASC Recommendations

The choice between different modalities in the treatment of patients with critical leg ischaemia (CLI) depends on different criteria. Few randomised trials are available to aid the decision making. However, the largest trial is the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial which was set up to

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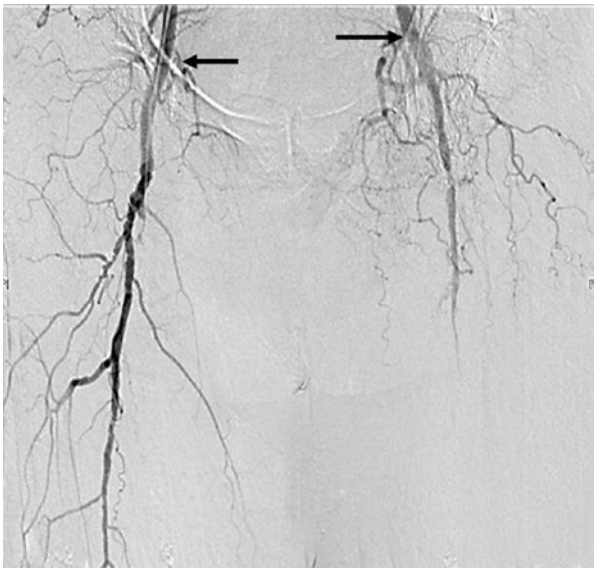

Fig. 24.1 Digital subtraction angiography (DSA) showing bilateral flush occlusion of the superficial femoral artery with sparing of the profunda femoris artery (arrows) in a non-diabetic patient

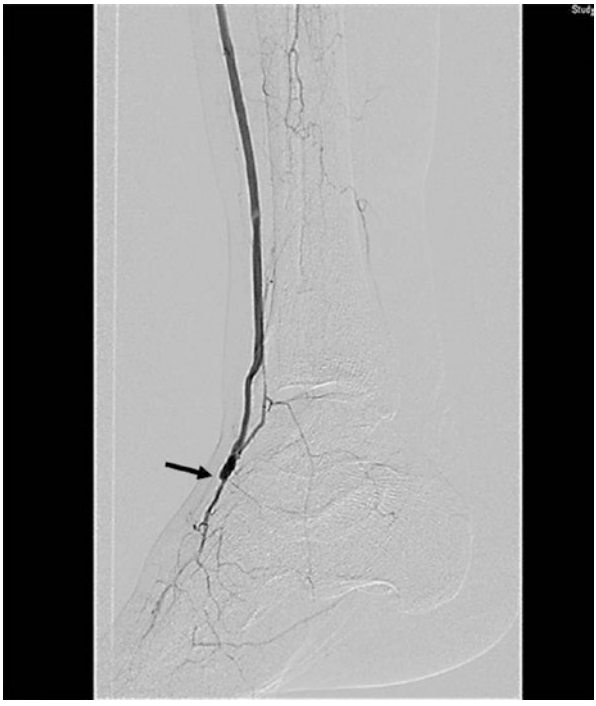

Fig. 24.2 DSA showing a vein bypass graft to an isolated dorsalis pedis artery (arrow) in a diabetic patient with proximally occluded crural arteries

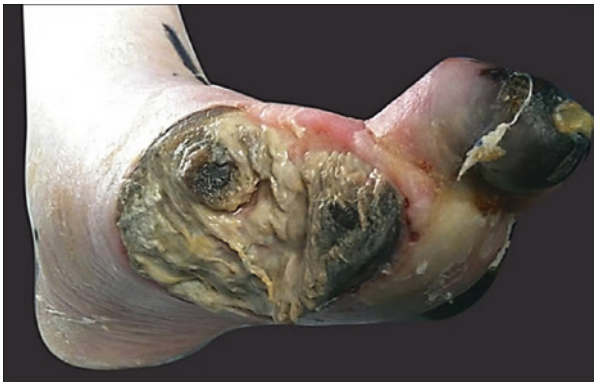

Fig. 24.3 Severely necrotic and infected hallux and second toe amputations stump with gangrene of the adjoining toe

Fig. 24.4 Post-plantar bypass with synchronous wound debridement and toe amputation showing excellent bleeding bed

evaluate outcomes comparing bypass surgery-first to angioplasty-first strategies. Amputation-free and overall survivals were used as end-points for the outcome. The interim analysis of this trial published in 2005 [1] showed that in patients with severe lower limb ischemia (rest pain, ulceration, gangrene) due to infra-inguinal disease, bypass surgery-first and balloon angioplasty-first revascularisation strategies led to similar short-term clinical outcomes, although in the bypass-first group there were more expenses and morbidity compared to the angioplasty-first group.

In 2010, the trial authors published a 2.5-year final intention-to-treat analysis of 'amputation-free survival and overall survival of 452 enrolled patients randomised to either bypass surgery-first or angioplasty-first revascularisation strategy [2]. The results showed that there was no significant difference in amputation-free survival or overall survival between the two strategies. However, for those patients who survived for at least 2 years after randomisation, a bypass surgery-first revascularisation strategy was associated with a significant increase in overall survival and a trend towards improved amputation-free survival.

There are 3 new clinical randomised controlled trials comparing outcomes in patients with infra-inguinal disease and CLI. BASIL 2 is a multi-centre randomised controlled trial comparing outcomes between 'vein bypass first' and 'endovascular first' revascularisation strategy, in terms of clinical and cost-effectiveness, for severe limb ischaemia involving infra-popliteal disease. BASIL 3 is a multi-centre randomised controlled trial of clinical and cost-effectiveness of drug coated balloons, drug eluting stents, and plain balloon angioplasty revascularisation strategies for severe limb ischaemia due to femoro-popliteal disease. The BEST-CLI is a prospective, multicentre, randomized, open label, comparison trial to evaluate the effectiveness of best surgical (OPEN) compared to best endovascular (EVT) revascularization in patients with critical limb ischaemia in centres in USA and Canada-2100 subjects will be recruited from approximately 120 multidisciplinary vascular centers and practices in the US and Canada [3].

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) was published in January 2000 as a result of cooperation between fourteen medical and surgical vascular, cardiovascular, vascular radiology and cardiology societies in Europe and North America [4]. In this document recommendations for either endovascular or open surgery were based on the symptoms as well as the extent and degree of the disease and its anatomical territory. In 2007, an update of the recommendations (TASC II) was published with a focus on the aorto-iliac and femoro-popliteal territories [5]. Recently the European Society of Cardiology together with the European Society for Vascular Surgery have published joint guidelines on the diagnosis and treatment of peripheral arterial diseases [6].

The chapter authors firmly believe that infra-inguinal disease patient selection for either angioplasty, open bypass surgery or hybrid techniques should be tailored to each patient each on their own merits on the basis of regular multidisciplinary meeting discussions covering all aspect of care to ensure the best outcome. This is a dynamic process that will require close monitoring in the acute phase of managing CLI to be able to adapt promptly to evolving complications and unexpected deterioration of the revascularisation process.

Post-revascularisation wound care plays an essential role in the success of these different modalities. This can be a challenging and time-consuming process that could require plastic surgery in-put. The authors rely heavily on offering patients with significant tissue loss split-thickness skin grafts to enhance healing and reduce the time-to-healing in these patients (Fig. 24.5).

24.3 Imaging and Planning

Several imaging modalities are available for clinicians to use in patients with CLI requiring revascularisation. The authors rely heavily on the use of duplex scans in the diagnosis and planning of treatment tailored for each patient. Duplex scan allows the choice of either to proceed with angioplasty as a definitive treatment or

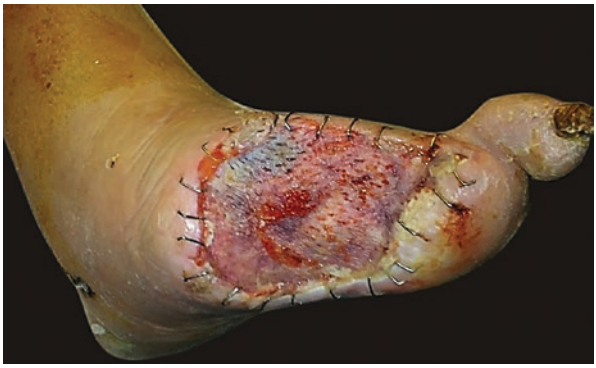

Fig. 24.5 Split-thickness skin graft of the amputation wound with good healing result

as a part of a hybrid strategy (see below) or to proceed to another non-invasive diagnostic modality if open bypass surgery is deemed necessary. Computerised tomography angiography (CTA) or magnetic resonance angiography (MRA) (Figs. 24.6 and 24.7) can be used to delineate the extent of the disease and to select the distal anastomosis site in patients requiring infra-inguinal bypass surgery. Both techniques have their own merits and limitations but both are non-invasive. This avoids the use of the more invasive digital subtraction angiography (DSA) that should be only reserved for patients requiring angioplasty.

Based on the duplex scan, the length and the site of stenosis and or occlusion will dictate which treatment modality should be used. In symptomatic long occlusions affecting the superficial femoral artery following duplex assessment, the patient should be offered an attempt at angioplasty and stenting if not fit for open surgery. However, although the authors apply the "angioplasty-first strategy" in CLI, they prefer to offer patients with long occlusions extending from the trifurcation into the crural and pedal arteries, open distal bypass surgery as a primary treatment option if these patients are fit to undergo major surgery.

In patients requiring pedal bypass surgery, when standard imaging modalities as CTA or MRA are not able to visualise a suitable pedal artery for bypass, the authors have regularly relied on duplex scanning of either the dorsalis pedis artery or the plantar arteries for target runoff (Figs. 24.8, 24.9, 24.10, and 24.11). Duplex can also assess the quality of these arteries by identifying the extent of calcification that could cause difficulty during surgery. This imaging modality is very reliable in patients with severe CLI with very low blood flow that cannot be detected in either foot by dedicated CTA or MRA.

24.4 Conduit for Infra-Inguinal Bypass

There is strong evidence that autologous venous conduits are superior to synthetic grafts from the short and long term outcomes in infra-inguinal bypass especially in distal bypass surgery. The majority of diabetic patients with tissue loss suffer a

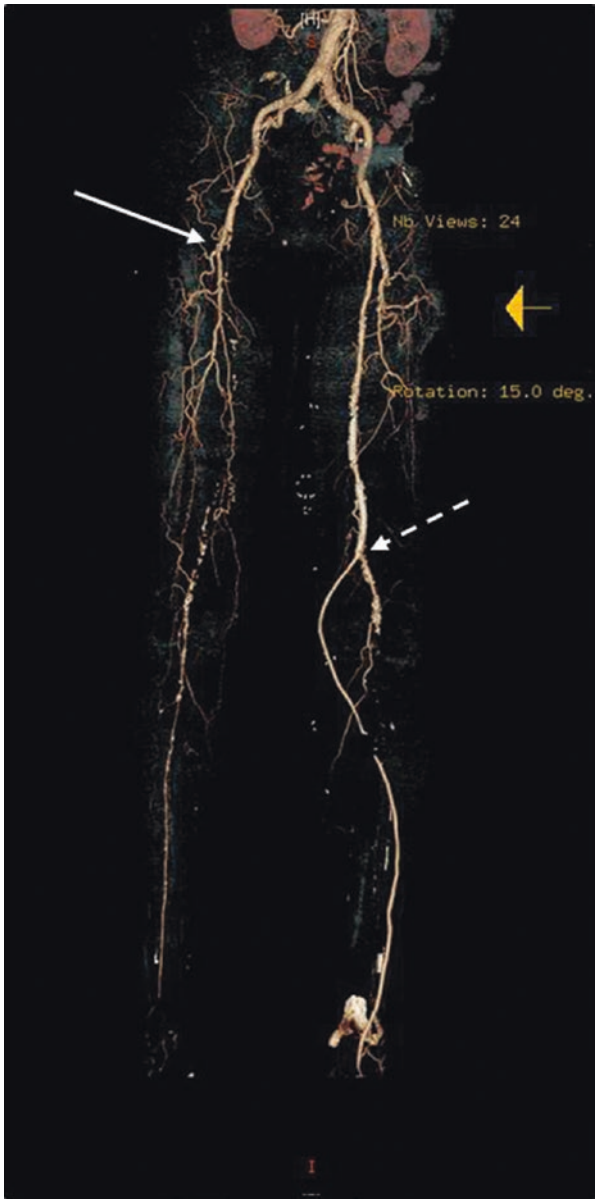

Fig. 24.6 Computerised tomography angiogram (CTA) showing occlusion of the right superficial femoral artery(unbroken white arrow) with diffuse calcification and severe disease of the crural arteries. On the left side, a patent popliteal to pedal bypass can be seen (broken white arrow)

high burden of microbial contamination with a significant risk of antibiotic resistant bacteria which increases the risk of synthetic graft infection and hence limb loss. The authors have a strong preference to using autologous venous conduits and have previously even shown that the great saphenous veins of small internal diameter calibre (less than 3 mm) have a favourable outcome in patients undergoing distal bypass surgery with primary, assisted primary, and secondary patency rates at 1 year for vein conduits <3 mm of 51.2%, 82.6%, and 82.6%, respectively, compared to

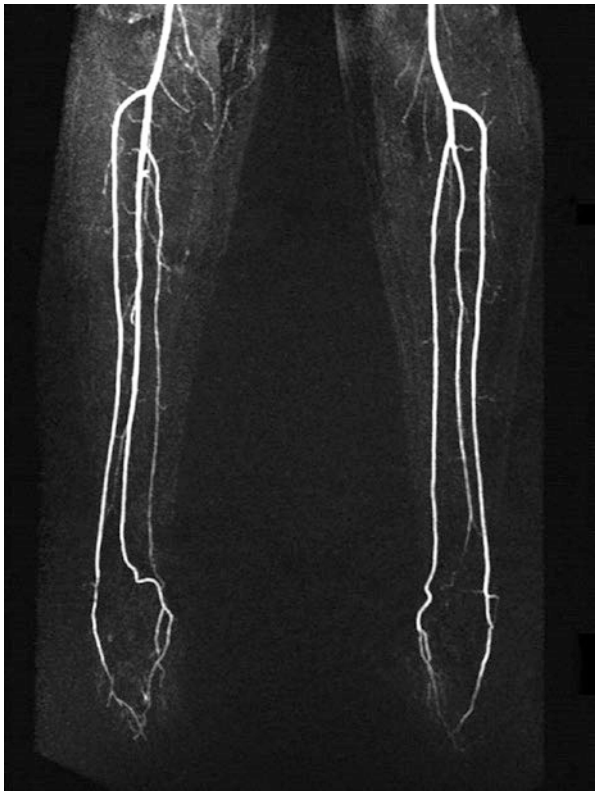

Fig. 24.7 Magnetic resonance angiography (MRA) showing bilateral patent trifurcation of the crural arteries

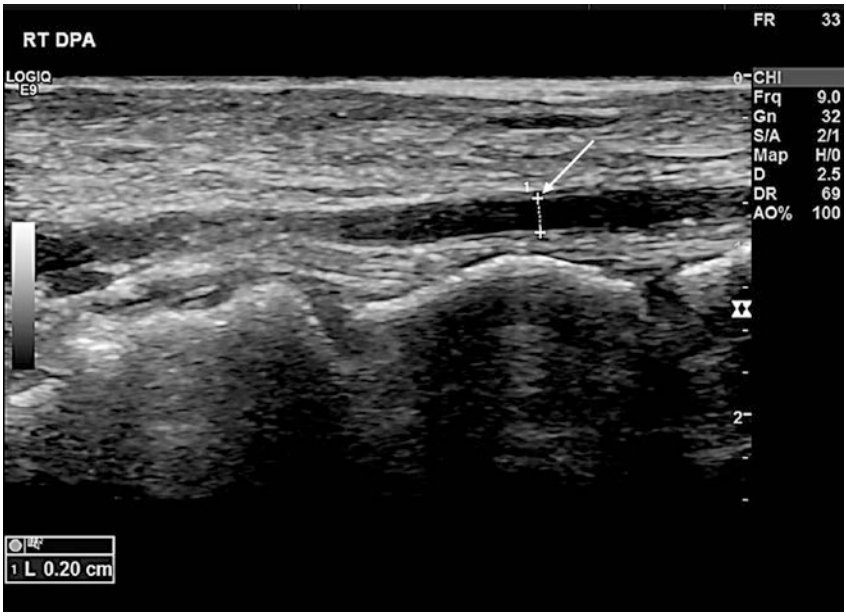

Fig. 24.8 Duplex scan of the dorsalis pedis artery (arrow) showing minimal wall calcification and an internal diameter of 0.20 cm

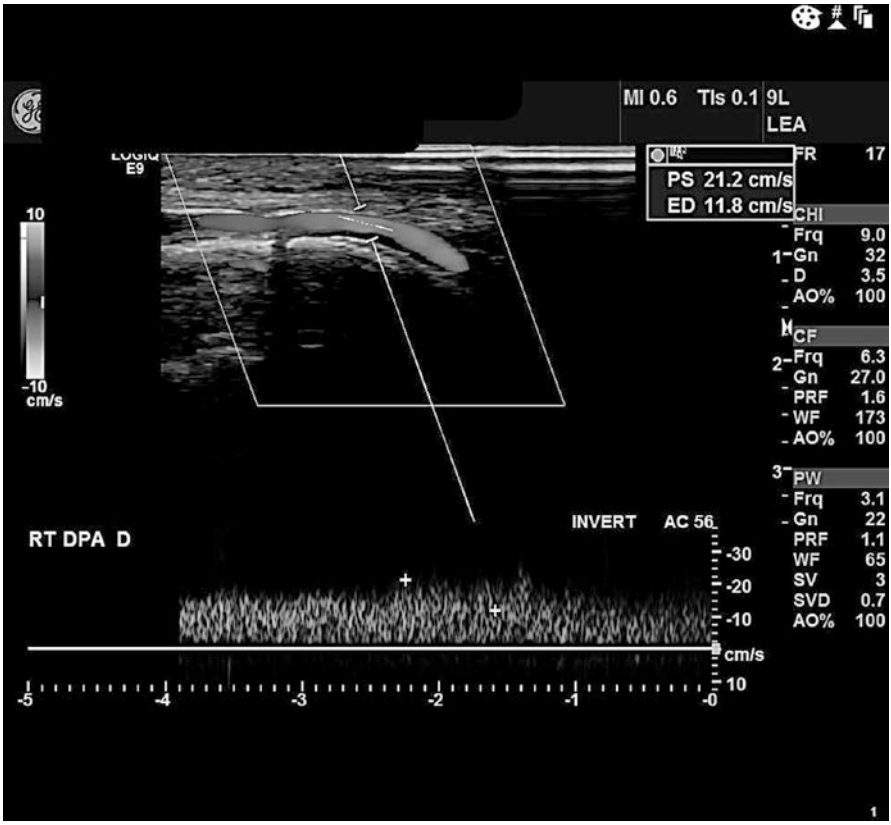

Fig. 24.9 Pre-operative duplex scan of the dorsalis pedis artery showing a patent artery with damped blood flow and a peak systolic velocity of 21.2 cm/s

68.4%, 93.3%, and 95.2% in venous conduit ≥3 mm group [7]. Secondary patency rate was significantly better in the larger venous conduit (P = .0392).

There is also good evidence supporting the use of arm veins to perform infra-popliteal bypass surgery with better outcomes compared to synthetic grafts. Using other surgical techniques, such as the profunda femoris artery as an inflow for infra-inguinal bypass or the use of hybrid techniques (see below) to help shorten the length of the venous conduit, helps in patients undergoing redo surgery or in patients who have previously undergone cardiac bypass surgery using the autologous veins.

24.5 Surgical Infra-Popliteal Bypass; Distal and Ultra-Distal Bypass

The authors have published a series comparing the outcomes of distal (bypass to the crural arteries) versus ultra-distal (bypass to the pedal arteries) in patients with CLI [8]. Two hundred and thirty bypasses were performed in 209 consecutive

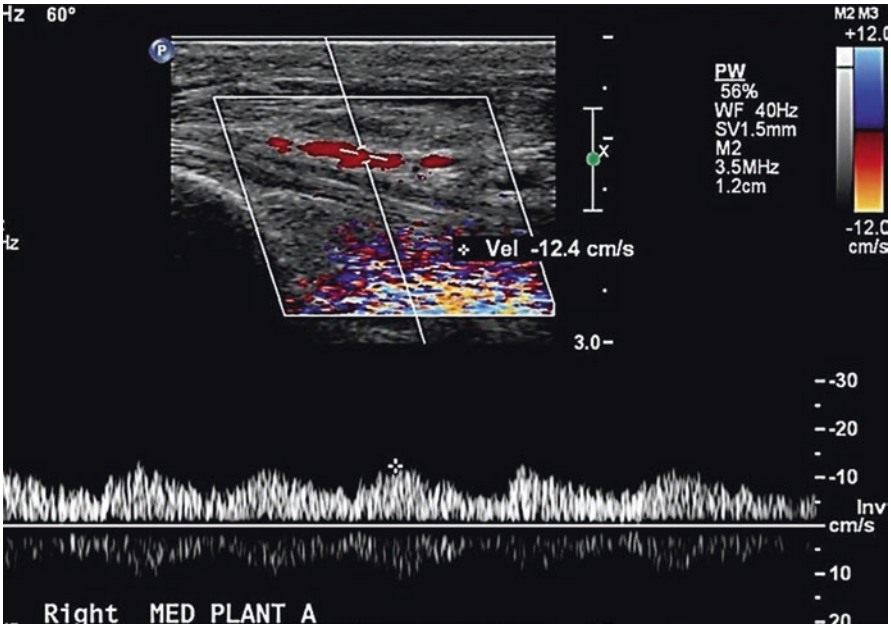

Fig. 24.10 Pre-operative duplex scan of the medial plantar artery showing a patent artery with severely damped blood flow

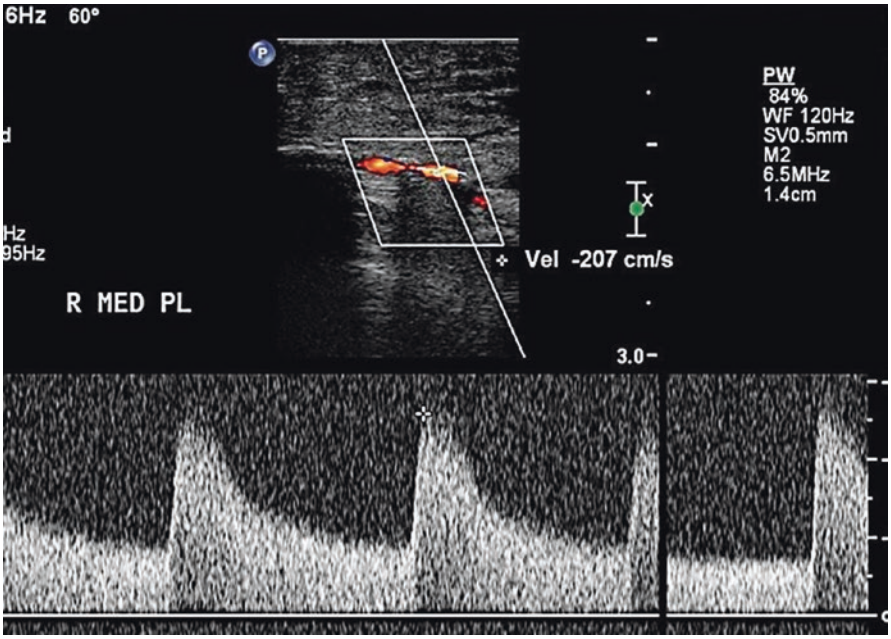

Fig. 24.11 Post-operative duplex scan of the medial plantar artery showing a significant improvement in blood flow with pulsatile waveform

patients of whom the majority were elderly males. One hundred and seventy-nine (78%) bypasses were classified as distal and 51 (22%) as ultra-distal. As expected the incidence of diabetes mellitus was significantly higher in the ultra-distal group ($p = 0.0025$) due to significant crural vessel disease in diabetic patients, with sometimes sparing of the dorsalis pedis and plantar arteries. At 1-year, the distal group primary, assisted-primary and secondary patency rates were 61.7%, 83.1% and 87.4% compared to 61.9%, 87.4% and 87.4% in the ultra-distal group respectively. Amputation-free survival at 12 and 48 months was 82.9% and 61.5% in the distal group compared to 83.0% and 64.9% in the ultra-distal group. This study show that both distal and ultra-distal bypass have comparable outcome regardless of the co-morbidities. The authors believe that medically fit elderly patients should still be offered ultra-distal bypass if indicated to avoid major amputation.

24.6 Outcome Of Distal and Ultra-Distal Bypass

Different outcomes have been reported in different races undergoing distal bypass surgery. In the majority of the American literature, poorer outcomes have been reported in the African-American population with a higher amputation rate and lower graft patency. The authors have published a series of Afro-Caribbean population undergoing distal bypass surgery with comparable results to the Caucasian population [9]. Despite more significant tissue loss as the presenting symptom in the Afro-Caribbean population, the primary, primary-assisted and secondary patency rates, and amputation-free survival at 12 months were similar in both groups.

24.7 Intra-Operative Monitoring and Optimisation and Post-Operative Mortality

Mortality rates following infra-inguinal bypass varies significantly in different studies. Analysis of surgical revascularisation procedures performed each year in England [10], and their outcome using hospital episode statistics, demonstrated a total of 21,675 femoro-popliteal and 3458 femoro-distal bypasses with a mean in-hospital mortality rates of 6.7 and 8.0% respectively. The 1-year survival rates were 82.8 and 79.1% which both increased over the study interval. The chapter authors have reported significantly lower mortality rates in 209 elderly high-risk patients undergoing 203 distal and ultra-distal bypasses (median age of 76 and 73 years respectively). Thirty -day mortality was 1.7% and 1-year mortality rate was 12.2% [8]. The authors have always attributed these low mortality rates to the meticulous intra-operative monitoring and optimisation of these patients.

In an observational case series, the authors also reported 120 elderly patients undergoing major infra-inguinal bypass between 2007 and 2012 [11]. Intra-

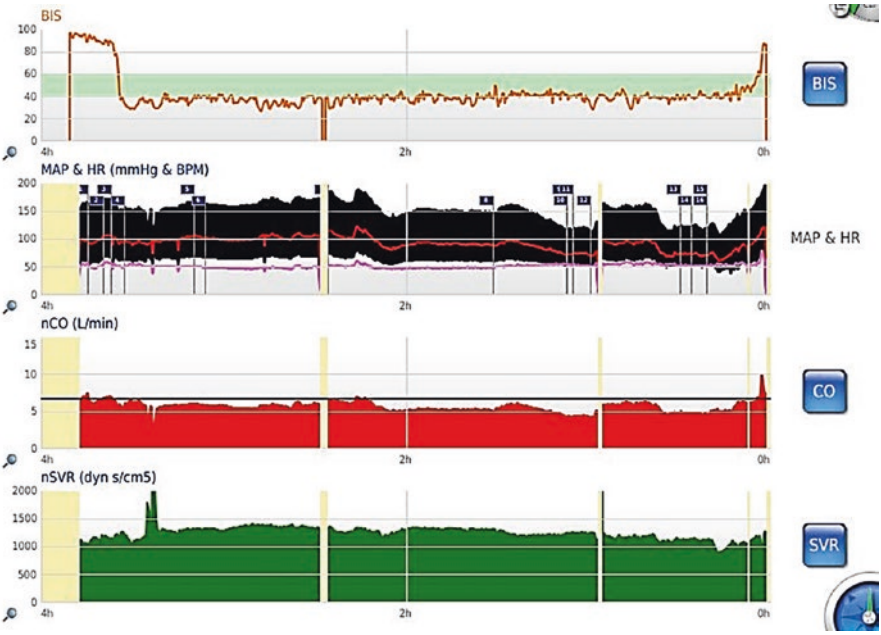

Fig. 24.12 Intra-operative trace of a patient undergoing a distal bypass showing the bi-spectral index (BIS), heart rate (HR), mean arterial pressure (MAP), cardiac output (CO) and systemic vascular resistance (SVR). (Courtesy of Dr. David Green, Consultant Vascular Anaesthetist, King's College Hospital, London, UK)

operative haemodynamic monitoring was used to maintain the nominal cardiac output and oxygen delivery throughout the surgery to within 10% of the pre-induction value (Fig. 24.12) so as to minimise build-up of oxygen debt which is a predictor of morbidity and mortality. Thirty-day mortality rate was only 0.8%, whereas, the V-POSSUM scoring indicated a predicted mortality of 9%. Similarly, the amputation rate was less than 2% at one year. Only 8% of patients were admitted to a high dependency unit postoperatively. The authors concluded that using this multimodal intra-operative monitoring with the specific aim of limiting build-up of oxygen debt had a positive impact on this group of high risk patients.

Figure 24.12 demonstrates the intra-operative monitoring trace of a patient undergoing a distal bypass. The bispectral index (BIS) trace at the top of the graph emphasises the importance of maintaining an adequate depth of anaesthesia. This sustains the blood pressure, as seen in the second trace and even more importantly cardiac output in the third trace. The horizontal black line indicates the starting cardiac output prior to induction of anaesthesia in the awake elective patient and demonstrates that the cardiac output has been maintained pretty well throughout the operation. This conserves oxygen delivery provided the haemoglobin concentration is also maintained and thus virtually eliminates build-up of oxygen debt and the necessity to repay this post operatively, a difficult task for these high-risk very frail patients.

These parameters are also maintained without excessive infusion of intravenous fluids which would tend to overload the patients and increase the risk of pulmonary oedema. The systemic vascular resistance (SVR) trace at the bottom of the graph in green indicates that there are no major changes in systemic vascular resistance which might cause problems in the blood supply to the ischaemic area of the limb.

24.8 Hybrid Revascularisation

Complex patients with CLI, especially treated in redo cases with limited venous conduit and poor distal run-off, may not be suitable for either distal bypass surgery or angioplasty alone. Some primary cases are also very complex for one modality of treatment only. Performing a pedal bypass from the common femoral artery down to the foot level is very challenging and crossing several joints that could cause mechanical failure of these grafts. Hybrid revascularisation involves the timely use of angioplasty of the inflow arteries followed by bypass surgery, or bypass surgery followed by distal outflow angioplasty to achieve straight-line flow to the ischaemic area. In few patients both inflow and outflow angioplasty is required before and after bypass surgery. The rational is the ability to treat multilevel extensive disease, by reducing the length of graft and by crossing fewer joints and hence achieving better outcome.

Angioplasty of the inflow arteries (stage I angioplasty) is performed to allow the proximal anastomosis to be taken from the most patent artery distally. This is followed by a bypass to the patent crural or pedal artery (stage II bypass). The distal run-off arteries could be treated if required by an angioplasty through the bypass graft (stage III angioplasty) to allow good blood flow to the pedal arterial arch (Figs. 24.13, 24.14, 24.15, 24.16, 24.17, 24.18, 24.19, 24.20, and 24.21).

This hybrid technique can achieve successful revascularisation in patients who otherwise would have been doomed to major amputation as they are labelled

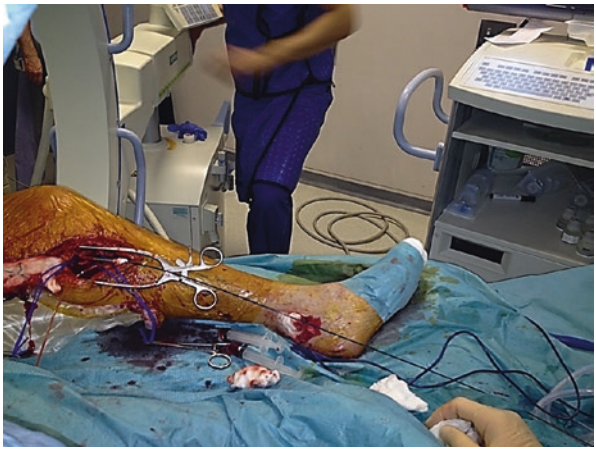

Fig. 24.13 Intra-operative hybrid retrograde angioplasty of the popliteal and superficial femoral arteries with synchronous posterior tibial bypass at the ankle level

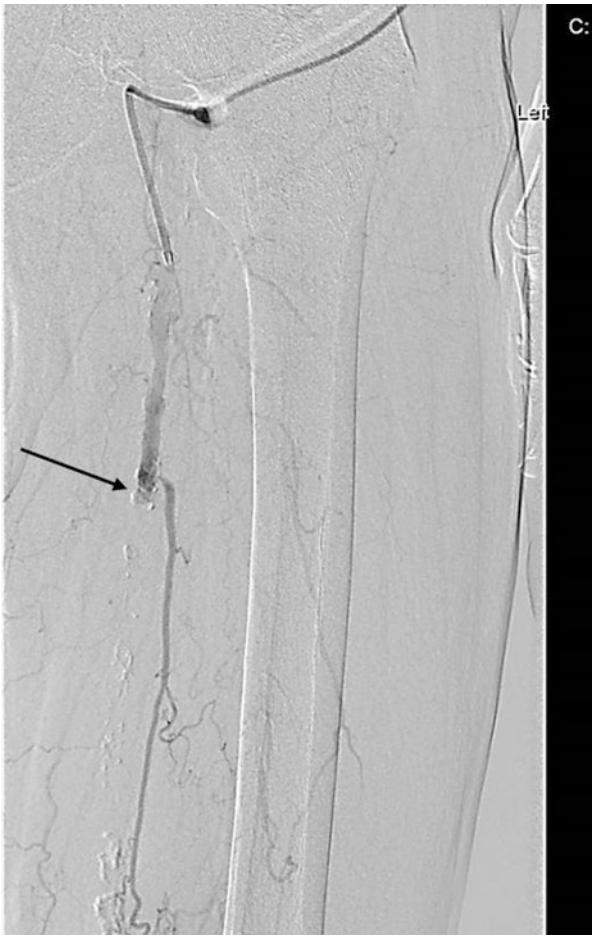

Fig. 24.14 Antegrade DSA demonstrating occlusion of the superficial femoral artery (arrow)

"no-option" for treatment CLI. This "no-option" for treatment is defined as CLI with no suitable treatment available using either revascularisation modalities. This is obviously a very subjective definition that will vary significantly between one surgeon or department to another.

Dosluoglu et al, have published a large series of 654 patients undergoing 770 procedures of which 67% of the cases had CLI [12]. The revascularisation procedures included 29% open bypass (226 cases), 57% endovascular (436 cases) and 14% (108 cases) hybrid procedures of both endovascular and surgical bypass. The study showed a patency rate similar between three groups, as well as, overall survival. However, the limb salvage in CLI was better in the hybrid group although this group had increased morbidity and mortality rates which was due to the higher risk patients in this group.

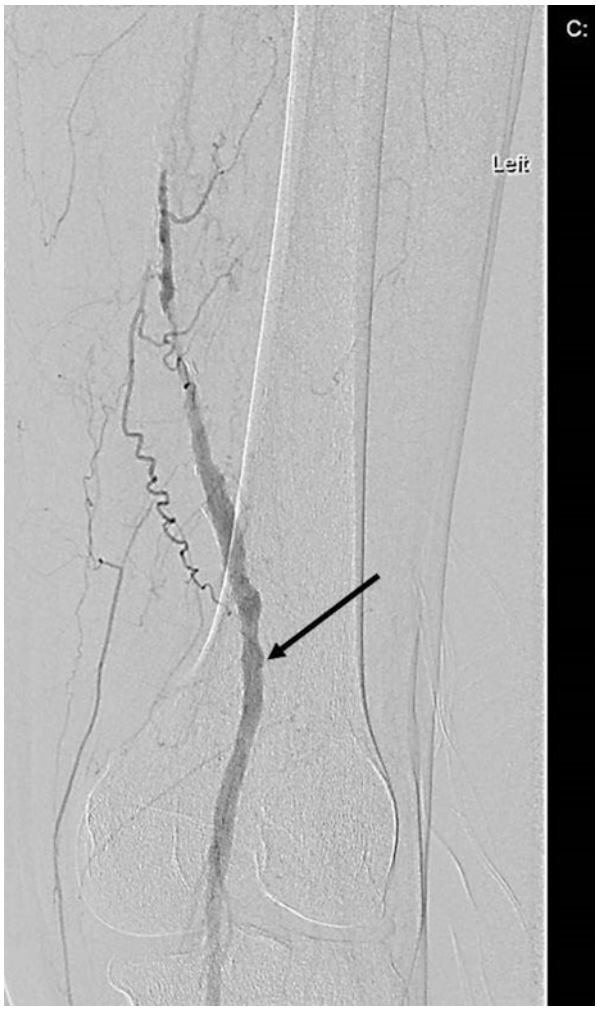

Fig. 24.15 DSA demonstrating reconstitution of the popliteal artery (arrow) above the knee level

24.9 Graft Surveillance Program

Postoperative bypass graft surveillance program using regular duplex scanning to detect graft abnormalities that could threaten blood flow and graft patency has been implemented for many years by different clinicians. The program's cost-effectiveness has been questioned in a publication by Davies et al. in a randomized controlled study published in 2005 [13]. In this study, patients were randomized either to duplex surveillance program or clinical examination only. The study showed that programed surveillance with duplex scanning did not demonstrate any additional benefit in terms of limb salvage rates for patients undergoing vein bypass graft operations compared to clinical follow-up only, but it incurred a £495 additional cost.

The chapter authors run a very strict duplex surveillance program for all patients undergoing bypass surgery. The majority are non-claudicant diabetic patients with

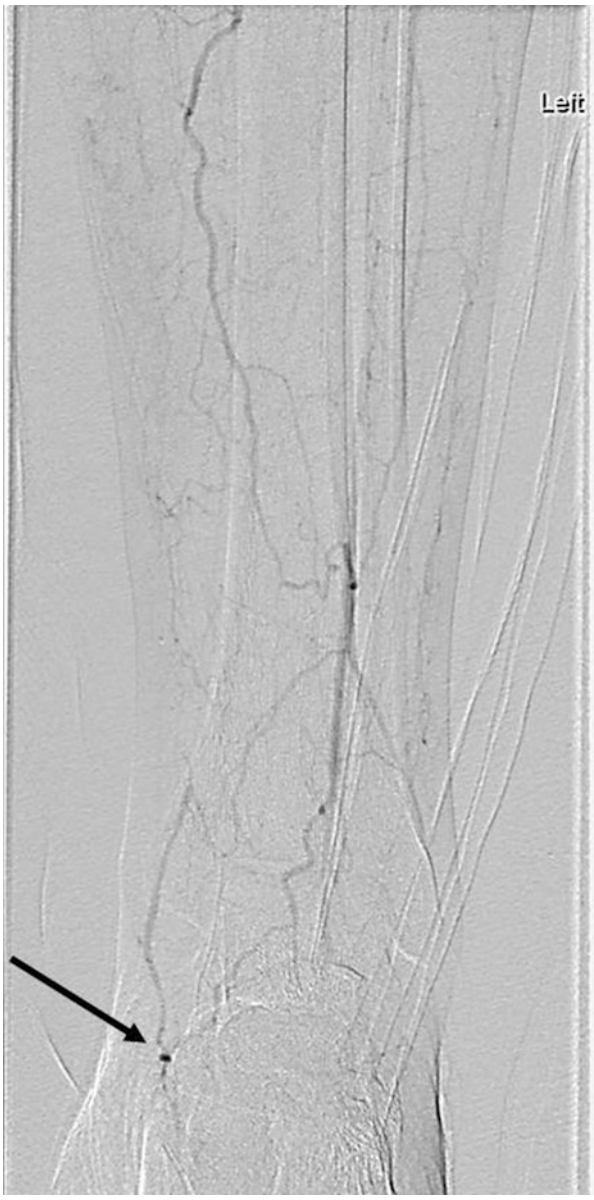

Fig. 24.16 DSA demonstrating a diseased but patent posterior tibial artery at the ankle level (arrow)

CLI and significant peripheral neuropathy. Hence, clinical assessment only is not reliable to assess them for recurring critical ischaemia. These patients can present acutely with recurrent CLI and occluded graft without clinical warning. All patients undergo a duplex scan at one week, then three monthly thereafter. Due to financial constraints, the program runs for one year only. However, if a bypass graft requires

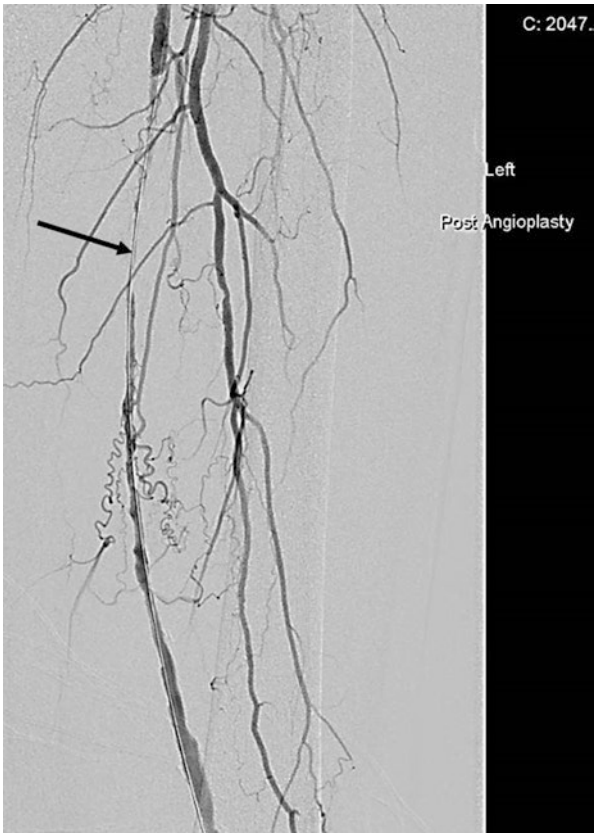

Fig. 24.17 DSA demonstrating a guide wire (arrow) passed through the occlusion in the SFA down to the patent popliteal artery as a stage I angioplasty of hybrid revascularisation

any surgical or radiological intervention, the program is extended for another year following each intervention.

24.10 Revascularisation in Acute Ischaemia

Acute limb ischaemia is caused by an abrupt decrease in arterial perfusion of the limb. Potential causes are progression of arterial disease, cardiac embolization, aortic dissection or embolization, graft thrombosis, thrombosis of a popliteal aneurysm or cyst, popliteal artery entrapment syndrome, trauma,hypercoagulable states and iatrogenic complications related to vascular procedures [6].

The acute ischaemic limb is recognised as a limb with severe hypoperfusion characterized by pain, pallor, pulselessness, poikilothermia (cold), paresthesiaes, and paralysis [14]. Within this presentation, there is a spectrum of symptoms. A patient with no underlying arterial occlusive disease who has an acute embolic occlusion at the femoral bifurcation can present with a profoundly ischaemic lower extremity, necessitating urgent intervention. In contrast, an acute embolic or throm-

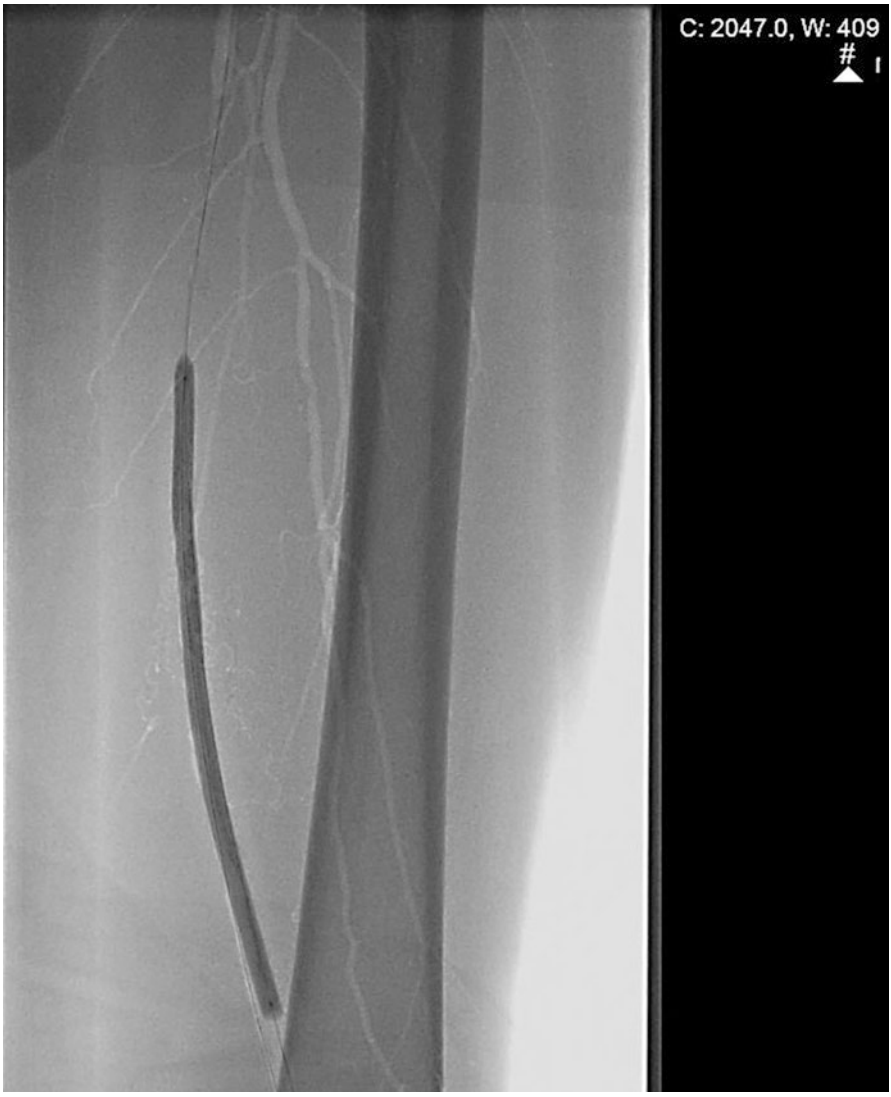

Fig. 24.18 DSA demonstrating balloon angioplasty of the SFA

botic occlusion of a chronically diseased but somewhat partially patent artery may be associated with only minor progression of chronic symptoms and moderate deterioration in haemodynamics [15]. Also, the diabetic patient with peripheral neuropathy may not feel the severe pain of acute ischaemia compared with a patient without neuropathy.

Acute limb ischaemia is a medical emergency and must be recognized quickly. Skeletal muscle can tolerate ischaemia for roughly 4–6 hours [16]. The acutely ischaemic lower limb can be divided into three categories. Category I refers to viable

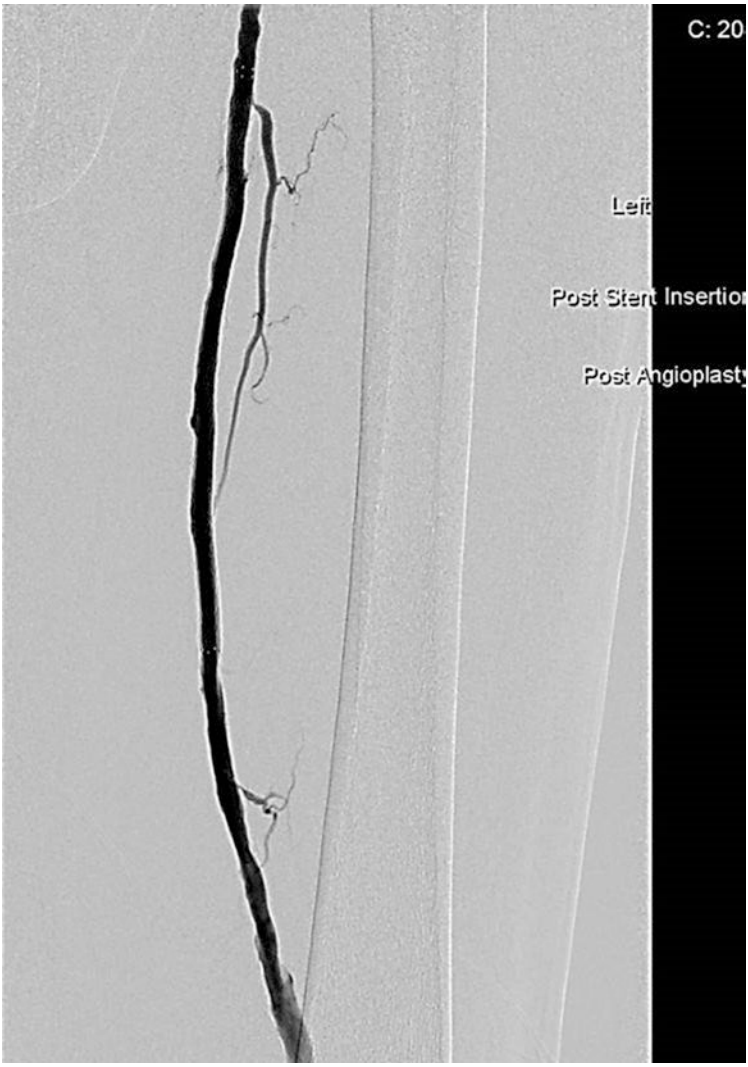

Fig. 24.19 DSA demonstrating successful SFA angioplasty and stenting

limbs that are not immediately threatened. There is no sensory loss nor muscle weakness and arterial and venous Dopplers are audible . Category II refers to threatened limbs. Category IIa limbs are marginally threatened and salvageable if promptly treated. Category IIb limbs are immediately threatened limbs and require immediate revascularization if salvage is to be achieved. Category III are irreversibly damaged limbs, in which case resultant major tissue loss or permanent nerve damage is unavoidable [17].

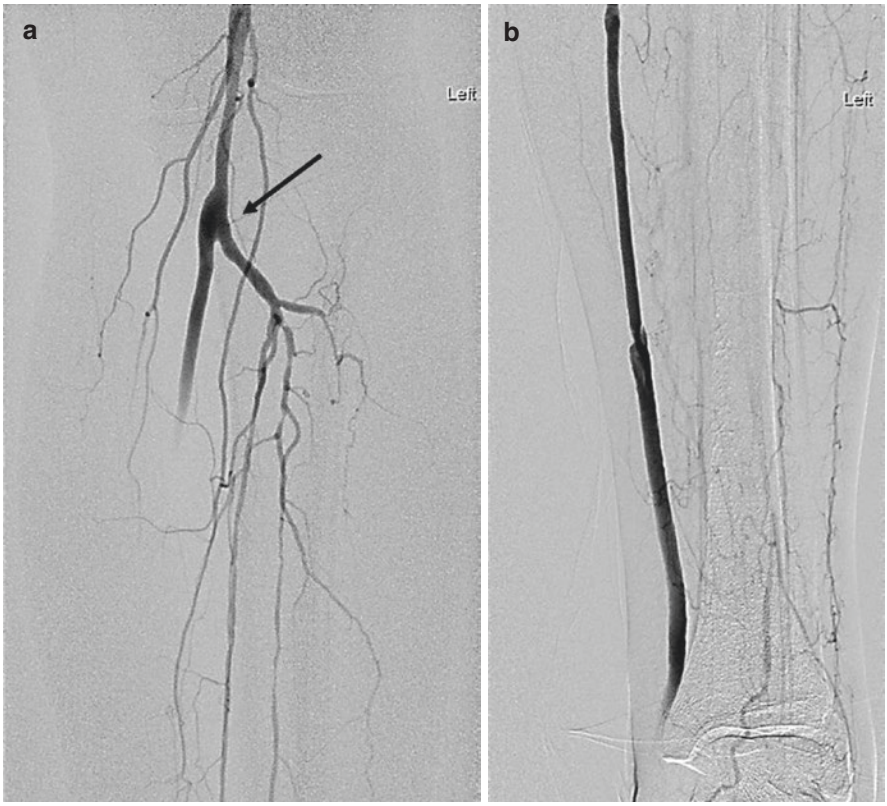

Fig. 24.20 (**a**) DSA demonstrating proximal anastomosis (arrow) of the distal bypass from the below knee popliteal artery to the posterior tibial artery at the ankle level as a stage II bypass of hybrid revascularisation. (**b**) DSA demonstrating bypass graft with slow flow at the level of the posterior tibial artery at the ankle

Once the clinical diagnosis is established, treatment with unfractionated heparin should be given, along with appropriate analgesia. For viable limbs (Category I), revascularization should be performed an on urgent basis (within 6–24 hours). For immediately threatened limbs (Category IIa and IIb), revascularization should be performed as an emergency (within 6 hours).

Although surgical or catheter-based thromboembolectomy and bypass grafting have been used in the treatment of acute ischaemia, thrombolytic therapy and percutaneous transluminal angioplasty are also treatment options. Thus revascularisation strategies include percutaneous catheter–directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy) and surgical thrombectomy, bypass and/or arterial repair [6]. In patients with severe comorbidities., endovascular therapy is often favoured, owing to decreased morbidity and mortality. Thrombus extraction, thrombo-aspiration and

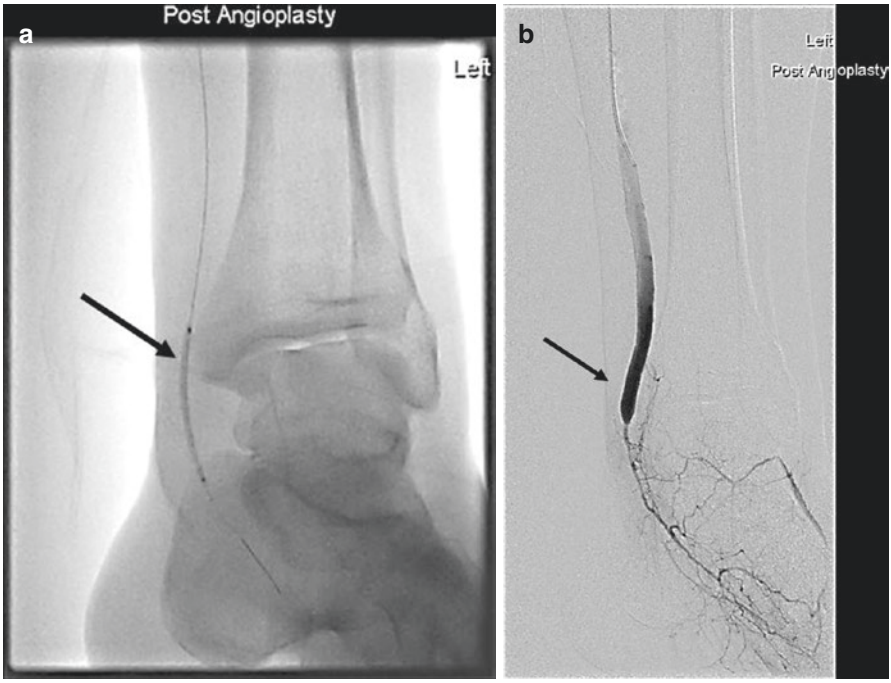

Fig. 24.21 (**a**) DSA demonstrating balloon angioplasty (arrow) of the posterior tibial artery as a stage III angioplasty of hybrid revascularisation. (**b**) DSA demonstrating successful angioplasty of the posterior tibial artery with good flow through the bypass graft (arrow) and patent posterior tibial artery into an incomplete pedal arterial arch

surgical thrombectomy are indicated in the case of neurological deficit, while catheter-directed thrombolytic therapy is more appropriate in less severe cases without neurological deficit. Catheter-directed thrombolysis can provide rapid restoration of arterial flow to a viable or marginally threatened limb, particularly in the context of recent occlusion, thrombosis of synthetic grafts, and stent thrombosis [18]. The modern concept of the combination of intra-arterial thrombolysis and catheter-based clot removal is associated with 6-month amputation rates of <10% [19]. There is no clear superiority of local thrombolysis vs. open surgery regarding 30-day mortality or limb salvage [20]. After thrombus removal, the pre-existing arterial lesion should be treated by endovascular therapy or open surgery. Lower extremity four compartment fasciotomies should be performed in patients with long-lasting ischaemia to prevent a post-reperfusion compartment syndrome.

Prolonged duration of ischemia is the most common factor in patients requiring amputation for treatment of acute limb ischaemia. Patients who have an insensate and immobile limb in the setting of prolonged ischemia (>6 to 8 hours) are unlikely to have potential for limb salvage with revascularization.

24.11 Conclusion

Open surgical treatment of infra-inguinal occlusive disease plays an important role in the management of critical ischemia (and also acute ischaemia) in diabetes. Distal and ultra-distal bypasses are well established in the treatment of the distal peripheral arterial disease in diabetes either as lone procedures or in combination with angioplasty as hybrid procedures.

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Chapter 25
Role of Angiosomes in Guiding Target Intervention for Open Procedures

Gianluca Citoni, Maurizio Taurino, and Bauer E. Sumpio

Peripheral arterial disease (PAD) has a prevalence of 3–10% in the general population and increases to as much as 20% in persons older than 70 years, particularly in smokers and patients with diabetes [1, 2]. Critical limb ischemia (CLI) is an advanced stage of PAD characterized by rest pain, presence of ischemic ulcerations or necrotic tissue [3]. In these patients, revascularization is critical for limb salvage, prolonging survival, and improving quality of life [1]. Forty percent of CLI patients that are not adequately revascularized risk major amputation within 1 year of diagnosis [4]. Vascular specialists have been appropriately aggressive in intervening on these ischemic limbs but the choice of vessel to be treated can often be arbitrary. The 'best vessel' approach, where the target outflow artery to be treated is chosen based on patency, technical suitability, length of bypass and available conduit, has been the traditional strategy used by interventionalists for many years [5, 6] and even endorsed by vascular consensus groups [1].

Despite an aggressive approach to revascularization, a number of large clinical series continue to report limb amputation rates of up to 20% despite patent bypass [7–9]. This unsuccessful outcome has led to enthusiasm for an angiosome-based revascularization strategy for the management of ischemic foot lesions [10–12]. Taylor and Palmer originally introduced the angiosome concept to assist with planning the design of tissue flaps. They defined the angiosome as a block of tissue, supplied by a named artery, whose territories in the integument and the underlying deep tissue correspond and are drained by a specific vein [13]. In the human body there are at least 40 angiosomes. In the foot and the ankle 6 angiosomes are

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described [14, 15]. Angiosome elements are delimited by choke vessels, which link adjacent angiosomes to each other and demarcate the border of each angiosome [14]. The dorsalis pedis artery supplies the dorsum of the foot, the posterior tibial artery supplies the medial ankle and the plantar foot and the peroneal artery supplies the anterolateral ankle and the rear foot (Fig. 25.1). An anastomotic system of pedal arch and loops permits a continuity of the angiosome perfusion.

Techniques for providing blood flow to the foot by either surgical bypass or endovascular strategies have been classified as either direct or indirect. Direct revascularization (DR), by definition, supplies blood flow to the specific artery perfusing the angiosome in which the wound is located. Indirect revascularization (IR) may also improve blood flow to the foot but does not directly perfuse the specific artery that supplies blood to the angiosome in which the wound is located. One of the critical elements that makes it difficult to completely differentiate DR from IR of the foot angiosome is the pedal arch, which is a major collateral that connects the anterior and posterior circulation in the foot. The presence or absence of these pedal arterial connections make it difficult to truly define indirect revascularization. Forefoot amputations, such as trans-metatarsal, Lisfranc, Chopart, frequently interrupt this foot arch. Likewise, a large proportion of patients with CLI and/or diabetes mellitus present with extensive foot wounds with deep infection that may exacerbate compartmentalization in the foot. Because of variations in the arterial anatomy

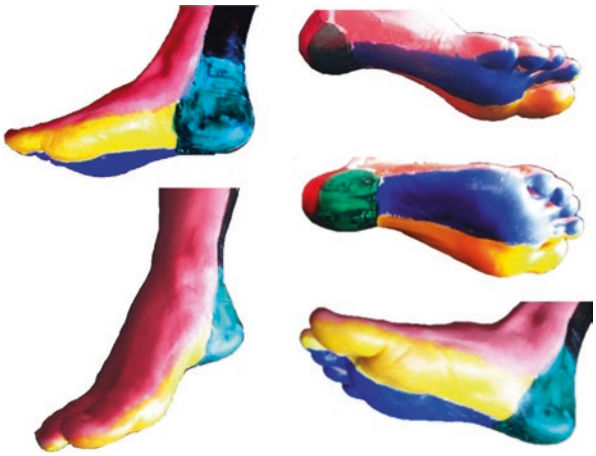

Fig. 25.1 The six angiosomes of the foot and ankle. One angiosome fed by the anterior tibial artery (ATA), three by the posterior tibial artery (PTA), and two by the peroneal artery (PA). The dorsum of the foot and dorsum side of the toes (pink). are supplied by the anterior tibial artery (ATA) that give rise to the dorsalis pedis artery. The posterior tibial artery (PTA) is the major supply to the plantar aspect of the foot via three angiosomes comprising the calcaneal branch, supplying the medial ankle (black) and the plantar heel (green); the medial plantar branch supplying the medial instep (yellow); and the lateral plantar branch, supplying the lateral and plantar forefoot (blue). The PA supplies the lateral ankle and plantar heel (red and green overlap) via the lateral calcaneal artery, and the anterior ankle via its anterior perforator (pink overlap). Note the overlap of the heel by both the medial calcaneal branch of the PTA and the lateral calcaneal branch of the PA

Table 25.1 Limitation of Angiosome model

Direct and indirect revascularization (quality of target vessel)
Angiosome concept has an anatomical point of view
The central role of the pedal arch for interangiosome connection
Forefoot amputation and diabetes
Extensive tissue damage
Angiosome variability

of the foot, [16] variability in the extent of an angiosome and the collateral connections between angiosomes are frequent. Therefore, although the concept of the angiosome is an attractive model to help guide management of CLI, there are many aspects that allows critical discussion on its applicability to all patients (Table 25.1.)

25.1 Direct and Indirect Revascularization (Quality of Target Vessel)

There is no question that clinicians would opt to revascularize a blood vessel that directly feeds an involved angiosome if the vessel is easily accessible, has an acceptable lumen and good run-off. The issue arises if the target vessel does not meet that criteria and the surgeon is forced to intervene on an alternative feeding vessel (IR). There have been several studies that compare outcomes after DR and IR strategies and they conclude that DR results in better limb salvage rates [17–19]. All of the studies except the analysis of Kabra et al. were retrospective. Kabra et al. reported that limb salvage in the DR group (84%) and in the IR group (75%) was not statistically significant ($p = 0.06$) [12]. The problem with the design of these studies, however, is that details on the status and quality of the pedal arch were not consistently evaluated. Therefore, patients who were classified as having an IR may in fact have a DR of the angiosome if the pedal arch was intact enabling perfusion of the affected angiosome. In this regard, Rashid et al. studied the impact of direct angiosome revascularization on the healing of the foot and reported that the time to healing after direct angiosome revascularization was not different than indirect angiosome revascularization [11]. However, when the quality of the arterial pedal arch was taken into account, healing and time to healing of foot tissue loss was significantly influenced by the quality of the pedal arch rather than the angiosome revascularized [11]. A recent systematic review comparing DR and IR in ten retrospective studies, showed that only half found a significantly increased limb salvage rate in the DR group compared to IR, while the others were unable to detect relevant differences between these two groups [10]. The benefit of the DR compared to IR in CLI has not been well characterized but a randomized controlled trial may not be ethical in these patients, as the selection of a distal target vessel should be dictated by best surgical principles, and not simply by chance. Nonetheless, it is clear that the DR/IR concept should be re-assessed by carefully integrating information

regarding the collateral vessel, interangiosome variability (discussed below) and the integrity of the pedal arch.

25.2 The Concept of Angiosome is Anatomical Not Physiological

It is important to emphasize that in their initial publication, Taylor and Palmer emphasized that the basis of their proposed angiosome concept was on the structural anatomy of the feeder vessel territory [20]. They did not and could not assess the perfusion levels and extent of a selective vessel. Current imaging modalities, such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), and digital subtraction angiography (DSA), can identify the exact location of the arterial lesions but do not provide information with regards to perfusion of the angiosomes [21, 22]. Newer technologies such as laser-assisted indocyanine green (ICG) and perfusion MRA are now under evaluation and may be useful in the future [23]. Furthermore, perfusion-dependent biomolecular changes such as decreased nitric oxide production, increased platelet activation, reactive oxygen species, leukocyte adhesion, and impaired oxygen exchange are some of the physiologically relevant microvascular changes that occur in critical limb ischemia and these are not currently evaluated in the clinical setting [24]. The current anatomical angiosome concept cannot answer these questions and so a physiologic, perfusion angiosome model needs to be established. Some perfusion based tests, such as hyperspectral imaging and technetium scans are currently being evaluated [22].

25.3 The Importance of Arterial Pedal Arch for Interangiosome Connection

The pedal arch defines the connection between the anterior and posterior circulation in the foot. The pedal arch is primarily constituted by the dorsalis pedis artery and the lateral plantar artery. The lateral plantar artery is one of the two main branch vessels of the posterior tibial artery. An arterial pedal arch classification has been proposed [8]—complete pedal arch (CPA) (Fig. 25.2a), incomplete pedal arch (IPA) (Fig. 25.2b, c) and no pedal arch (NPA) (Fig. 25.2d). Healing and time to healing of foot tissue loss were significantly influenced by the quality of the pedal arch rather [11]. It is evident that wounds may fail to heal because of impaired local perfusion due to insufficient vascular connections between the revascularized artery and the local ischemic area. The revascularization of the wounds through their specific artery is not always possible, and collateral vessels may be the only way that can provide flow to the involved ischemic ulcer.

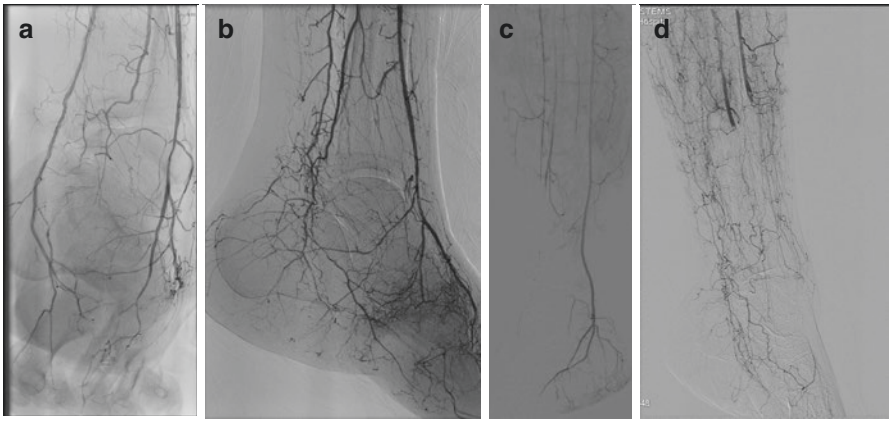

Fig. 25.2 (**a**) Complete pedal arch (CPA). (**b**) Incomplete pedal arch (IPA) with dorsalis pedis arch only. (**c**) IPA with plantar arch only. (**d**) No pedal arch (NPA)

Varela et al. utilized DSA to compare outcomes of DR and IR in CLI patients with and without satisfactory collateral vessels. If adequate collaterals were present, IR was equivalent to DR in wound healing and limb salvage. The lack of collateral vessels, and in particular the lack of patent pedal arch, may be used as parameter in assessing which patients should be directed for DR. [17] These observations underscore that the pedal arch has an essential role on wound healing and limb salvage. Taken together, these studies emphasize that the quality of pedal arch should be constantly evaluated in patients that do not undergo a DR of the involved angiosome.

25.4 Forefoot Amputation and Diabetes

The goal of forefoot amputations is to excise the necrotic tissue but to preserve as much of the native foot as possible. However, forefoot amputations may disrupt the foot arch network. Francois Chopart first described amputation through the talonavicular and calcaneocuboid joints in 1792 [25] but McKittrick et al. first described transmetatarsal amputation as a limb salvage technique [26]. Forefoot amputations are often considered to be minor operations with very low mortality rates. However, they have a high rate of reintervention. A retrospective study reported that after a forefoot amputation, 26% of diabetic patient population returned for subsequent forefoot amputations and 36% returned for subsequent major amputations [27]. Forefoot amputation usually interrupts the dorsalis pedis artery and lateral plantar artery (Fig. 25.3). If the level of foot amputation is proximal to these arteries there may be an interruption of pedal arch, which is an obvious obstacle to IR. This impairment to revascularization can be deleterious especially in diabetic patient. Diabetic patients are particularly disposed to foot ulcers [28] and subsequent forefoot amputation if revascularization or wound care is not possible for medical or

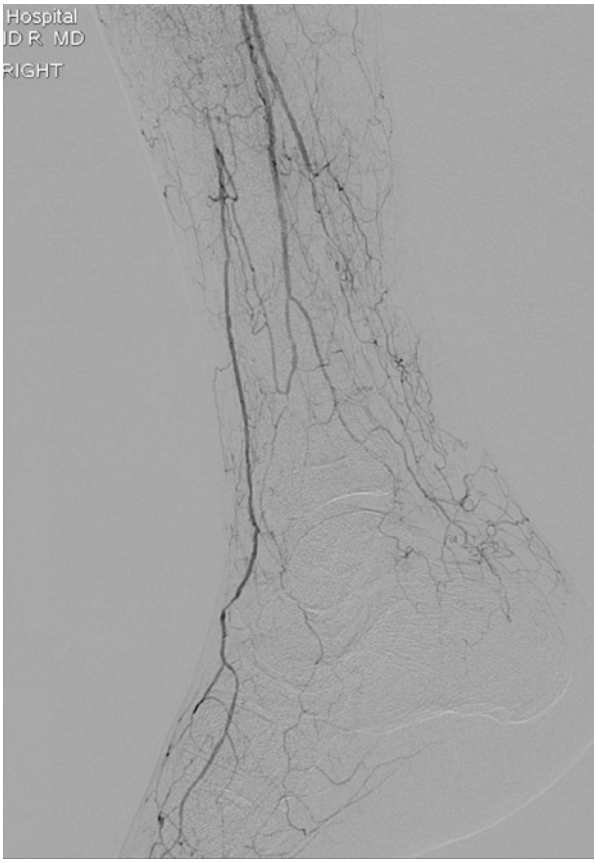

Fig. 25.3 Forefoot amputation and pedal arteries interruption

technical reasons. PAD in patients with diabetes is typically infra-popliteal, multi-segmental, preferentially located in crural arteries with the pedal vessel relatively spared and the choke vessels tend to be compromised [29–31]. Analysis of the status of the collateral vessels and the integrity of pedal arch are critical and may represent a specific patient subgroup that defines their outcomes.

25.5 Extensive Tissue Damage

It is clear that a large group of patients with CLI presented with extensive foot wounds and deep infections. In one series, only one third of patients with DM and CLI have a single angiosome involved in the tissue loss, 45% of patients had 2 angiosomes involved and more than 20% of patients had 3 angiosomes involved [32]. Patients with more than one angiosome affected by extensive tissue loss (Fig. 25.4) are not easily analyzed using the angiosome-oriented concept

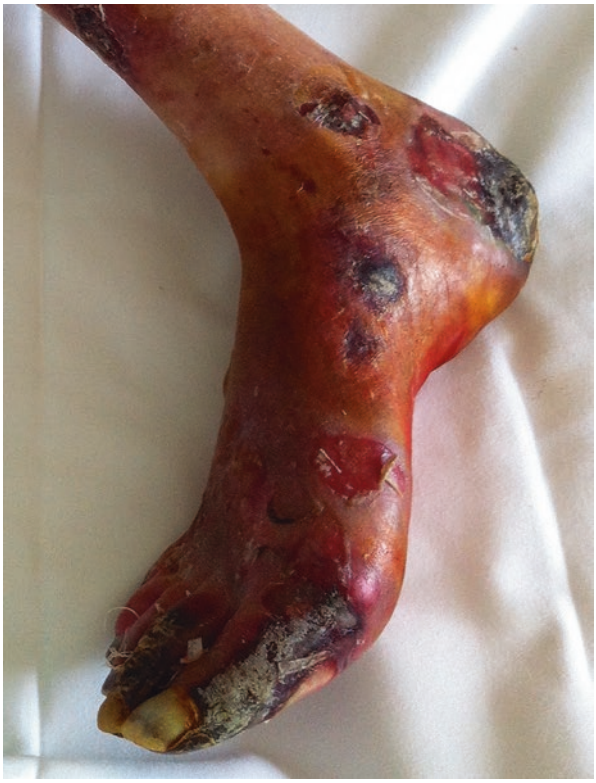

Fig. 25.4 The patient is an 68 years old female with a past medical history including hypertension, hyperlipidemia, smoking cigarette, atrial fibrillation presenting with a non-healing ulcer in more than 1 angiosome of the right foot with extensive tissue loss

and so attempts at classifying the intervention as being DR or IR is problematic. Studies analyzing the utility of the angiosome concept need to be careful in analyzing the extent of the territories encompassed by the wounds.

25.6 Angiosome Variability

The angiosome anatomy, interangiosome connections, and angiosome overlap as it pertains to the lower extremity has been carefully described by Attinger et al. [14, 33] Variations of the arterial anatomy of the foot are frequent. For example, the dorsalis pedis artery is absent in 6.7% of the cases, and the arcuate artery is absent in 33%. The dorsalis pedis artery arises from the peroneal artery in 6.7%. The dorsalis pedis artery crosses under the extensor halluces longus tendon at the ankle in 54%, above the ankle in 43%, but below the ankle in only 3% [16]. These variations of the arterial anatomy of the foot suggest that the angiosome that needs to be revascularized may not be perfused by the predicted artery [34]. This helps explain why technical success may not always equate directly with clinical success. This clinical failure can be explained with the tremendous variability of the angiosome of the

foot as indicated by laser-assisted indocyanine green (ICG) imaging [35]. Rother et al. evaluated the angiosome concept with regard to the microcirculation of the foot in patients with critical limb ischemia using combined laser Doppler flowmeter and white-light tissue spectrophotometry. They did not find any correlation with the angiosome and changes in microperfusion of the foot in patients with CLI. There was no significant differences between DR and IR of the angiosome with respect to the microcirculation parameters of the revascularized leg, such as oxygen saturation, blood flow or velocity [36].

25.7 Conclusion

The above review emphasizes the necessity to reconsider the angiosome concept. Although initially conceived as an anatomic delineation, for angiosomes to be clinically relevant it has to be evaluated from a physiologic standpoint. We have discussed several limitations of relying solely on the angiosome concept in the management of patients with CLI: quality of target vessel, anatomical and non-physiologic basis for the angiosome, the central role of pedal arch, interruption of pedal arch due to forefoot amputation, extensive tissue loss, and angiosome variability. The angiosome model should not be used as an absolute algorithm for interventions on CLI patients but should be a guide to assist with a patient-specific strategy for revascularization. Further well-structured prospective studies are needed to assess the value of integrating the interangiosome concept, the status of the pedal arch and the anatomic-physiologic perfusion angiosome model.

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Chapter 26
The Angiosome Concept: Does It Apply to the Ischaemic Diabetic Foot?

Hisham Rashid, Raghvinder Pal Singh Gambhir, and Hani Slim

26.1 Introduction

The angiosome concept was first introduced by Taylor and Palmer in 1987 in an attempt to help plan different myo-cutaneous flaps during reconstructive plastic surgery [1]. They described the angiosome as a "composite anatomical territory supplied by a named artery." Two thousand anatomical studies were performed to enable them to map the whole human body and identify every feeding artery to each angiosome. However, they also mentioned that choke vessels and true anastomoses link different angiosomes, giving the pedal anastomosis between the anterior tibial/dorsalis pedis and the posterior tibial/plantar arteries as an example of these true anastomoses.

Later on, this angiosome concept was further studied by Attinger and colleagues in 2006 [2] by mapping of the different foot and ankle angiosomes. They examined 50 cadaver dissections by injecting the leg arteries with methyl methacrylate. Six angiosomes were identified in this area supplied by the tibial arteries (Fig. 26.1). The anterior tibial artery becoming the dorsalis pedis after crossing the ankle supplies the dorsum of the ankle and the foot. The posterior tibial artery divides into the medial and lateral plantar and the calcaneal arteries which supply specific areas in the foot. The calcaneal branch supplies the medial heel, the medial plantar to the instep, and the lateral plantar to lateral mid-foot and forefoot. The peroneal artery supplies the antero-lateral portion of ankle and rear foot.

In a letter to the editors of the British Journal of Plastic Surgery in 1992 [3], Taylor and Palmer emphasised that this angiosome concept was not a physiological study and they were careful not to make this extrapolation. However, wound healing is a patho-physiological process that is reliable on good blood supply. The concept

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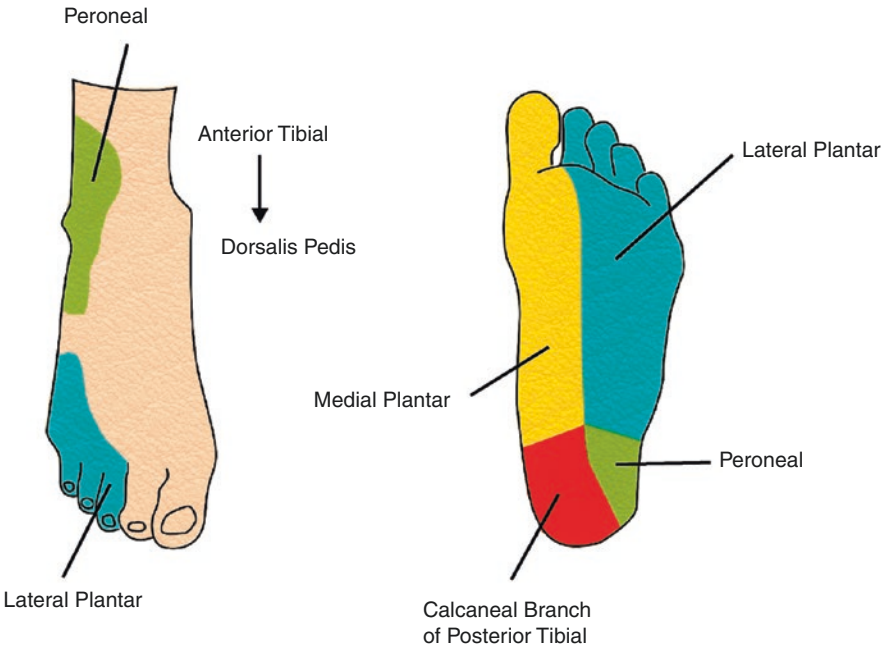

Fig. 26.1 The six angiosomes of the foot and ankle

of targeted angiosome revascularisation does support the vascular surgical principle of "straight line flow" in achieving healing. Hence, in principle, this angiosome concept should improve healing rate, as well as, the time-to-healing.

Achieving wound healing in patients with peripheral vascular disease is a complex process that is definitely multifactorial. Restoration of the blood flow (revascularisation) by performing bypass surgery, angioplasty or both (hybrid) to the level of the tissue loss is an integral part in managing ischaemic wounds and achieving limb salvage. The depth and size of the wound as well as the presence of exposed joints and osteomyelitis also contribute significantly to the complexity of the wound healing process. Furthermore, other important factors including diabetes, renal failure, hypo-albuminaemia and resistant infections play a significant role in impairing complete healing in these patients.

26.2 Published Evidence

The authors firmly believe that direct revascularisation of the tissue loss corresponding angiosome in patients suffering with critical leg ischaemia (CLI) in both the diabetic and non-diabetic populations should improve healing and time-to-healing in keeping with the "straight line flow" concept in the management of critical ischaemia (Figs. 26.2 and 26.3). However, several published articles studying targeted

Fig. 26.2 (**a**) Posterior tibial artery bypass with the surgical incision pointing to the area of tissue loss simultaneously treated by a split-thickness skin graft. (**b**) Wound fully healed rapidly following successful direct angiosome revascularisation

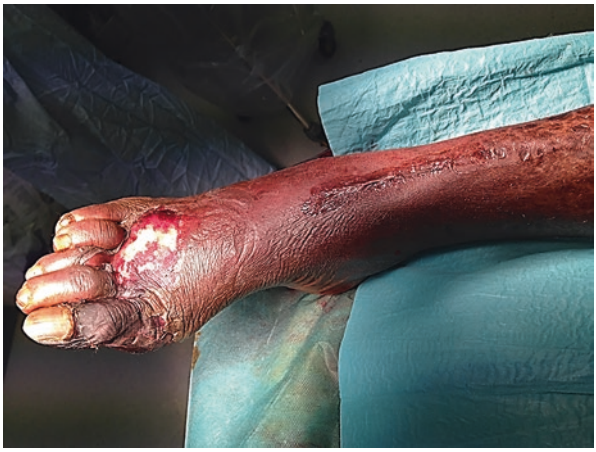

Fig. 26.3 Dorsalis pedis bypass revascularising the gangrene angiosome area. Complete healing should be achieved following amputation of the affected toes and skin of the dorsum of the foot

angiosome revascularisation in CLI have questioned the ability to prove the validity of applying this principle to all patients.

These articles which examine the angiosome concept in patients with CLI have reported variable outcomes comparing direct and non-direct angiosome revascularisation using open surgical bypass, angioplasty or both modalities simultaneously. One of the early studies looking at angiosome revascularisation using distal bypass surgery, was published by Neville and Attinger in 2009 [4]. They studied 52 non-healing foot ulcers in 48 patients using direct and indirect revascularisation of the angiosome in patients with CLI. There was significant improvement in the healing and amputation rates of the patients having direct revascularisation. However, the time-to-healing was not significantly different between the two groups. This improvement in healing and amputation rates was also echoed in other studies using distal angioplasty for direct angiosome revascularisation [5, 6].

In 2012, Kabra et al., published a study [7] looking at outcomes using both angioplasty and bypass in patients with CLI. In both modalities, the limb salvage rates

were not significantly influenced by the angiosome revascularised. However, the rate of ulcer healing was significantly better in the direct revascularisation group.

In a comprehensive study published by Azuma et al. in 2012 [8] looking at factors influencing wound healing, including angiosome revascularisation using distal bypass surgery in a largely diabetic population (81%) with CLI, the authors found that the healing rate was slower in the indirect revascularisation group compared with the direct revascularisation group especially in the end stage renal disease (ESRD) patients. However, using a propensity scoring system, there was no difference between the two groups, concluding that the angiosome concept is not important particularly in the non-ESRD patients. Although direct angiosome revascularisation had a positive impact on wound healing, this effect was lost when a propensity score was applied including other factors such as diabetes, renal failure and hypo-albuminaemia. The authors concluded that these co-morbidities as well as the site and the extent of the ischaemic wounds are more important than targeted angiosome revascularisation.

The authors have published their own series [9] looking into angiosome revascularisation using distal and ultra-distal bypass surgery in patients with CLI in a largely diabetic population. They also compared the outcomes of wound healing as influenced by the quality of the arterial pedal arch. In this series, revascularisation of the specific angiosome corresponding to the area of tissue loss was only possible in 45% of patients. Based on digital subtraction angiography, the arterial pedal arch was divided into, complete, incomplete or non-existing with only a leash of arteries supplying the distal foot and toes. Only 19% of patients in this series had a complete pedal arch, while the majority (62%) had an incomplete pedal arch comprising either the anterior tibial/dorsalis pedis or posterior tibial arteries. The outcome of this study showed that the quality of the arterial pedal arch significantly influenced the healing rate and time-to-healing rather than the direct or non-direct angiosome revascularisation.

Several meta-analyses have been published in recent years looking at studies comparing outcomes in direct and non-direct angiosome revascularisation. Sumpio et al. in 2013 performed a systematic review of published data regarding the angiosome concept in peripheral vascular disease [10]. The authors concluded that the available evidence was not strong enough and also lacked consistency in reporting outcomes, Without the availability of prospective studies which should also include perfusion studies, the recommendation of the angiosome concept for revascularisation could not be sustained.

However, another meta-analysis performed by Bosanquet in 2014 compared outcomes of direct vs. indirect angiosome revascularisation of crural arteries in patients with CLI using both open and endovascular modalities [11]. This meta-analysis concluded that direct revascularisation of the tibial vessels appeared to improve wound healing and limb salvage rates without impacting the mortality or re-intervention rates. However, they also concluded that the quality of evidence in these studies is low.

In severe peripheral vascular disease, especially in diabetic patients with significant crural atherosclerosis, the ability to perform targeted angiosome revascularisation is limited to less than half the patients making the angiosome concept unfeasible.

26.3 Why there is Discrepancy in Angiosome Revascularisation Outcomes

The authors believe there are several reasons for this discrepancy in the reported outcomes in published data. Most series report angioplasty and distal bypass surgery outcomes for angiosome revascularisation only at the crural arteries level rather than extending this information into the pedal-plantar angiosome level that reflects the level of revascularisation at the foot. This coupled with the quality of the arterial pedal arch as reported by the authors would fully represent the quality of angiosome revascularisation which is more influenced by the quality of the arterial pedal arch rather than the angiosome revascularised [9]. The authors were also very keen to document the angiosome artery revascularisation down to the level of the pedal and plantar level to be able to comment on the quality of the revascularisation at the foot level. They also highlighted the quality of the arterial pedal arterial arch as a decisive factor influencing the success of angiosome revascularisation.

Another important factor in the conflicting outcomes is the outcome endpoints of angiosome revascularisation. Most published series have reported limb salvage and amputation-free survival as well as wound healing and time-to-healing. The authors believe that since wound healing is multifactorial, assessing angiosome perfusion using indocyanine green or other modalities should be the primary endpoint with wound healing and time-to-healing as secondary end-points. This will allow clinicians to assess the success of revascularisation by mapping the angiosome revascularised and then assessing wound healing as a direct result of this procedure.

Braun et al., in 2013 published their experience in using indocyanine green angiography in early evaluation of revascularisation in patients with CLI undergoing, angioplasty, surgical bypass or both [12]. They were able to demonstrate rapid visualisation of regional foot perfusion concluding that this technique offers quantitative information about reperfusion before and after revascularisation. Benitez et al. in 2014 highlighted the importance of this technique as well as other perfusion techniques including transcutaneous oxygen, hyper-spectral imaging, nuclear diagnostic imaging, and laser Doppler in assessing successful angiosome revascularisation [13].

26.4 Outcomes of Angiosome Revascularisation Comparing Bypass Surgery and Angioplasty

A comprehensive study comparing outcomes of targeted angiosome revascularisation using different modalities was published by Spillerova et al. in 2015 [14]. In this large series of 744 patients including both diabetic and non- diabetic patients, the outcomes following angiosome-targeted revascularisation using angioplasty or bypass surgery were studied and wound healing and limb salvage in both modalities

were compared using a propensity score and adjusted analysis. The results of this study showed that angiosome-targeted revascularisation had better wound healing and limb salvage compared to indirect angiosome revascularisation. However, bypass surgery had a significantly better wound healing than angioplasty before and after adjusting the data.

Furthermore, in a study of 545 diabetic patients with critical limb ischaemia and tissue loss, indirect endovascular revascularisation resulted in worse wound healing and poorer leg salvage rates compared with direct endovascular revascularisation. However, in bypass surgery, the angiosome concept is less relevant and the artery with the best runoff should be selected as the outflow artery [15].

26.5 Conclusion

Angiosome revascularisation concept is complementary to the "straight line flow" principle in managing peripheral vascular disease in patients with CLI. The available published data has conflicting outcomes in the absence of large prospective randomised studies. However, there is enough evidence from published series to support direct angiosome revascularisation, which, when feasible, has a positive impact on wound healing and limb salvage in CLI including diabetic patients. However, it may not be possible to perform targeted angiosome revascularisation in 50% of ischaemic limbs. Furthermore, the impact of the quality of the arterial pedal arch cannot be overemphasised in the outcome of direct vs. non-direct angiosome revascularisation. It is mandatory when reporting clinical outcomes of targeted angiosome revascularisation to include wound healing, time-to-healing as well as tissue perfusion to be able to study the direct effect of angiosome revascularisation. This will hopefully help clinicians to reach a consensus about the success of angiosome revascularisation in patients with CLI.

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Chapter 27
Presentation and Management of the Renal Ischaemic Foot

Hani Slim, Joanne Casey, Jennifer Tremlett, and Michael E. Edmonds

27.1 Introduction

Diabetic patients in renal failure present a major problem in terms of foot care, with high rates of morbidity and mortality [1]. There is marked predisposition to minor foot trauma leading to ulceration. In addition, renal patients are characterised by rapid onset of necrosis in the foot often secondary to minor unsensed trauma (Figs. 27.1 and 27.2). Classically, this is dry digital necrosis. It may be precipitated by trauma and can spread to involve the mid-foot and hind foot (Fig. 27.3). Wet necrosis, secondary to a septic vasculitis, can also occur in the renal foot either as a complication of dry necrosis or as a primary infective complication. End stage renal disease (ESRD) is associated with a fourfold higher risk of diabetic foot complications, notably infection, ulcer and gangrene [2]. Traditionally, diabetic foot disease has a poor prognosis in renal failure in diabetes. However, the outlook can be improved by understanding the vulnerability of the diabetic patient in renal failure and by setting up services to provide preventative care, to rapidly treat ulceration and infection and to perform early revascularisation.

27.1.1 Vulnerability of the Renal Patient

The renal patient is complicated by both microvascular and macrovascular disease. The microvascular disease which causes nephropathy in diabetes also causes peripheral neuropathy. Almost all subjects with ESRD due to diabetic nephropathy

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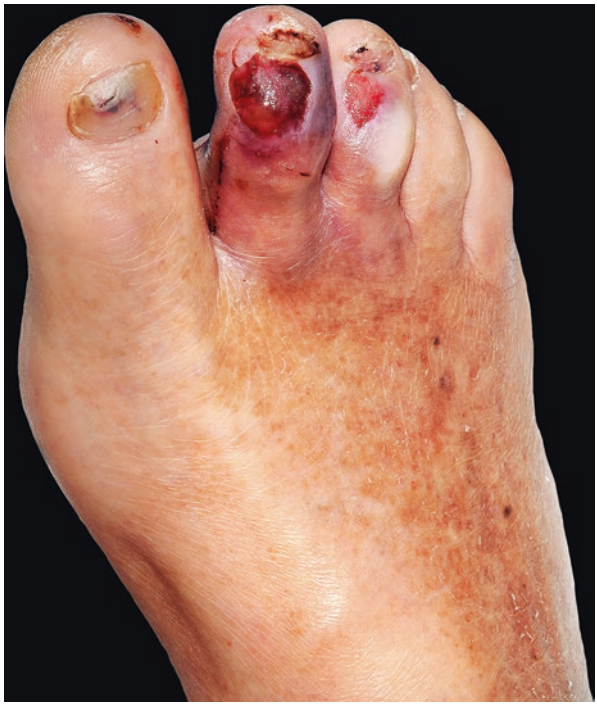

Fig. 27.1 Minor trauma leading to soft tissue injury to the second toe and loss of epithelium on the third toe

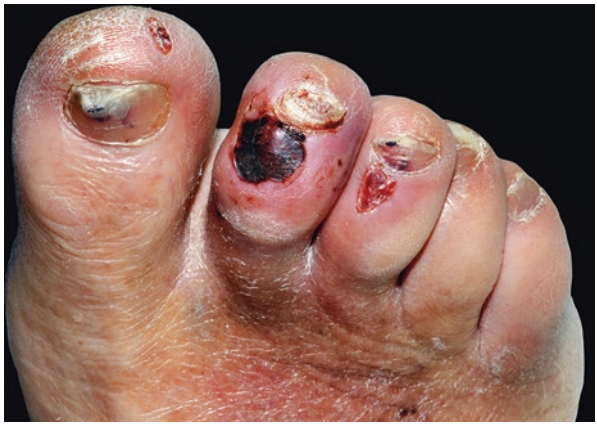

Fig. 27.2 Five days later, there is a classical patch of necrosis on the second toe and healing response on the third toe

will have concurrent peripheral neuropathy which is often exacerbated by uraemia [3]. In addition, many of the patients, especially those on dialysis will have arterial disease with extensive vascular calcification and this is associated with substantial risks for both morbidity and death in the ESRD population. Thus patients with renal failure and peripheral arterial disease commonly have significant co-morbidities including ischaemic heart disease and hypertension [4].

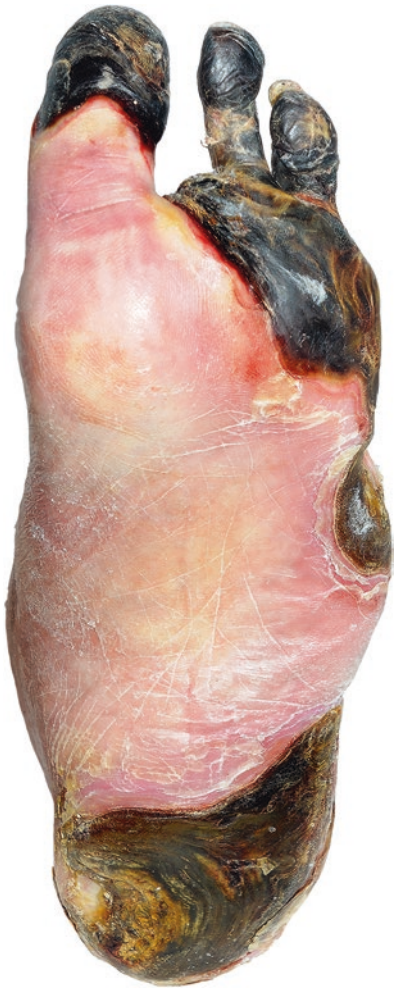

Fig. 27.3 Extensive necrosis in renal ischaemic foot

Diabetic patients in renal failure often have anaemia, which leads to low tissue oxygenation and impaired wound healing. Also, diminished mobility and manual dexterity compromises the ability to perform foot self-care or foot inspection. In a study of subjects on dialysis of whom 42.2% had diabetes, only 75% had adequate vision, 60% had adequate dexterity and 55% had adequate flexibility to perform self-care [5].

The presence of neuropathy and peripheral arterial disease in the background of renal failure leads to increased susceptibility to infection. Uraemia impairs many aspects of the mechanisms of defence against infection [6]. Patients in renal failure deteriorate more rapidly when infected, compared with patients without renal failure and are prone to foot infections with gram negative bacteria such as *Enterobacter cloacae, Stenotrophomonas maltophilia, Pseudomonas, Serratia marcescens* and *Citrobacter koseri* and also including organisms with extended sensitivity beta lactamases.

27.1.2 Diabetic Foot Problems and Renal Failure

Although the highest risk for foot ulceration and amputation is found in patients on dialysis, increased risk has also been noted in patients with chronic kdney disease (CKD) stages 4 and 5 compared with stage 3 [7]. In multivariate analyses of 669 patients of whom 38% were diabetic, (539 in group CKD 3, 540 in group of CKD 4–5 (of whom 411 individuals progressed from CKD 3), and 259 in a group undergoing dialysis treatment (of whom 159 progressed from CKD 3 and 99 progressed from CKD 4–5))) the hazard ratio for incidence of foot ulceration was 4.0 (95% confidence interval [CI], 2.6–6.3) in CKD 4–5 and 7.6 (95% CI, 4.8–12.1) in dialysis treatment compared with CKD 3. Hazard ratios for incidence of major amputation were 9.5 (95% CI, 2.1–43.0) and 15 (95% CI, 3.3–71.0), respectively. In a systematic review of non-randomized studies that quantified the major risk factors for foot ulceration and amputation in adults treated with dialysis, meta-analysis showed that ulceration and/or amputation were associated with male sex, current smoking, diabetes mellitus (increasing with longer duration), retinopathy, coronary artery disease, elevated serum phosphate and glycated haemoglobin, lower serum albumin, previous ulceration or amputation, peripheral arterial disease and neuropathy [8].

A high incidence of diabetic peripheral neuropathy and peripheral arterial disease is associated with fivefold increase in foot ulcerations on dialysis when compared to those not undergoing renal replacement therapy. Diabetic patients with ischaemic foot lesions on dialysis have reduced chance of healing, and a higher risk of major amputation and death when compared to patients who were not dialysed [9].

In a cross sectional observational study of 450 adults with ESRD, of whom 94% were on haemodialysis and of whom 50.2% had diabetes, there was a high prevalence of previous foot ulceration (21.6%), current foot ulceration (10.0%), and lower extremity amputation (10.2%) [10]. Current foot ulcers were predominantly neuroischaemic (69.1%), located on the dorsal, medial or lateral toes (52.9%) and had a median duration of 3.0 (IQR, 1.2–6.0) months.

A further study documented trends in the prevalence and identified risk factors of lower limb amputation in Australian patients on dialysis [11]. There was a high prevalence of amputation of 13.3% and associated risk factors were the presence of diabetes (OR 1.67 [1.49–1.88] $p < 0.001$), history of foot ulceration (OR 81 [18.20–360.48] $p < 0.001$), peripheral arterial disease (OR 31.29 [9.02–108.56] $p < 0.001$), peripheral neuropathy (OR 31.29 [9.02–108.56] $p < 0.001$), foot deformity (OR 23.62 [5.82–95.93] $p < 0.001$), retinopathy (OR 6.08 [2.64–14.02] $p < 0.001$), dyslipidemia (OR 4.6 [1.05–20.05] $p = 0.049$) and indigenous background (OR 3.39 [1.38–8.33] $p = 0.01$) with 75% of the amputees having Aboriginal heritage. Higher HbA1c and CRP levels as well as low serum albumin, haemoglobin and vitamin D levels had a strong association with amputations ($p < 0.05$).

Other reports have confirmed an increased risk of lower-extremity amputation among diabetic patients on dialysis. In a population of 400 patients with diabetes and foot ulcers, of whom 14 (4%) were dialysis-treated, the amputation rates were higher in the dialysis-treated patients (57%) than in others with CKD (25%) or without CKD (5%) [12].

There is a close temporal association between commencement of dialysis and occurrence of foot ulceration and amputation [13]. A retrospective analysis of 90 patients with diabetes who started dialysis, showed that the cumulative incidence of foot ulceration and amputation increased just before the initiation of dialysis and then was highest during the next 2 years. Incidence rate of foot ulceration was sharply increased by 3.35 (95% CI: 1.59–7.04) in the first year after initiation of dialysis, followed by an increased rate of 4.56 (95% CI: 2.19–9.5) in the second–fifth year. The increased incidence rates of major amputation were 31.98 (95% CI: 2.09–490.3) and 34.01 (95% CI: 1.74–666.2), respectively.

It is not clear if the main driver of foot complications is ESRD or dialysis treatment itself. In patients with diabetes, there is a trend towards reduced transcutaneous oxygen pressure on the dorsum of the foot, for at least 4 h after dialysis [14]. Hypotension either during dialysis or post-dialysis may lead to reduced peripheral blood flow to preserve central circulation and predispose to ulceration in patients with distal peripheral arterial disease. Haemodialysis is also associated with changes in cutaneous microcirculation, which differ between people with and without diabetes. In those without diabetes, there is an increase in cutaneous blood flow during haemodialysis, whereas blood flow is reduced in diabetic patients as a possible consequence of abnormal vasomotor regulation due to distal neuropathy [15]. As well as ulceration, high rates of amputation have also been associated with the onset of dialysis. In a retrospective study of 47 patients, 86% of whom were Maoris, the median time between starting dialysis to having an amputation was 7 months (range 2 weeks–40 months) [16].

27.1.3 Causes of Foot Ulcers in Diabetic Patients in Renal Failure

When the effect of renal function on the formation, severity, and outcome of diabetic foot lesions was studied, renal insufficiency, peripheral neuropathy, and peripheral arterial disease (PAD) were each independently associated with ulcer formation [17]. In a further observational study, there was a strong association between the stage of CKD and ulceration as well as amputation and this was probably not just related to the presence of PAD [18]. The presence of renal impairment reduces the ability of the body to repair soft tissue damage from minimal trauma and even individuals with moderate CKD (eGFR <60 ml/min per 1.73 m^2) have an increased risk of ulcer and amputation.

However, there are several causes of foot ulcers in relation to dialysis [19]. Foot ulceration may be caused by resting on a couch for several hours three times weekly during dialysis, especially on insensate heels or with toes pushing against the end of the bed [20]. Dialysis may lead to haemodynamic changes and large fluid shifts which may predispose to postural dizziness, falls, and trauma to the foot. Dialysis-treated patients are less likely to examine their feet regularly and to attend podiatry clinics. They are more likely to be engaged in possible foot-damaging behaviours such as barefoot walking [20].

27.1.4 Survival of Diabetic Foot Patients on Dialysis

The risk of poor outcome, namely non healing lesions, major amputation and death among diabetic patients with critical foot ischemia was increased 8.9 times in those on dialysis in a specialised tertiary care centre [21]. When people with no renal disease were compared to patients on dialysis using a proportional hazard model, the dialysis patients had a 290% increase in hazard for death. Individuals who were on dialysis and had a high-level amputation had significantly lower survival rates after amputation than individuals with no renal disease [22].

27.2 Management

27.2.1 Preventative Diabetic Foot Care

It is vital to stress the importance of preventative foot care among renal patients with peripheral arterial disease. Meticulous foot care is critical for the prevention of digital gangrene and amputation [17]. Foot care should be provided whilst patients are having their dialysis and there is a need for routine foot care programs for patients with ESRD on the dialysis unit [23]. It is possible to make a positive impact on the high rate of amputation among patients with diabetes receiving dialysis through early detection and intervention. Regular foot screening and education can assist in identifying and preventing ulcer-initiating incidents and thus reduce lower extremity amputation in these patients [24].

A preventive foot care program for diabetic renal transplant recipients reduced the numbers of episodes of digital gangrene and major amputations and increased the rate of foot ulcer healing [25]. Institution of a podiatry program with education about foot care, assessment, and treatment by a podiatrist in a tertiary care hospital reduced the number of amputations in patients with diabetes on peritoneal dialysis [26].

27.2.2 Ulceration, Infection and Necrosis

As well as preventative care, it is important to treat urgently patients who develop ulcers and infection encouraging rapid attendance to open access clinics. There is a propensity for necrosis in the diabetic foot of patients in renal failure. Dry necrosis can be removed surgically preferably after revascularisation. If angioplasty or open bypass is not possible, then a decision must be made either to amputate the toes in the presence of ischaemia or to allow the toes to autoamputate. Surgical amputation should be undertaken if the circulation is not severely impaired, as indicated by a transcutaneous oxygen tension >30 mmHg on the dorsum of the foot. The recent use of negative pressure wound therapy (NPWT) promptly applied to such amputation wounds has encouraged healing in these ischaemic limbs even though they could not be revascularised.

Wet necrosis is caused by infection and this should be removed urgently by surgical debridement when it is associated with severe spreading cellulitis. This should be done whether pus is present or not. In cases when the limb is not immediately threatened and the necrosis is limited to one or two toes, it may be possible to control infection with intravenous antibiotics and proceed to urgent revascularisation and then digital or ray amputation The risk of an inferior outcome namely, non healing, amputation and death among diabetic patients with critical foot ischemia and on dialysis was increased 5.4 times when the C-reactive protein (CRP) was above the second quintile (cut-off value 8 mg/dl) [21].

27.2.3 Revascularisation

CKD is a risk factor for poor short term outcome after infrainguinal revascularisation in diabetic patients with foot ulcer or gangrene. Initial studies of revascularisation in diabetic patients with renal failure produced only moderate success with concern for long term survival of dialysis patients. However, it is now agreed that favourable results can be obtained even in ESRD, with the majority of studies reporting 1-year limb salvage rates of 65–75% after revascularisation among survivors [27]. Creatinine clearance itself predicts inferior outcome and long-term postoperative survival after lower extremity revascularisation [28]. Patients with critical limb ischaemia may benefit from revascularisation compared with medical therapy alone at all levels of renal impairment and thus revascularisation should not be withheld in these patients at any level of renal impairment [29].

The following discussion of revascularisation in patients with renal failure refers to case series which include both diabetic and non- diabetic patients although the proportion of diabetic patients in each series is usually high and is noted when reported.

27.2.3.1 Surgical Bypass

Initial Approach to Revascularisation

Initially, there was a reluctance to carry out open bypass in patients with advanced renal failure and foot problems because of concern about poor outcomes and patient co-morbidities. Early reports suggested that primary amputation might be indicated in patients presenting with ESRD and severe peripheral ischaemia. In femoral-popliteal-tibial reversed vein bypasses performed for limb salvage in 226 patients without ESRD and 19 patients (46% diabetes) with ESRD, 18-month primary patency rates were comparable (85% and 89%),but limb salvage was significantly lower (76% vs 95%) in patients with ESRD [30]. The need for major amputation despite a patent bypass in diabetic patients with ESRD who have extensive foot gangrene or ischaemic ulceration, occurred sufficiently often that it was suggested

that primary amputation should be considered in these patients instead of vascular reconstruction.

A further study reviewed 69 distal arterial reconstructions performed in 53 patients with ESRD (haemodialysis [n = 37], kidney transplantation [n = 10], peritoneal dialysis [n = 6]) for foot gangrene (n = 28), nonhealing ulcer (n = 25), or ischemic rest pain (n = 16) [31]. Diabetes was present in 82%. The 30-day operative mortality rate was 10%, and the patient survival rate at 2 years was 38%. The primary graft patency rate was 96% at 30 days, 72% at 1 year, and 68% at 2 years. Eleven of 22 foot amputations performed during the mean follow-up period of 14 months (range 3–96 months) occurred within 2 months of revascularisation. Reasons responsible for limb loss included graft failure (n = 9), foot ischaemia despite a patent bypass (n = 8), and uncontrolled infection (n = 5). Overall, 59% of amputations were performed in limbs with a patent bypass to popliteal or tibial arteries. The limb salvage rate at 1 year decreased from 74% to 51% in patients admitted with gangrene. Only two of seven patients admitted with forefoot gangrene underwent salvage of the foot. It was concluded that failure of foot salvage in patients with ESRD and critical ischemia was due to wound healing complications rather than graft thrombosis. Earlier referral for revascularisation, before the development of extensive tissue necrosis and infection was advised.

In a further series to determine whether infrainguinaI bypass surgery was worthwhile in patients with critical limb ischaemia and renal failure, results of bypass were reviewed in twenty-two patients with moderate renal failure, of which 18 (82%) had diabetes [32]. Ten patients with ESRD requiring dialysis, three patients with functioning kidney and one transplant patient underwent 39 bypass procedures for critical limb ischaemia consisting of 6 femoro-popliteal, 14 femoro-crural and 19 femoro-pedal bypasses. The immediate, 1-month, and 1-year primary patency rates were 97%, 84%, and 70%, respectively. The limb salvage was 93% at 1-month and 72% at 1-year follow-up. One-year patency and leg salvage rates were 81% and 79% in non-dialysis patients, and 47%and 37% in dialysis patients. At 1-year follow-up, 55% of surviving patients had salvaged limbs. None of the patients on dialysis was alive with salvaged legs 4 months after revascularisation. Among preoperative risk factors, only serum creatinine showed a statistical significance in predicting leg salvage and survival. It was concluded that revascularisation was successful in non dialysis patients with renal failure but remained controversial in patients on dialysis.

Particular caution regarding distal bypass was advised with patients with hypoalbumenaemia and severe coronary artery disease [33]. In a series of 21 consecutive patients on long-term dialysis who underwent 20 infrainguinal bypass grafts and 5 endovascular procedures for critical leg ischemia, 2-year follow-up, patency rate was 74%, leg salvage rate was 85%, and survival rate was 23%, whereas 23% of patients were alive with salvaged leg. Patients on haemodialysis achieved better survival outcome than patients on peritoneal dialysis ($p = 0.02$). Multivariate analysis showed that low serum level of albumin had an effect on both the survival rate and on the rate of patients alive with salvaged legs ($p = 0.009$; $p = 0.005$) respectively as did also coronary artery disease ($p = 0.0002$; $p = 0.001$) respectively. Patients with-

out coronary artery disease achieved an alive and salvaged-leg rate at 1- and 2-year follow-up of 68% and 41%, respectively, but only 12% of patients with coronary artery disease survived with salvaged leg after 1 year, and none of them survived with salvaged leg at 2-year follow-up ($p = 0.003$). Similar results were seen in a further series of 39 patients with ESRD (56% had diabetes) who underwent revascularisation of 56 limbs. The primary patencies for all infrainguinal procedures at 1 and 2 years were 77% and 68%, respectively. At 3 years, 39% of patients were alive, and 84% of the limbs were salvaged [34].

Recent Progressive Approach to Revascularisation

After initial concerns, there has been an increasingly progressive approach to revascularisation in patients with renal failure admittedly in the background of high mortality. In a study of 146 consecutive patients (177 limbs) who underwent infrainguinal revascularization of whom 92% had diabetes and 91% had tissue loss, the limb salvage rates were 80% and 80% at 1 and 3 years [35]. The in-hospital mortality rate was 3% and the 1-year and 3-year cumulative survival rates were 60% and 18%, respectively. In a further outcome study, the cumulative assisted primary patency rate was 62% at 1 year and 62% at 2 years [36]. The limb salvage rate was 56% and 50% at 1 and 2 years, respectively. Limb salvage rates were lower than graft patency rates because of progressive necrosis despite a haemodynamically functioning bypass graft. Although overall patient survival rates were modest, they were comparable with the rates of other patients with ESRD.

Several other studies have indicated that infrainguinal bypass can be successful in achieving limb salvage in patients with ESRD. In a further series, of whom, 88% of patients were diabetic, 93% were hypertensive, and 44% were smokers, the 12- and 48-month graft patency was 64% and 38%, respectively [37]. The limb salvage rate was 65% and 58% at 12 and 48 months. Four limbs were lost despite a patent graft. Other series have confirmed that an increasingly aggressive approach to limb salvage in patients with ESRD using infra inguinal bypass in selected cases with vein conduit allows the majority of these patients to avoid major limb amputation [38]. Two further studies have confirmed that infrainguinal revascularisation can be performed in dialysis-dependent patients with acceptable patency and limb salvage rates, but noted that long term survival is poor. In patients with ESRD undergoing 37 bypass procedures for critical limb ischaemia (rest pain 2; tissue loss 35) with 13 femoro-popliteal and 24 femoro-tibial bypasses with autogenous (67.6%) or prosthetic (32.4%) materials, the cumulative primary patency rate was 88% at 1 month and 81% at 2 years. The limb salvage rate was 94% and 86% at 1 month and 2 years, respectively. The median age in this series was 62 years and 79% had diabetes [39].

Although revascularization of ischaemic limbs in dialysis patients can be achieved with an excellent initial graft patency and reasonable limb salvage, patient survival is poor and costs are high. Cumulative primary and secondary patency rates at 2 years were 65% and 79%, respectively [40]. Limb salvage was 67% and 59% at 1 and 2 years, respectively but patient survival was poor (47% at 2 years). Peritoneal

dialysis was predictive of poor survival (P < .001). Four of 5 patients on peritoneal dialysis died within 3 months of intervention. Extensive tissue loss was predictive of a diminished rate of limb salvage (P = .027). Thus, diabetic patients with ESRD can have an acceptable graft patency and limb salvage but suffer a higher perioperative mortality and morbidity and reduced survival [41].

A further series stressed the impact of uncontrolled infection [42]. Arterial reconstruction was performed on 56 limbs in 46 patients in the ESRD group and 78 limbs in 73 patients in the non-ESRD group. However, major amputation was performed in 6 of 48 limbs with patent grafts in the ESRD group because of uncontrolled infection or progression of necrosis. The limb salvage rate after arterial reconstruction was significantly lower in the ESRD group than in the non-ESRD group (p = .0019). The postoperative survival rate was lower in the ESRD group than in the non-ESRD group, although this difference was not significant (p = .052). Associated cardiovascular disease and systemic infection were the most frequent causes of death in the ESRD group. Although there was no significant difference in graft patency between the two groups after distal bypass surgery, the limb salvage rate was significantly lower in the ESRD group than in the non-ESRD group (p = .03).

Meta-analysis of infrainguinal arterial reconstruction for critical ischemia in patients with end-stage renal disease has confirmed its usefulness in selected patients with ESRD. Meta- analysis using random-effects modelling indicated the following estimates at one- and two-year follow-up: 79% (95% CI, 70–87%) and 74% (63–85%) for graft patency; 77% (69–84%) and 73% (64–81%) for limb salvage; and 59% and 42% for patient survival [43].

27.2.3.2 Endovascular Intervention

As with surgical bypass, there has been controversy on the role of endovascular intervention in diabetic patients with critical limb ischaemia who also have ESRD.

Severe CKD (class 4 and 5) impacts on outcomes of infrainguinal percutaneous vascular interventions (PVI) [44]. When 879 PVIs were reviewed, patients with severe CKD patients (14% of total) were significantly (P < .05) more likely to have diabetes (64% vs 46%), critical limb ischaemia (72% vs 11%), and need a multilevel PVI (34% vs 19%) or tibial intervention (35% vs 20%) compared with the remainder of the cohort. A Cox proportional hazards regression risk-adjusted for age, critical limb ischaemia, diabetes, coronary artery disease- showed that severe CKD increased the risk of late mortality (hazard ratio [HR], 2.4; 95% CI, 1.8–3.2; P < .01), amputation (HR, 2.1; 95% CI, 1.1–3.9; P = .02), and death or amputation (HR, 1.8; 95% CI, 1.3–2.4; P = .04).

Early and intermediate term results of endovascular treatment of lower extremity ischaemia in patients on dialysis indicated that the incidence of limb salvage among dialysis patients was modest with a high rate of major amputations in a series of 50 limbs (41 patients) of whom 82% had diabetes, including 22% with gangrene, 45% with non-healing wounds, 31% with rest pain and 4%.with debilitating claudication [45]. Nineteen patients required amputations after a mean follow-up of 12 months

(1–51 months). Freedom from amputation at 5 years was 40%. Factors associated with amputation included non-healing wounds or gangrene (68% and 36% respectively) and diabetes ($P < 0.05$). The survival rate was 80% after 5 years. However, in another series of diabetic patients with critical limb ischemia, and ESRD, endovascular treatment achieved limb-salvage in 58.6% of the limbs during a mean follow-up period of 12.4 months [46].

Three studies from Italy showed that percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. In a series of 599 diabetic patients with critical limb ischemia and foot ulcer, 99 dialyzed (Ds) (16.5%) and 500 not dialyzed (NDs) (83%), the outcomes of the whole population were 48.9% healing, 11.3% major amputation, 12.7% death, 27.1% non healing [9]. On multivariate analysis, dialysis was a negative predictor of healing and a positive predictor of major amputation. Outcomes for Ds and NDs were respectively: healing (30.3 vs 52.6%), major amputation (14.4 vs 10.8%), death (21.1 vs 11%) and non-healing (34.2 vs 25.6%) ($p = 0.0004$). Amputation occurred earlier in Ds than in NDs. According to the multivariate analysis in Ds, ischaemic heart disease and lower rise in transcutaneous PO_2 were negative predictors for healing and HDL cholesterol and carotid artery disease were predictive factors of death among NDs. In a further series of 107 patients, cumulative limb salvage rates at 12, 24, 36 and 48 months were 86, 84, 84 and 62% with a median follow-up of 22 months [47].

A third study from Italy on 90 limbs of 79 patients (64.4% male, mean age 67.2 years) all with ischaemic ulcer, of whom 77.8% had diabetes and 17.8% had ESRD, demonstrated that infrapopliteal angioplasty was of low procedural morbidity and mortality and is a safe technique [48]. When performed for tibial stenoses or occlusions <3 cm, ulcer healing occurred after initial angioplasty in 41 (55.4%) non-ESRD and four (25%) ESRD limbs. Subsequent revascularization procedures were required in 21 (23.3%) limbs, including six bypasses and 15 repeat angioplasties, of which three underwent subsequent bypasses. Major amputation was required in 11 (14.9%) non-ESRD and seven (43.7%) ESRD limbs. Limb salvage was 84.4% and 80.2% in those without ESRD at 1 and 3 years respectively and 52.5% and 52.5% in those with ESRD ($p = 0.01$). Thirty-day mortality was 2.2%. Overall survival was 82.2% and 62.1% at 1 and 3 years, respectively, and did not differ significantly between patients with and without ESRD ($p = 0.66$).

Finally, a percutaneous technique for deep plantar vein arterialization has been described in diabetic patients with no-option critical limb ischemia [49, 50]. Gandini reported in 9 diabetic ESRD patients (mean age 69 years; 5 men) with no-option critical limb ischaemia that an arteriovenous fistula (AVF) was created between the posterior tibial artery and plantar vein in 7 patients. The mean $TcPO_2$ at 1 month was 30 ± 17 mm Hg (vs 7.3 ± 2.2 at baseline). Six ulcers healed over an average of 21 ± 4 weeks. Three of the 9 patients had below-knee amputations. Kum reported deep vein arterialisation in 7 patients who had diabetes and severe tissue loss with no option critical ischaemia. At 6 months, 86% of patients had avoided major amputation, and at 12 months, 71% of patients (5 of 7) had done so. Complete wound healing was achieved in 57% of patients (4 of 7) at 6 months and in 71% of patients (5 of 7) at 12 months. The median healing time was 4.6 months [50].

27.2.3.3 Complimentary Roles of Open and Endovascular Therapies

Having considered the individual roles of open bypass and endovascular intervention, it is important to take into account the complimentary roles of open and endovascular therapies and the respective use of each in diabetic patients with renal failure.

Recent reports have come from the Critsch registry which analysed in-hospital outcomes in patients treated for critical limb ischaemia and end-stage renal disease compared to critical limb ischaemia patients with normal renal function [51]. The study cohort was divided into patients with ESRD (n = 102) and patients with normal renal function (n = 674; (glomerular filtration rate > 60/mL/min/1.73 m(2)). The first-line treatment strategies in ESRD patients were endovascular treatment in 64% (n = 65), bypass surgery in 13% (n = 13), patch plasty in 11% (n = 11), and no vascular intervention in 13% (n = 13). In non-ESRD patients, endovascular treatment was applied in 48% (n = 326), bypass surgery in 27% (n = 185), patch plasty in 13% (n = 86), and no vascular intervention in 11% (n = 77). ESRD patients had a 2.62-fold higher risk of amputation or death and a 3.14-fold higher risk of amputation during the in-hospital stay compared to patients with normal renal function. This outcome influences the choice of type of intervention and explains that two-thirds of these high-risk patients had endovascular intervention.

In a longitudinal cohort study of haemodialysis patients enrolled in special studies of the United States Renal Data System, 800 underwent an initial revascularization procedure by surgical bypass or angioplasty [52]. The overall incidence of subsequent amputation was 16.3/100 person-years, 22.6 for bypass, and 5.7 for angioplasty. The risk of amputation was higher for bypass versus angioplasty [relative hazard (RH) 4.00; 95% CI 2.46–6.57], for black versus white patients (RH 1.49; 95% CI 1.04–2.15), for uninsured or patients on Medicaid versus patients with private insurance or on Medicare (RH 1.65; 95% CI 1.12–2.72), and for patients with diabetes versus no diabetes (RH 2.51; 95% CI 1.67–3.76). The risk of all-cause (RH 1.37; 95% CI 1.10–1.70), cardiac (RH 1.50; 95% CI 1.08–2.09), and infectious (RH 2.17; 95% CI 1.10–4.29) mortality was greater among patients who underwent bypass compared with patients who underwent angioplasty.

In a Finnish study of 1425 patients who underwent infrainguinal revascularization for critical limb ischaemia, 95 patients had ESRD (eGFR <15 ml/min/m^2), and of them 66 (70%) underwent percutaneous transluminal angioplasty (PTA) and 29 (30%) underwent bypass surgery [53]. PTA and bypass patients with ESRD had significantly lower overall survival compared with patients with none or less severe renal failure. (at 3-year, 27.1% vs. 59.7%, $p < 0.0001$), leg salvage (at 3-year, 57.7% vs. 83.0%, $p < 0.0001$), and amputation free survival (at 3-year, 16.2% vs. 52.9%, $p < 0.0001$). ESRD was an independent predictor of all-cause mortality (RR 2.46, 95% CI 1.85–3.26). In regional multicenter registry for haemodialysis dependent patients (N = 689) undergoing open surgical bypass (n = 295) or endovascular intervention (n = 394) for lower extremity revascularization, overall survival at 1, 2, and 5 years survival was 60%, 43%, and 21%, respectively [54]. Survival, amputation

free survival (AFS), and freedom from major adverse limb event outcomes did not differ significantly between revascularisation techniques.

27.2.4 Multidisciplinary Approach

The various aspects of care described in this chapter should be co-ordinated in a multidisciplinary approach [55]. With regard to the preventative aspects of care both of the diabetic foot but also to overall cardiovascular morbidity, a collaborative multidisciplinary approach to include vascular surgeons, vascular medicine specialists, nephrologists, wound specialists has been proposed [56]. The Study of Heart and Renal Protection (SHARP)study, using combination of simvastatin/ezetimibe showed a 17% overall reduction in major adverse cardiac events in CKD patients [57]. However, ESRD patients have not been shown to benefit from statins. The Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis reported a nonsignificant 4% reduction of myocardial infarction, stroke, cardiovascular death, or all-cause mortality despite a mean 43% low-density lipoprotein cholesterol (LDL-C) reduction [58].

In a multidisciplinary approach at King's College Hospital, the team includes vascular surgeons, diabetologists, nephrologists, podiatrists and vascular scientists, interventional radiologists, nurses and orthotists. This optimises and expedites surgery and minimises the potential loss of information between involved specialists. The great saphenous vein conduit as gold standard is widely recognised and autologous vein is used for bypass grafting in the vast majority of cases. A strict follow up protocol after surgery which includes regular clinic visits in short intervals until wound healing is combined with a defined duplex surveillance program. The one year amputation free survival rate is similar in patients with chronic renal failure and in patients without renal failure.

27.3 Conclusion

Recent data indicate that by proper selection, favourable results can be obtained after revascularisation even in ESRD patients, with the majority of studies reporting 1-year limb salvage rates of 65–75% after revascularisation among survivors [27]. Both endovascular intervention and open bypass have achieved such limb salvage rates. The preferential use of endovascular-first approach is appealing in this vulnerable group of patients, but the evidence for endovascular usefulness is limited. The necessity for complete revascularisation of the foot may be even more important than in other patients with an ischaemic ulcerated diabetic foot because there are a number of factors counteracting healing in these patients [12].

Structured interdisciplinary inpatient care after surgery, as well as the continued care by the diabetic foot clinic after hospital discharge is important. It is also vital

to treat infections aggressively especially post-operative infections and limit the extent of any necrosis which may compromise the integrity of the foot and lead to amputation despite a successful bypass. Earlier referral for revascularisation, before the development of extensive tissue ischemia and infection is also key. Rapid treatment of ulcers is crucial and patients should have prompt access to expert care to treat wounds and prevent extensive necrosis. Multidisciplinary care is vital to the care of the diabetic patient in renal failure.

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Chapter 28
Ischaemic Charcot Foot

Hani Slim and Michael E. Edmonds

Although the classical presentation of Charcot neuroarthopathy (CN) is of a hot red swollen foot, later presentations are characterised by deformity and ulceration, which may be complicated by infection. Severe deformity may need surgical correction. Charcot patients who have reached the stage of significant foot deformity and sometimes ulceration may also have peripheral arterial disease (PAD). It is unlikely that significant ischaemia was present at the onset of the CN but in the time interval from onset of the Charcot foot to acquiring deformity, it may have developed. Such patients also can occasionally present with rest pain. This must be differentiated from unilateral neuropathic pain which occasionally occurs in the Charcot limb.

The PAD is usually infrapopoliteal but may be also femoro-popliteal. In a series of 85 patients with diabetes and Charcot foot, the prevalence of PAD was 40% [1]. Caravaggi et al. reported a rate of ischaemia of 4.4% but only included patients with critical limb ischaemia using a threshold of transcutaneous oxygen pressure of ≤30 mmHg [2].

Chantelau [3] reported a PAD rate of 12.5% in an investigation assessing the early diagnosis of Charcot foot. Sohn et al. [4] reported that PAD was present in 26.9% of US military veterans with Charcot foot. Bem evaluated 82 diabetic patients with "ulcerated Charcot" and reported that 29 of 82 patients (35.4%) had been diagnosed with PAD from the angiographic findings of lower limb of stenosis of >70% or occlusion [5]. Bem also compared the rates of PAD in patients who had an ulcerated Charcot foot with that of patients without Charcot foot who had developed a new foot ulcer. They found that patients with foot ulcers without Charcot foot had a PAD rate of 48% compared with a rate of 35.4% in patients with ulcerated CN

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(p = 0.12). It is possible that the true rate of PAD in patients with CN in these cited studies was underestimated because of the methods of diagnosing PAD.

During the past decade, an association among Charcot foot, diabetic neuropathy, and medial arterial calcification (MAC) has also been noted. Jeffcoate et al. has reported that 80% of patients with CN had radiographic findings of MAC [6]. Although MAC may not be associated with luminal obstruction, studies have demonstrated that MAC is associated with increased rates of mortality and lower limb amputation. Also, the dynamics of the artery are negatively affected by MAC by reducing the elasticity and compliance of the arterial wall and this can result in decreased perfusion [7, 8].

There are few studies showing the effectiveness of endovascular treatment in cases with Charcot foot and PAD. In a series of patients with íschaemic foot and also CN, who had endovascular treatment, the limb salvage rate was 90% and mean time to heal 197 days. A complete revascularization indicated as achieving patency of three tibial vessels, with patency of dorsal and plantar circulation of the foot, was accomplished in 6 (60%) of cases. In the other 4 (40%) patients, two tibial vessels recanalization (peroneal artery and one of the anterior or posterior tibial arteries) was carried out, with one vessel direct to the foot. The healing time of surgical and orthopaedic treatment in patients with complete revascularization was 184 ± 13.6 days compared with 218.5 ± 11.7 days in patients with incomplete revascularization (p = 0.003). Prior to treatment, TcPO2 was 11.3 ± 5.2 mmHg and after revascularization was 55.7 ± 7.3 mmHg [9, 10].

In a further study, the one-year limb preservation rate in all patients with ischaemic diabetic foot wounds both with Charcot and without Charcot foot who underwent endovascular treatment of infra-popliteal arteries was found to be 81% [11]. This rate was 92.7% in patients without Charcot foot and 59.1% in cases with Charcot foot. The mean survival time of limb salvage after angioplasty in patients with Charcot foot was 9.95 months (STD ± 0.57) and was 11.68 months (STD ± 0.20) in patients without Charcot. Thus, overall, limb preservation rates with endovascular treatment in diabetic patients with ischaemia but without Charcot foot were better than in diabetic patients with ischaemia and Charcot foot.

In conclusion, arterial disease may compromise ulcer healing and surgical and orthopaedic interventions and thus all patients with this advanced presentation of CN should be investigated for vascular disease. All Charcot foot patients with ulceration and those being considered for surgery should be investigated with duplex arterial ultrasound. If surgery is planned for Charcot foot, revascularisation, within a multidisciplinary approach, should be considered before surgery for limb preservation.

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Chapter 29
Ischaemic Foot—Debridement and Skin Grafts

Raghvinder Pal Singh Gambhir and Rajesh Kumar Balasubramanian

29.1 Introduction

Diabetic foot ulcers (DFU) are defined as non-traumatic lesions of the skin on feet of diabetic patients. DFU will affect 15% of people with diabetes at some point in their lives [1]. The management costs of DFU are enormous and the outcomes remain poor. Despite numerous advances in wound research, healing is often delayed for weeks or months. Complete wound closure is achieved in only 25–50% of chronic wounds and foot ulceration is a precursor for a major limb amputation [2].

The National Institute for Health and Care Excellence (NICE) document highlights the importance of early effective management of DFU to prevent amputations, reduce complications, decrease mortality and improve overall quality of life [3].

The management of DFU is multidisciplinary and the accepted standard therapy includes good glycaemic control, treatment of infection, wound debridement, moist dressings, pressure off-loading and revascularisation. To heal a chronic DFU and prevent its recurrence, a number of modalities may have to be used in combination. These include surgery, negative pressure wound therapy, hyperbaric oxygen therapy and growth factors. What is more important, however, is appropriate patient education for regular foot care to prevent ulcers and their complications.

Recent guidelines have redefined the ischaemic foot as a foot with chronic limb threatening ischaemia (CLTI) [4]. In diabetes, this includes two main clinical entities, the neuroischaemic foot and the critically ischaemic foot. This chapter concentrates on debridement and skin grafts mainly in the neuroischaemic foot with ulceration although it is important to stress that such feet should also be primarily be considered for revascularisation if merited by the degree of ischaemia.

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29.2 Definition

Debridement is derived from a French word 'desbrider' which literally means to unbridle a horse. It is a technique aimed at removing nonviable and necrotic tissue from a wound. Experience gained from management of war wounds strongly supported surgical debridement as a necessary component of wound bed preparation for healing by secondary intention.

In chronic diabetic foot wounds, debridement aims to remove the hyperkeratotic epidermis (callus) from the wound edge, to excise all the necrotic tissue and fibrin from the wound bed and also remove any biofilm which often harbours and protects bacteria [5].

Wound bed preparation by application of an appropriate effective debridement technique is essential for healing of chronic wounds [6]. Debridement should not be considered as an episodic event but as continual process occurring at macroscopic and microscopic level to assist healing. There are a wide variety of commercial products available with variable debriding properties and cost. Indications for each and their efficacy are not clearly established. There is little scientific evidence to guide the clinician to the most effective method.

29.3 Types of Debridement

Several methods are currently used for debridement. Each has its advantages and they are often used in conjunction with each other. Debridement can broadly classified as:

- Surgical/sharp
- Enzymatic
- Autolytic
- Mechanical
- Biological/Maggot debridement therapy (MDT)

Adjuncts to the standard DFU therapy include:

- Hyperbaric oxygen therapy (HBOT),
- Negative pressure wound therapy (NPWT)

Recent systematic analysis have not shown superiority of any one method for promoting wound healing, though the level of evidence is of low to moderate grade [7, 8].

29.3.1 Surgical Debridement

Surgical debridement is the most effective and efficient method to remove all devitalized/dead necrotic tissue. It aims to convert the physical, molecular and cellular environment of a chronic non-healing wound into a more responsive acute healing environment [9].

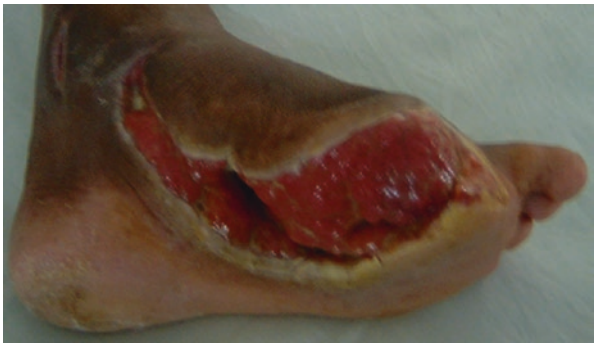

Fig. 29.1 A diabetic foot wound laid open and in the process of granulating with negative pressure wound therapy

Clinical experience strongly supports debridement as a necessary component of wound bed preparation. While the rationale for surgical debridement is logical, the critical question has always been the timing. Serial debridement has been shown to increase wound healing rates and rates of closure [10].

Debridement has to be extensive and needs to lay open the tendon sheaths as shown in Fig. 29.1.

29.3.2 Enzymatic Debridement

Enzymatic debriding agents are an effective alternative way for removing adherent slough or eschar from wounds. They may be used as the primary debridement agents though more often they are used after initial surgical debridement. They are not commonly used in the diabetic foot.

Collagenase is an enzymatic debriding agent that selectively digests the collagen holding the necrotic tissue onto healthy tissue. It is selective to necrotic tissue and has been shown to promote granulation, sustain epithelisation while maintaining debridement of necrotic slough [11]. Collagenase is normally used once a day. Solutions or dressings that contain acid or metal ions (e.g., silver containing compounds) adversely affect the enzymatic activity of collagenase. Evidence from systematic reviews confirms that collagenase ointment is a safe and effective choice for debridement of cutaneous wounds [12]. Studies have shown it to be more effective than placebo. However, evidence is equivocal for other agents like a papain-urea-based ointment or a polyacrylate dressing [13]. In a study on 52 patients, ulcers treated with serial sharp debridement plus adjunctive clostridial collagenase ointment (CCO) decreased in size more rapidly than ulcers treated without adjunctive CCO debridement [13].

29.3.3 Autolytic Debridement

It is a process through which the white blood cells phagocytize the necrotic tissue in the wound bed. This occurs optimally in a moist wound environment and a number

of products are available to promote this debridement. Meta-analysis of three randomised control studies did not find any difference between different types of autolytic products. Some of the products available include hydrogels, hydrocolloids and alginate dressings [14].

Hydrocolloids are a combination of gel-forming polymers that can absorb a moderate amount of exudate, to form a soft, minimally adherent gel in the wound bed. This helps to retain the wound's natural moisture and promotes autolytic debridement of necrotic tissue. They usually come in the form of sheets, which are placed directly over the wound bed.

Hydrogels have high water content and help in keeping the wound moist and therefore should not be used in wounds with excessive exudates. These dressings are used in non-infected wound with minimal exudate often as bridging before skin grafting.

There is evidence to suggest that application of hydrogel increases the healing rate of DFU compared with saline gauze dressings or standard care. Pooling three RCTs which compared hydrogel with gauze or standard care suggested that hydrogels are significantly more effective in healing diabetic foot ulcers (Relative Risk 1.84, 95% Confidence Interval (CI)1.3 to 2.61) [14–16].

Alginates and hydrofibers are used when there is moderate to copious amount of exudate. Alginates are derived from seaweed and form a soft hydrophilic gel which provides a moist wound healing environment. An additional cover dressing should be used to secure the alginate dressing in place and to allow it to absorb additional drainage. Because wound fluid is required to "activate" the alginates, they are not effective in wounds covered with thick, dry tissue.

29.3.4 Mechanical Debridement

29.3.4.1 Hydrosurgical (Versa Jet)

High pressure jet of sterile saline travels parallel to the wound surface and creates a Venturi effect and selectively removes necrotic material without contamination. Unlike surgical debridement it does not remove any healthy tissue and is capable of removing deeply ingrained contaminants [17].

29.3.4.2 Ultrasound

As a therapeutic agent ultrasound has been studied extensively in chronic wound healing (Fig. 29.2). Low-frequency (20–30 kHz) ultrasound delivered at either low or high intensity via contact or noncontact techniques has been shown to reduce the size of the wound and improve complete healing rates when used in conjunction with standard wound therapy. In patients with Wagner classification 1–3 ulcers, early healing appears to be facilitated by either low-frequency low-intensity noncontact ultrasound or low-frequency high-intensity contact ultrasound [18].

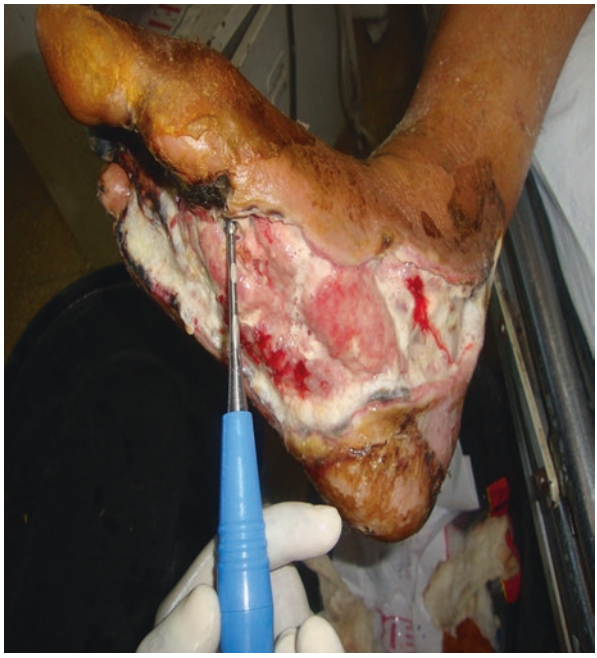

Fig. 29.2 Ultrasonic-assisted wound debridement

Ultrasonic mist debridement uses acoustic energy to remove devitalized tissue from the wound bed and to promote wound healing [19].

Pain, when reported, has been successfully addressed with topical analgesia.

In another study, a statistically significantly higher percentage of wounds treated with mist therapy and standard of care healed as compared with those treated with the standard of care alone (53% vs 32%, P = 0.009) [20]. There is however insufficient evidence to determine whether ultrasonic mist therapy effectively debrides necrotic tissue in chronic wound beds.

29.3.5 Biological Debridement/Maggot Debridement Therapy (MDT)/Biosurgery/Larval Therapy

For centuries maggots have been known to help debride and heal wounds. The term 'biosurgery' describes the use of living maggots on chronic long standing wounds to remove devitalized tissue and improve wound healing. Ambroise Pare was the first person to document the beneficial effect of larvae on suppurative wounds [21].

Maggot therapy employs the use of laboratory-reared sterile larvae of the common green-bottle fly, Phaenicia (Lucilia) sericata. First introduced in the USA in 1931 it was routinely used until the mid-1940s when, with the advent of antimicrobials, its use declined. It was reintroduced in early 1990s and is FDA-approved [22].

Sterile maggots (50–1000) are introduced in the wound and left for 1–3 days. It is useful for purulent, sloughy wounds and can be used in both ambulatory and hospitalized patients. Wound healing enhancement action may be derived from maggot excretions/secretions, which contain proteolytic enzymes that liquefy necrotic tissue. The maggots separate the necrotic tissue from the living tissue, making surgical debridement easier [23, 24]. It is especially useful in large necrotic wounds resistant to conventional treatment. The offensive odour from the necrotic tissue and accompanying pain from the wound decrease as the larvae alter wound pH and healthy granulation tissue is formed over the wounds. Maggots also have antimicrobial activity in particular against gram positive bacteria. With an increasing number of patients suffering from multi-resistant bacteria infected wounds—e.g. methicillin-resistant Staphylococcus aureus—MDT has a definite place [25].

Patients may complain of tickling, itching sensation or may have pain which may require analgesia. Others may have psychological and esthetic issues with its use but it has proven to be an effective and safe option for debridement. Clinical experience with MDT, strongly suggests that this technique is an effective and safe method of debridement for selected patients [26, 27]. It reduces time taken to achieve bacterial negativity, granulation, healing of lesions and was superior to other conventional debridement in preventing amputations [28–30]. There are however a number of limitations when considering its local applicability and future developments in delivery system may help to improve its acceptability.

A novel concept in MDT technology has been to create strains of transgenic L. sericata that express and secrete Human platelet derived growth factor-BB (PDGF-BB) [22] PDGF-BB is known to stimulate cell proliferation, survival and promotes wound healing.

The effectiveness of maggot debridement therapy may vary between free range and bagged/contained maggots. In a study of 64 patients treated with either free-range or bagged/contained maggots, outcomes were significantly better with the free-range ($P = .028$). These patients required fewer mean number of maggot applications and less total number of maggots per treatment [31].

Based on these evidences, presently, larval therapy is recommended for debridement in a chronic wound which is not responding to conventional debridement [2].

29.3.6 Adjunctive Therapies to Wound Healing

29.3.6.1 Hyperbaric Oxygen Therapy (HBOT)

Hyperbaric oxygen therapy (HBOT) has been used as an adjunct to standard methods of care and has been shown to decrease the risk of infection, improve healing

as well lower the risk of extremity amputations. The rationale behind using HBOT is to deliver higher concentration of oxygen to counter the presence of hypoxia in the non-healing chronic wounds. The technique requires a person being placed in a compression chamber under greater than one atmosphere absolute (ATA) pressure of 100% oxygen. The pressure increases the level of oxygen dissolved in the blood plasma affecting the immune system, wound healing, and vascular tone. Treatment regimens vary from 90 to 120 min daily for approximately 30 sessions [31]. Complications associated with HBOT are infrequent but may include claustrophobia, ear, sinus or lung barotrauma, temporary worsening of short sightedness and oxygen poisoning.

A Cochrane review showed there is some evidence that the addition of HBOT to a standard wound care regimen in people with foot ulcers due to diabetes results in a significant improvement in wound healing by six weeks. However this benefit is not evident at 1 year or longer [32]. In terms of amputation, HBOT does not appear to significantly improve the minor amputation rate in people with foot ulcers due to diabetes. In a meta analysis by Liu et al. [33], HBOT improved the rate of healing and reduced the risk of major amputations in patients with diabetic foot ulcers in selected cases. The quality of the evidence assessing the efficacy of HBOT as an adjunct to standard therapy for people with non-healing diabetic foot ulcers is low, and the results are inconsistent [8, 34, 35]. More adequately powered trials are needed to prove the value of HBOT in DFU.

A Canadian study estimated it to be cost-effective over a 12 year time horizon. The calculated cost for patients receiving HBOT was 40,695 Canadian dollars compared with 49,786 for standard care alone. Quality-adjusted life-years (QALYs) were 3.64 for those receiving HBOT and 3.01 QALYs for controls [36].

There have been three recent studies assessing the role of hyperbaric oxygen in the diabetic ischaemic foot. A randomised double blind study showed faster healing and closure of wounds in a mixed population of good perfusion and inoperable peripheral arterial disease receiving HBOT compared with hyperbaric air [37] but two subsequent studies did not show statistically significant differences in outcomes. HBOT did not offer an additional advantage to comprehensive wound care in reducing the indication for amputation or facilitating wound healing in patients with chronic DFUs [38] and in a further study of 120 patients with an ischaemic wound, there was no significant difference in wound healing or limb salvage in response to HBOT [39]. Furthermore, a cohort study comparing the effect of HBOT with other conventional therapies administered within a wound care network, demonstrated that HBOT did not improve the likelihood of healing of the diabetic foot ulcer nor prevented amputation [40]. In conclusion, probably HBOT is useful in a specific group of patients whose ulcer is resistant to healing but currently no high quality evidence is available to recommend HBOT as an adjunct routinely.

29.3.6.2 Negative Pressure Wound Therapy (NPWT)

Negative pressure wound therapy has revolutionised wound management in the last 2 decades. Several RCTs have demonstrated its benefits in early wound healing and closure in diabetic ulcers leading to reduced hospital stay, reduced rate of amputations and improvement in the quality of life compared to standard therapy [41–43].

It stimulates angiogenesis and granulation tissue formation and causes wound contraction [44–46]. Use of vacuum therapy also reduces the number of times of dressing changes. It can be applied in both hospital and community ambulatory setting. It is also being applied as adjuncts over skin grafts [47, 48].

Newer generation of foams in vacuum therapy include silver impregnated foam. Another recent development has been negative-pressure wound therapy with cyclical instillation of saline. This helps in removing dead tissue, diluting toxic products and reducing bacterial load [49, 50].

29.3.7 Alternative Therapies

Traditional therapies based on natural origin products from plant extracts and honey are interesting alternatives. Current trend is to combine the use of traditional healing agents and modern products/practices, such as nanofibers containing silver nanoparticles. Aloe vera can be loaded into alginate hydrogels and hydrogel sheets containing honey [51].

29.4 Autologous Tissue Grafting

Autologous skin grafts include split skin graft (SSG), full thickness skin grafts, and occasionally free or pedicled flaps. SSG has been the ‘gold standard’ for wound closure, when the wound does not heal by primary intention [52, 53]. Its use shortens the duration of healing and hospital stay. The technique of harvest and placing the graft is fairly standard. Epidermis with a superficial part of the dermis is harvested from an undamaged skin donor site and is applied to a healthy granulation tissue on the wound bed. A prerequisite for success is good perfusion and absence of infection [54, 55]. Any seroma or haematoma can potentially affect the imbibition and can result in the loss of grafts. Addition of NPWT helps in removal of seroma/haematoma and improves graft survival [56].

The use of mesh skin grafts is the simplest technique to expand the amount of available donor skin [57]. The cosmetic and functional results may however vary. The lack of dermis in the interstices of the stretched meshed skin graft, and slow epithelialisation from graft margins across interstices, may result in a greater graft contraction, and ‘crocodile skin’ appearance of the scar. Split skin grafts can shrink by about 20%.

The donor site heals by keratinocyte migration from hair follicles, sweat glands and edges of the wound. It heals within a week and can be used for further SSG reharvesting. Generally, the thicker the SSG, the longer it will take to heal the donor site.

Pinch grafting is an alternate method for closure for soft tissue loss in the diabetic foot. Where tendons are exposed, SSG is not a suitable option and focal flaps or free or pedicled flaps should be considered.

One of the problems with SSG is its success rate in plantar weight bearing areas, though there is no significant difference in the healing rate between plantar or other sites. Durability in pressure areas is a problem and risk of repeated breakdowns can be reduced by appropriate pressure offloading (Figs. 29.3 and 29.4).

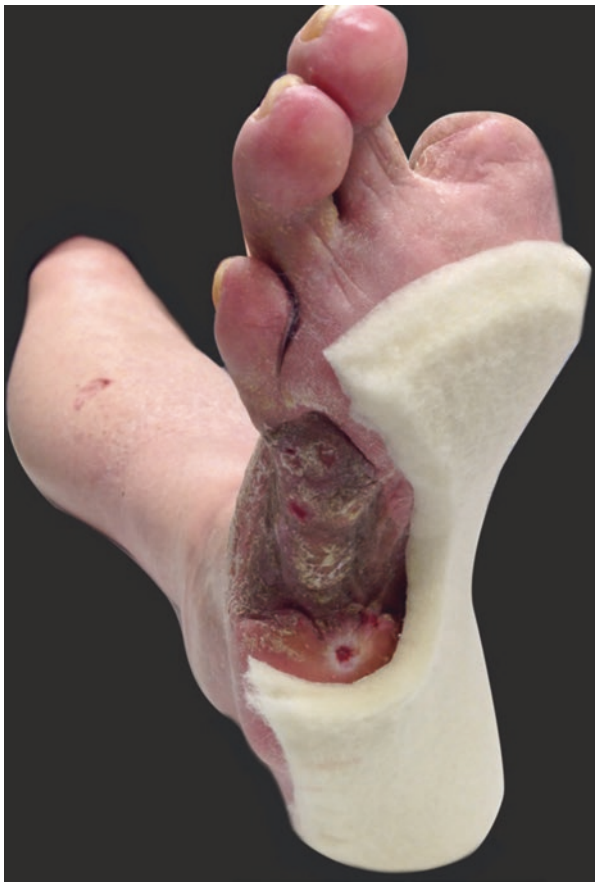

Fig. 29.3 Felt pads being used to offload a healed and grafted wound on the plantar surface

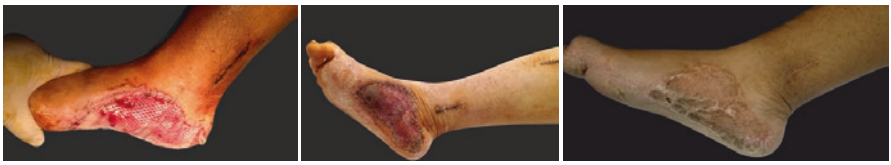

Fig. 29.4 Split skin graft over previously debrided wound showing maturation of skin graft on follow-up

29.5 Conclusion

Despite significant advances in wound care, the management of diabetic foot ulcers (DFUs) remains a major therapeutic challenge. Debridement in some form is considered a prerequisite for healing. More robust evidence is needed to determine the efficacy and cost effectiveness of the multiple debridement techniques available.

Even when healed, diabetic foot ulcer should be regarded as a life-long condition and treated accordingly to prevent recurrence. New public health strategies are needed to reduce the burden of care.

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Chapter 30
Ischaemic Foot—Wound coverage: Tissue Substitutes

Raghvinder Pal Singh Gambhir and Amila Weerasekera

30.1 Introduction

The provision of a permanent durable cover for full thickness skin defects in diabetic neuropathic and vascular insufficiency ulcers remains a challenging clinical problem in spite of number of advances in tissue engineering technology. Numerous studies have shown the high morbidity and risk of amputation associated with non healing wounds [1]. Current management of diabetic foot ulcers consists of pressure off-loading, infection control, wound dressings or topical agents, intensive control of blood glucose and vascular reconstruction. However complete healing is never achieved in 25% patients and another 28% will end up with an amputation [2].

As previously described, the ulceration may develop in the two main entities of the ischaemic foot, namely the neuroischaemic foot, in which there is mild to moderate ischaemia and the critically ischaemic foot with severe ischaemia. Revascularisation is mandatory in the critically ischaemic foot and depending on the degree of ischaemia, revascularisation may need to be carried out in the neuroischaemic foot whilst also paying attention to specifically treating the ulcer. However, in cases of mild ischaemia, conservative measures may be carried out first, without initially resorting to revascularisation. This would also apply to a subgroup of neuropathic feet which has some distal ischaemia.

The importance of achieving stable wound coverage in diabetic foot cannot be overemphasised. The treatment goal is for the wound to heal and stay healed. Traditionally all defects have been covered by split skin grafts. The short term outcomes are satisfactory. However, in long term, the inability of split skin graft to withstand high plantar pressures leads to repeated breakdown and predisposes to further tissue necrosis and sepsis. It invariably results in further debridement, higher

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amputation, prolonged stay, delay in regaining full mobility, greater morbidity and mortality and increased expenditure on the health service.

A number of products are available for temporary and permanent wound coverage including cultured skin substitutes, scaffolds and tissue substitutes. This has been an area of extensive research and development over the last 3 decades and there is a substantial need for such products. Current practice guidelines for management of diabetic foot recommend tissue substitutes as adjunctive therapy for difficult to heal wounds [2].

30.2 Tissue Substitutes

Bio-engineered skin and tissue substitutes may be derived from human tissue (autologous or allogenic), nonhuman tissue (xenogenic), synthetic materials, or a composite of these materials. They have been variously classified as listed in Table 30.1 [3] Some of these products are designed to provide dermal replacement, some epidermal and a few both and they can be used as either temporary or permanent wound coverings. The cellular products contain autologous or allogenic keratinocytes and fibroblasts. Acellular products provide a scaffolding/ matrix of collagen, hyaluronic acid or fibronectin.

Regulations governing the use of the tissue substitutes vary among countries. Some tissue substitutes are considered to be derivatives of cadaveric tissues and are classified as banked human tissue and therefore are governed by the tissue banks standards. Other products are classified as medical devices and are regulated by the U.S. Food and Drug Administration (FDA) or equivalent agencies.

The regeneration of healthy and functional skin in diabetic patients remains a huge challenge. Tissue substitutes are thought to promote wound healing by

Table 30.1 Classification of Skin/Tissue substitutes [3]

S. no.	Criteria	Classification	Sub classification
1	Anatomical structure	Dermo-epidermal (composite)	
		Epidermal	
		Dermal	
2	Duration of cover	Permanent	
		Semi-permanent	
		Temporary	
3	Type of biomaterial	Biological	Autologous
			Allogeneic
			Xenogeneic
		Synthetic	Biodegradable
			Non-biodegradable
4	Presence or absence of cells	Cellular	
		Acellular	

countering several pathophysiological mechanisms operating in diabetes mellitus. They stimulate intrinsic healing pathways by increasing the availability of growth factors, cytokines and reducing matrix metalloproteinases (MMPs) activity [4, 5].

Epidermal substitutes are manufactured using keratinocytes isolated from a skin biopsy and cultured on top of a matrix. To culture autologous cells, a skin biopsy of 2–5 cm^2 is obtained from the patient [1]. For allogenic preparations, cells are derived from neonatal foreskin. When using allogenic sources, precautions are necessary to prevent disease transmission [6, 7]. During processing, all cellular structures including Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles are removed. These keratinocytes are plated and can be arranged in sheets or suspended in a solution to be sprayed on to a wound. Both preparations are used as epidermal substitutes.

Similarly, dermal fibroblasts are isolated, cultured and incorporated into dermal substitutes. Dermal substitutes provide greater strength and stability and prevent wound contraction.

Acellular components may be biological or synthetic. Biological polymers include collagen, elastin, glycosaminoglycans which form the extracellular matrix of the human dermis. They are obtained from cadaveric skin or animal tissue such as bovine collagen and porcine dermis or intestinal submucosa. To improve mechanical stability of tissue substitutes, natural polymers may be chemically cross-linked to other natural or synthetic polymers [8–10].

Synthetic skin substitutes are constructed of non-biological molecules and include absorbable substances such as polyglactin, polycaprolactone, polylactic acid and non absorbable compounds such as nylon, polyurethane, and polytetrafluoroethylene [11]. Some manufactured products have a removable semi permeable silicone layer on top to prevent moisture loss and infection. Table 30.2 lists some of the available dermal, epidermal and composite products [2, 3].

30.3 The Ideal Skin Substitute for Diabetic Foot Ulcers

In the search for the ideal tissue substitute for diabetic foot ulcers, several key properties have been described. Theoretically, an ideal skin substitute should be a composite epidermal and dermal substitute, with a functional neurovascular elements, appendages and pigmentation [12]. It should not elicit an excessive inflammatory response and be capable of healing without scar. It should be resistant to infection, be able to withstand shear forces and have the ability of self renewal. It should have a long shelf life, be easily stored, and be readily available. The aim in diabetic foot disease is to optimize the structural properties of the matrix to enhance cellular function and healing as opposed to providing just a wound cover. It has to do more than tissue repair; it has to regenerate. Such a substitute is however not available [13, 14].

Table 30.2 Skin substitutes

Dermal substitutes				
Cellularity	Source and composition	Brand	Duration of cover	Advantages/disadvantages
Cellular	Allogenic cryopreserved neonatal fibroblasts cultured on bioabsorbable Polyglactin mesh	Dermagraft Advanced BioHealing, Inc., USA	Temporary or Permanent	Shelf life-6 month Semitransparency allows wound inspection The scaffold biodegrades in 2 weeks
	Allogenic neonatal fibroblasts seeded onto silicone covered bioabsorbable scaffold	TransCyte Advanced BioHealing, Inc.,USA	Temporary	1.5 year shelf life Easy to remove
Acellular	Allogenic lyophilized cadaveric dermal matrix	AlloDerm LifeCell Corporation, USA	Permanent	2 year shelf life Can vascularize over exposed bone and tendon
	Allogenic cadeveric micronized dermal matrix	GraftJacket Wright Medical Technology, Inc., USA	Permanent	2 year shelf life Pre meshed
	Xeno—Porcine Dermal tissue	Permacol Surgical Implant Tissue Science Laboratories plc, UK	Permanent	
	Porcine intestinal submucosa	OASIS Cook Biotech Inc. USA	Permanent	
	Synthetic bilayered matrix of cross-linked bovine type 1 collagen and chondroitin-6-sulfate glycosaminoglycan with a thin silicone backing	Integra Dermal Regeneration Template. Integra NeuroSciences, USA	Permanent	
	Silicone + Porcine Collagen	Pelnac Standard/Pelnac Fortified Gunze Ltd, Japan	Semi-permanent	

	Silicone + Porcine Collagen	Biobrane/Biobrane-LUDL Laboratories, Inc., USA	Temporary	Less aggressive adherence. Dressing naturally separates from wound
Epidermal substitutes				
Cell source	**Arrangement**	**Brand**	**Duration of cover**	**Advantages/Disadvantages**
Autologous cultured keratinocytes	Confluent cell sheets	Epicel Genzyme Biosurgery, USA	Permanent	Culture time -3 weeks Shelf life- 1 day Can cover a large area Take rate-variable
		Laserskin Fidia Advanced Biopolymers, Italy	Permanent	Shelf life- 2 days Transparency allows wound inspection
	Subconfluent cell suspension	CellSpray Clinical Cell Culture company (C3), Australia	Permanent	
		Bioseed-S BioTissue Technologies Germany	Permanent	Dressing naturally separates from wound.
Dermo epidermal tissue substitutes				
Source	**Type**	**Brand/source**	**Duration of cover**	**Advantages/disadvantages**
Allogenic	Cadaveric skin	From tissue banks	Temporary	
Allogenic + xenogenic	Cultured keratinocytes on bovine type I collagen seeded with allogenic fibroblasts	Apligraf (Graftskin) Organogenesis Inc. USA	Permanent	5 day shelf life
Allogenic + xenogenic	Cultured keratinocytes and fibroblasts on bovine collagen sponge	Orcel Ortec International, Inc, USA	Temporary	9 month shelf life Cannot be used in patients allergic to penicillin, gentamycin, streptomycin, or amphotericin B
Allogenic + synthetic	Cultured keratinocytes + fibroblasts on synthetic matrix	PolyActive HC Implants BV. The Netherlands	Temporary	

In spite of significant progress that has been made there remain inherent limitations with insufficient take rates, lack of mechanical stability, lack of differentiated structure of normal skin and high costs.

30.4 Clinical Evidence to Support Therapeutic Efficacy

In the last three decades a number of trials have shown the efficacy of tissue engineered products in healing diabetic foot ulcers, pressure ulcers and other chronic wounds.

Numerous studies have shown the ability of cultured human autologous keratinocytes to adhere to wound beds, resulting in re-epithelialization of both acute and chronic wounds. However, 2–3 weeks are needed for graft cultivation. Cultured autologous epidermal and dermal cells seeded on collagen-elastin scaffolds and transplanted to tissue defects show characteristics similar to the healthy human skin [15, 16].

Animal studies in sheep, mice and pigs have shown the effectiveness of tissue-engineered skin substitutes in healing full thickness wounds [17–19]. In human studies too, application of tissue substitutes after excisional debridement of the wounds,results in faster healing [20–22].

Apligraf was the first skin substitute to be approved by FDA for the treatment of diabetic foot ulcers and was shown to heal non-infected, non-ischemic chronic plantar diabetic foot ulcers faster and in more patients than conventional therapy in a large-scale multi-center randomized prospective clinical trial [23]. Ipsilateral toe or foot amputation rate was also significantly reduced [23, 24]. Ulcer healing occurred in significantly more patients and in a shorter median time compared with saline-moistened gauze at 12 weeks' follow-up [23–25]. Osteomyelitis and lower-limb amputations were also less frequent in the treatment group [26].

Dermagraft is a bioengineered living human dermis. It contains human fibroblast cells which are obtained from neonatal foreskin and cultivated on a three-dimensional polyglactin scaffold. FDA approved its use in full-thickness diabetic lower extremity ulcers, which were present for longer than 6 weeks extending through the dermis but not to the tendon, muscle, or bone. In a prospective, single blinded randomized controlled trial, 30% of the Dermagraft patients were healed in comparison to 18.3% of the control patients at 12 weeks [27]. The incidence of local wound infection, osteomyelitis and cellulitis was significantly less in the Dermagraft group in than in control patients [28, 29].

Integra® Bilayer Matrix Wound Dressing is a non-living, 2 mm thick matrix composed of chondroitin-6-sulfate and bovine type 1 collagen and a semi-permeable polysiloxane (silicone layer). It acts as a scaffold to facilitate the migration of macrophages, fibroblasts and lymphocytes to initiate angiogenesis from the dermal wound bed and to create granulation tissue for support of local tissue or a split skin graft. Figures 30.1, 30.2, 30.3, 30.4, and 30.5 illustrate its use in

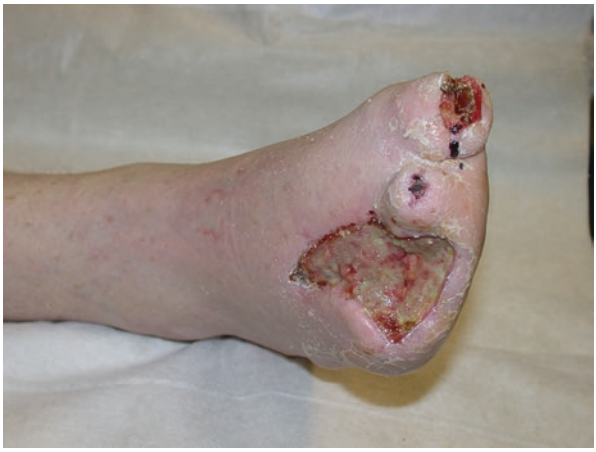

Fig. 30.1 Non-healing diabetic foot wound at 6 weeks

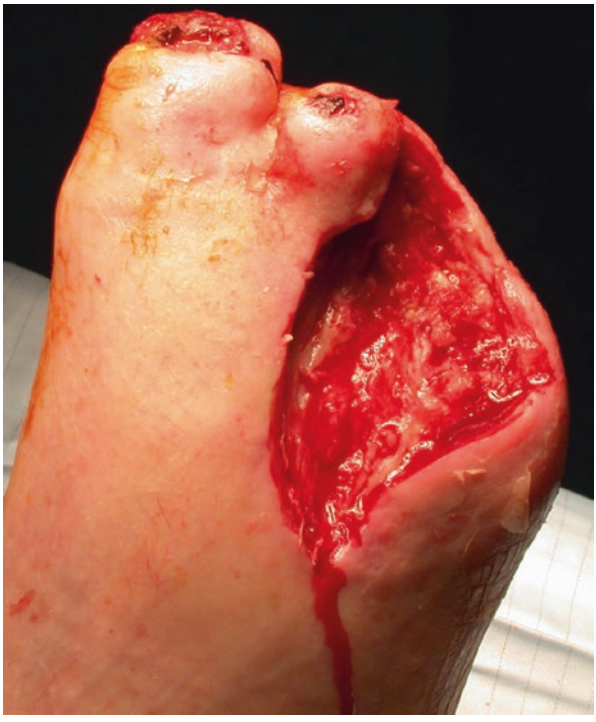

Fig. 30.2 Wound debrided before application of Integra® bilayer matrix wound dressing

one such patient. It takes 3 weeks for angiogenesis in dermal wound bed to create granulation tissue (neo-dermis) that can support a split thickness skin graft (STSG). The silicone layer is removed and the neo-dermis is covered by a STSG or cultured skin substitutes [30]. The final picture demonstrates a smooth, pliable, and hypopigmented skin.

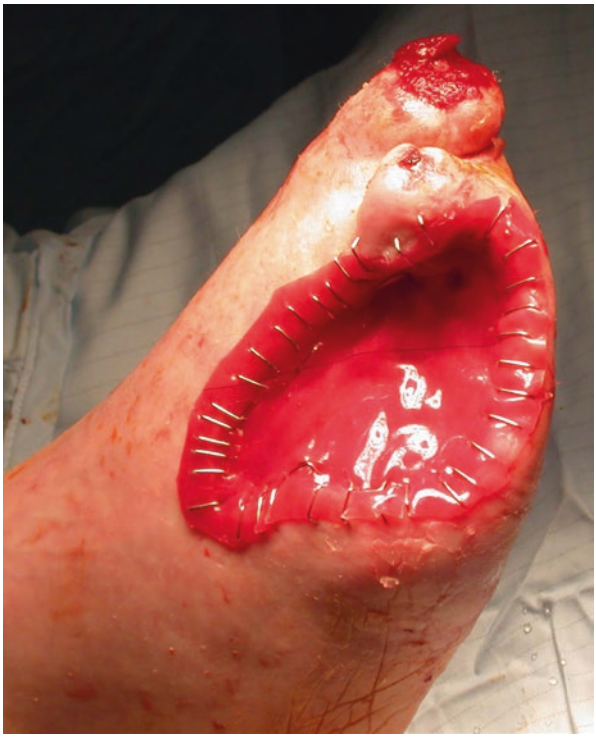

Fig. 30.3 Integra® bilayer matrix wound dressing application

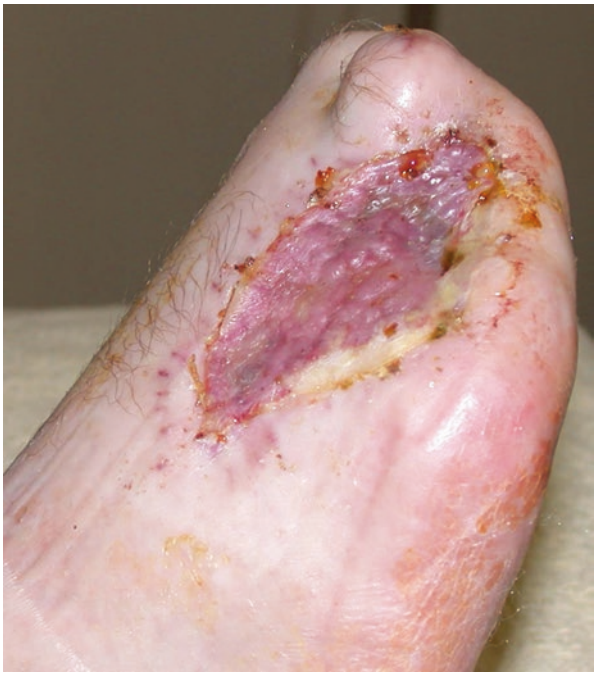

Fig. 30.4 After split skin graft on neo dermis

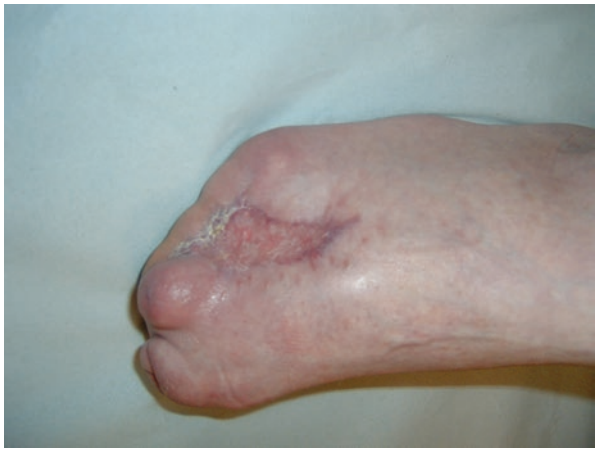

Fig. 30.5 One year follow up after Integra® bilayer matrix wound dressing application

30.5 Preparation of Wound Bed for Tissue Substitutes

It should be emphasized that the ulcer bed has to prepared as for skin grafting before application of tissue substitutes. The surgical principles remain the same. Contra- indications to their use include clinically infected ulcers, ulcers with sinus tracts, hypersensitivity to bovine/porcine derivatives or other additives. All storage condition requirements and instruction for use must be followed. Use of disinfectants may interact with certain preparations. Excessive exudate or wound haematoma may displace the tissue substitute and as with skin grafts, application of continuous negative pressure (vacuum therapy) may be helpful. In a recent systematic review of 17 randomized clinical trials conducted between 1996 and 2014, Santema et al. showed that skin substitutes increase complete healing rates after 6–16 weeks. No tissue substitute has however been shown to be superior to the others in promoting wound healing [1]. The investigators identified a number of drawbacks with clinical trials on tissue substitutes. Most studies had industry backing, blinding was not possible because the tissue substitutes could be visually identified and there was lack of uniform reporting standards.

The main goal of treating diabetic foot ulcers is to prevent lower limb amputations. Therefore this should be main outcome parameter of trials evaluating the new therapies. However, this requires a long-term follow-up to provide evidence on ulcer recurrence and the occurrence of lower limb amputations. The majority of the trials report ulcer size reduction as evidence of therapeutic efficacy, but for long term prevention of ulceration, the ulcer needs to heal and recurrence of ulceration prevented to reduce the risk of amputation.

30.6 Current Practice Guidelines

The Society for Vascular Surgery (SVS) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine guidelines on diabetic foot

management recommend biologics as adjunctive therapy when diabetic foot ulcers (DFUs) fail to show improvement(>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy. It is important to ensure that offloading was implemented, bioburden and exudates were controlled and vascular supply optimised before starting any adjunctive therapy. Specific recommendations for tissue substitutes are:

a) Living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix should be used for the treatment of DFUs when recalcitrant to standard therapy [2].

b) Extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue should be used as an adjunctive therapy for DFUs when recalcitrant to standard therapy [2].

However, the International Working Group of the Diabetic Foot(IWGDF) in their guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes did not recommend their routine use [31].

30.7 Cost Effectiveness of Skin Substitutes

The economic burden of non healing ulcers is high and includes costs of continued wound care, management of osteomyelitis, amputations and increased morbidity after amputation [26, 32, 33]. Healing of refractory ulcers is expected to reduce expenditure on all these significant health issues. The cost of tissue substitutes is high, but cost effectiveness studies have shown that the initial expenditure may be offset by savings in the long term due to increased ulcer-free time and a lower amputation rates.

Redekop et al. showed that treatment with Apligraft plus good wound care for DFUs results in 12% reduction in costs during first year of treatment compared to good wound care alone [26].

Gilligan et al. showed the cost-effectiveness of extracellular matrix (ECM) relative to human fibroblast-derived dermal substitute (HFDS) on diabetic foot ulcer (DFU) wound closure. Over 12 weeks, the expected cost per DFU was $2522 (£1634) for ECM and $3889 (£2524) for HFDS [33].

30.8 Conclusion

A number of tissue substitutes are commercially available and many others are in development. The true value of tissue-engineered skin products has not been realised as yet.

Evidence supporting their use is not strong enough to justify their use as primary treatment but they can offer a valuable adjunctive therapy. Further advances are needed to enhance their clinical efficacy as well as improve their cost effectiveness.

The ultimate goal is to have an off-the-shelf, complete full-thickness skin replacement.

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Part IV
Infected Diabetic Foot Including Osteomyelitis

Chapter 31
Introduction to the Infected Foot: Limb Salvage Pathway and Algorithm

Michael E. Edmonds, Bauer E. Sumpio, and Nina L. Petrova

31.1 Background

A separate section has been devoted to the infected foot because it is the greatest cause of tissue necrosis and tissue loss in the diabetic foot. It is important for the health care professional to have a working knowledge of diabetic foot infection and its management (Chap. 32). Infection plays a crucial role in the natural history of the diabetic foot, complicating ulceration in the neuropathic foot, the Charcot foot and the neuroischaemic foot (Chap. 33). Osteomyelitis in the diabetic foot results from a soft tissue infection that spreads into the bone, involving first the cortex and then the marrow (Chap. 34). Underlying osteomyelitis is seen in 15% of patients with diabetic foot ulcers, and in 20% of patients with diabetic foot infections [1, 2].

It is estimated that 40–80% of all diabetic foot ulcers develop an infection at some time, leading to poor outcomes. A 12-month prospective observational study of clinically infected diabetic foot ulcers indicated that the healing incidence at 1 year was only 44.5% once wound infection had developed [3]. Up to 58% of diabetic foot ulcers are already infected at initial presentation to a diabetic foot clinic and one-third of these present with both infection and peripheral arterial disease [4, 5]. Peripheral arterial disease predisposes to the occurrence of infection and also makes the infection more severe [6]. Diabetic foot infections with underlying

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peripheral arterial disease have a high risk of amputations which is increased by 90% compared to those without peripheral arterial disease [7, 8].

In response to the acceptance of the importance of infection, the WIfI classification has included infection as a specific component. An increase in the infection component of the WIfI score has been associated with incomplete wound healing and was an independent predictor of major amputation, re-intervention, and stenosis events in patients treated with infrapopliteal endovascular interventions [9].

31.2 Rationale for Management of Diabetic Foot Infection

Infection in the diabetic foot is a medical emergency. Signs and symptoms of infection may be minimal but nevertheless pathology proceeds rapidly. The end stage of tissue death is quickly reached and there is a limited period of opportunity for intervention. Timely intervention by the practitioner can save many diabetic feet. It is one of the greatest challenges for the health care professional to diagnose and treat infection early in diabetic patients.

At no other stage in the natural history of the diabetic foot is early diagnosis and intervention so important. Twenty four hours of untreated infection can destroy the diabetic foot. One of the most important advances in diabetic foot care has been the realisation that diabetic foot patients undergo repeated crises from the rapid onset of foot infection and need a special form of easily accessible care in the multidisciplinary diabetic foot clinic. The critical factor in saving limbs is making a rapid diagnosis of infection and administering the correct treatment early to prevent tissue destruction.

31.2.1 Step 1. Classification into Neuropathic/Charcot Foot or Neuroischaemic or Critically Ischaemic Foot

It is first important to establish whether the infected foot has palpable pulses and is an infected neuropathic foot (Chaps. 35 and 36) or an infected Charcot foot (Chap. 37) or whether the foot pulses are absent and it is an infected neuroischaemic or critically ischaemic foot (Chaps. 38 and 39) (Fig. 31.1).

31.2.2 Step 2. Grading Infection and Tissue Loss

It is important to grade infection (grade 1–3) and tissue loss (grade 1–3) according to the WIfI classification in order to give appropriate empirical antibiotics (Chap. 40).

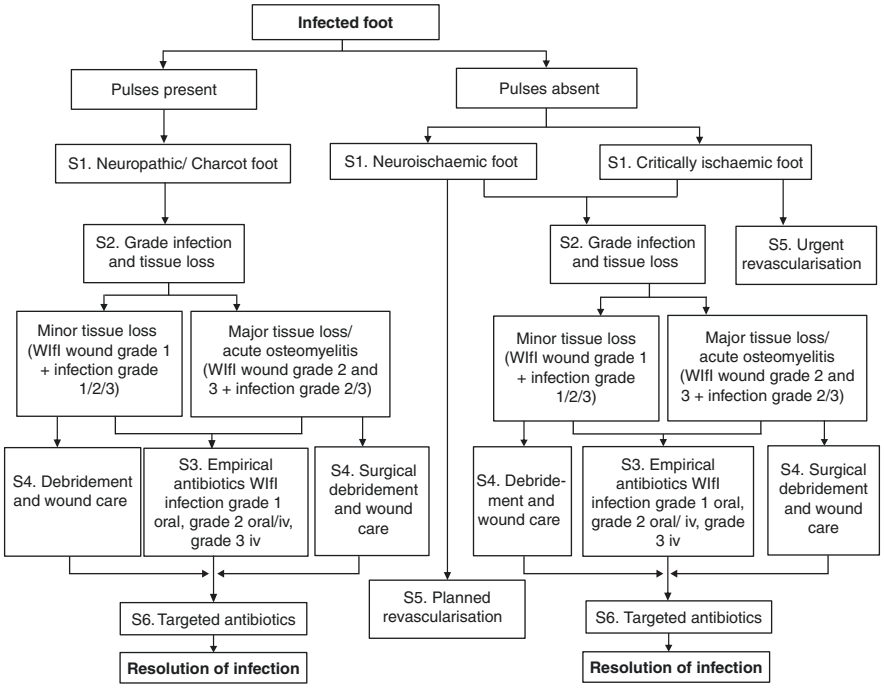

Fig. 31.1 Algorithm for limb salvage pathway of infected diabetic foot. WIfI gradings of wound, ischaemia and infection are explained in Chap. 1. The prefixed numbers (S1–6) refer to the intervention steps described in the text

31.2.3 Step 3. Commencement of Antibiotics

In both ischaemic and non-ischaemic limbs, the foot with minor tissue loss, namely WIfI wound grade 1, can be complicated with infection grade 1 (erythema < 2 cm) grade 2 (erythema > 2 cm) or grade 3 and should be given appropriate oral/intravenous empirical antibiotics (Chap. 40).

The foot with major tissue loss (WIfI wound grade 2 or 3) is usually associated with infection grade 2 or 3 and should be treated with oral/intravenous empirical antibiotics (Chap. 40).

31.2.4 Step 4. Debridement and Wound Care

This important step is debridement and wound care and it must be determined whether the patient needs scalpel debridement in the clinic or surgical debridement in the operating theatre to remove infected tissue.

The foot with minor tissue loss, WIfI wound grade 1 and complicated with infection 1 (erythema < 2 cm) or 2 (erythema > 2 cm) or grade 3 can be treated with scalpel debridement either in the clinic or operatively followed by wound care (Fig. 31.1).

The foot with major tissue loss/acute osteomyelitis (WIfI wound grade 2 or 3) is usually associated with infection grade 2 or 3 and should be treated with surgical debridement in the operating theatre (followed by wound care) as well as oral/intravenous empirical antibiotics. Such feet often need operative removal of infected sloughing tissue and also drainage of abscess (Fig. 31.1).

31.2.5 Step 5. Revascularisation

A decision needs to be made the on timing of revascularisation in the ischaemic feet. The critically ischaemic foot will need urgent revascularisation. Timing of revascularisation for the neuroischaemic foot will depend on the degree of ischaemia and the extent of tissue loss, necrosis and infection. Although the algorithm states that revascularisation can be planned, nevertheless it will need to take place promptly if there is considerable tissue loss with infection and may need to be combined with operative debridement.

31.2.6 Step 6. Change to Targeted Antibiotics

When the results of wound cultures from the foot are available, the empirical antibiotics should be changed to targeted antibiotics as determined by antibiotic sensitivities.

31.3 Conclusion

Infection in the diabetic foot is a medical emergency. Signs and symptoms of infection may be minimal but nevertheless pathology proceeds rapidly. The end stage of tissue death is quickly reached. However, early diagnosis followed by timely intervention with debridement and wound care, antibiotics and revascularisation if the infected foot is ischaemic, can save many infected diabetic feet.

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Chapter 32
Infected Diabetic Foot Including Osteomyelitis: Microbiology

Surabhi K. Taori

32.1 Introduction

In the United Kingdom, it is estimated that by 2025 more than five million people will have diabetes. Approximately 10% of people with diabetes will develop foot ulcers [1]. The incidence of culture proven osteomyelitis is around 20% [2]. Hence the problem of infected diabetic feet and consequent osteomyelitis is gradually increasing, adding to the overall healthcare burden of chronic infections.

Some bacteria are more virulent than others though microbiology results of chronic wounds can demonstrate true pathogens as well as colonizers. This, accompanied by the muted response to infection exhibited by the diabetic patient, may lead to interpretive dilemmas. In the following chapter, microorganisms commonly found in the infected diabetic wound are discussed with a view to describing their pathogenesis and clinical relevance. Classical and modern microbiological techniques and sample collection methods relevant for pathogen identification are included and followed by some antimicrobial susceptibility and stewardship issues to consider when interpreting laboratory results and formulating an antimicrobial treatment plan.

32.2 Microbial Pathogenesis

Microbial characteristics of chronic wounds: In non-immunosuppressed patients, local signs of inflammation are generally obvious and hence antibiotic therapy can be initiated if these are present. However, in diabetic patients, these signs are often

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absent till the infection becomes systemic. Hence to determine infection in a wound, it has been suggested that three microbial markers may be used to determine outcome and hence a guide to therapy if present. These are

(a) microbial load: the total number of bacteria per gram of tissue
(b) microbial diversity: the variety of different bacteria in the tissue
(c) the detection of pathogens: classical pathogens being Staphylococci, Gram-negative bacteria, anaerobes, beta-hemolytic Streptococci

A prospective cohort study [3] used culture based technology to analyse the above three factors for 77 patients every 2 weeks for up to 26 weeks for association with the outcomes of

(a) rate of healing *defined as* weeks to complete wound closure and percent reduction in ulcer surface area per week.
(b) development of complications wound deterioration, new osteomyelitis, and/or a new amputation due to diabetic foot ulcer (DFU) infection

However, their findings suggested that none of the three bioburden dimensions was significantly associated with weeks-to-closure or percent reduction in surface area per week. Ulcer duration, depth, and surface area were found to be better at predicting weeks to closure (*c*-statistic = 0.75).

Another study used 16S amplicon sequencing to characterise the microbiome of new and recurrent ulcers and found that higher microbial diversity (lower dominance statistic and higher Shannon value) correlated with lower HbA1c value and shorter duration of diabetes whereas other ulcer characteristics, including predominant genera and bacterial morphology did not show a correlation with the patient characteristics [4].

Biofilm: Biofilms are communities of micro-organisms (bacteria or fungi, mono or polymicrobial) attached to a surface, or one another, and encased within a matrix of extracellular polymeric substance (EPS). This includes derivatives from the host such as fibrin, platelets or immunoglobulins.

Chronic wound infections are especially susceptible to biofilm formation as they have a moist nutrient rich environment. Biofilms induce chronic inflammation and predispose to clinical infection. Special features of biofilms which need to be considered when managing chronic wounds are the slow growth of bacteria within the biofilm which in turn affects their response to antibiotics and tolerance to prolonged antimicrobial therapy (reported to be 1000 times more tolerant than the free living bacteria) [5]. Penetration into biofilms varies with antibiotics and commonly used antibiotics such beta lactams (including carbapenems) have reportedly low penetration. As a result, a consensus document published in 2016 recommends that patients with DFU should undergo surgical, sharp and/or mechanical debridement and the wound managed by antimicrobial dressings and antiseptic soaks [6]. Investigation for the presence of biofilm was also thought to be relevant though these tests are not routinely available in most diagnostic labs.

Microbiology: Microorganisms isolated from diabetic wounds vary from skin commensals like *Staphylococcus epidermidis* to true pathogens like *Staphylococcus*

aureus and *Streptococcus pyogenes*. However, differentiation between colonizing organisms and true pathogens is difficult but needless to say of paramount importance to ensure appropriate therapy. In addition, compared to non-immunosuppressed patients, the pathogenic potential of common colonisers in diabetic wounds is not certain. Some studies have tried to address the significance of some of these isolates but more evidence is needed.

Our understanding of the microorganisms associated with diabetic wounds and osteomyelitis is changing with the greater application of 16S ribosomal ribonucleic acid (rRNA) gene sequencing.

Incidence of pathogens in DFU and Diabetic Foot Osteomyelitis (DFO): The relative incidence of various microorganisms has been studied over the years. However, there are variations in technique of sample collection and laboratory culture which are no doubt responsible for the variation in results. For example, within anaerobic culture itself there are differences in sensitivity between various commonly used methods [7, 8]. In addition, the complement of culture media used by each laboratory may have an impact on isolation of aerobic bacteria if appropriate selective media are not used, as this may result in overgrowth of commensals like some Gram-negative bacteria, especially the swarming *Proteus spp.,* leaving Gram- positive organisms like Staphylococci and Streptococci undetected. Nevertheless, for many years, traditional culture methods have been used to determine the microbiological profile of diabetic foot ulcers and osteomyelitis. Common examples of organisms isolated are given in Table 32.1. Both Gram-positive and-Gram negative bacteria are frequently isolated but there are variations in isolates reported from different countries. For example, a large multicenter study from Turkey, using conventional culture, reported 36.4% Gram-positive organisms with *Staphylococcus aureus* the most common within this

Table 32.1 Common bacteria found in diabetic foot specimens

Aerobic bacteria		**Common examples**
	Gram-positive	*Staphylococcus aureus*
		Coagulase negative Staphylococci
		Beta-haemolytic Streptococci
		Enterococcus faecalis
	Gram-negative	*Escherichia coli*
		Klebsiella pneumoniae
		Pseudomonas aeruginosa
		Acinetobacter baumanii
		Proteus spp
		Enterobacter cloacae
		Citrobacter spp
		Serratia marscecens
		Stenotrophomonas maltophila
Anaerobic bacteria	Gram-positive	*Peptostreptococcus spp*
	Gram-negative	*Bacteroides fragilis*
Fungi		*Candida albicans*

group (11.4%) and 60.2% Gram-negative organisms (commonest *Escherichia coli* (15%)) [9]. Another study from Morocco included a mixture of diabetic foot samples and reported *Enterobacteriaceae* (31.8%) as the most frequent followed by *Staphylococcus aureus* (12.6% (including 4.7% methichillin resistant *S. aureus* (MRSA)) and non-fermenting Gram negative bacteria (11.7%) [10]. However, a recent study from the UK reported *Staphylococcus aureus* as the most common organism (detected in 40% samples by culture and 50% by PCR) in swabs taken from clinically uninfected ulcers [4]. Gram-positive organisms have also been reported as the major pathogens (58.3%) in bone samples taken from diabetic foot osteomyelitis [11]. It is possible that these differences are related to the warm climate in the countries which reported Gram- negative predominance [11]. However, the reported microbiological spectrum is likely to be different in the future as more studies perform panbacterial PCRs overcoming the limitations of conventional culture methods.

Staphylococcus aureus has emerged to be the most frequently isolated organism among diabetic feet regardless of the type of sample or clinical syndrome. In the following section, salient features of some important microbes with relevance to diabetic foot infections including osteomyelitis will be discussed.

1. *Staphylococcus aureus* including MRSA: it is estimated that *S. aureus* is a colonizer of 30% of the population mostly in the nose but also skin, perineum, and pharynx and rarely the gastrointestinal tract, vagina and axillae [12]. Although *S. aureus* can cause many serious infections like infective endocarditis, septic arthritis, prosthetic joint infection, intravascular catheter infections, pleuro-pulmonary infections, meningitis and epidural abscesses, its pathogenic potential to cause skin and soft tissues infections and osteomyelitis is of particular relevance to this review.

   Leukocytes are the major agents of defence against this organism. In addition to the impaired function of these cells in patients with poorly controlled diabetes, the pathogen itself has features which enable it to escape their attack: blocking chemotaxis, sequestering host antibodies, polysaccharide capsule (biofilm) formation to protect against host defences and to resist destruction after ingestion by phagocytes.

   Regardless of the type of osteomyelitis, *S. aureus* is still the commonest pathogen identified.

   A non-systematic review of diabetic foot infection (DFI) studies reported that the unweighted proportion of all bacterial isolates from DFI that were *S. aureus* was 30% (19% MSSA 11% MRSA) [13]. Although there is considerable variation in literature on the outcomes of DFI caused by MRSA, it has been reported that, compared with MSSA it may be associated with a significantly higher body temperature and total leukocyte count and a longer healing time after surgical treatment, although not associated with significant difference in limb salvage rates [14].

   Significant virulence factors which contribute to the pathogenicity of *S. aureus* are discussed below.

   (a) Panton Valentine leucocidin (PVL toxin): This a toxin which causes lysis of white blood cells. A recent metanalysis also found that PVL producing

strains are strongly associated with skin and soft-tissue infections, as opposed to pneumonia (OR 0·37, 95% CI 0·22–0·63), bacteraemia (0·10, 0·06–0·18), or colonising strains (0·07, 0·01–0·31) and that surgical interventions are more likely in skin and soft-tissue infections with PVL producing *S. aureus* strains than non PVL strains [15]. The quantity of PVL produced in vitro by a strain of *S. aureus* does not seem to correlate with the severity of illness. Similarly, the ability of a strain to cause invasive infection in animal models does not seem to be correlated with PVL production independent of the strain type [16].

(b) Alpha haemolysin: This toxin plays a role in cell lysis cells and helps in penetration into keratinocytes [17]. It is associated with skin and soft tissue infections but in contrast to PVL, the quantity of alpha hemolysin produced does appear to correlate with the severity of infection at least in sequence type 93 (ST93) MRSA [18]. The finding that skin disease with *S. aureus* strain SAP149 was attenuated after vaccination against alpha haemolysin in mice shows the potential for future development of preventative strategies [19].

(c) Phenol soluble modulins (PSM): These also lyse human cells and their proteolytic products facilitate *S. aureus* colonization and dispersion on skin. In vitro levels of PSM appear to be higher in MRSA strains associated with severe skin and soft tissue infection as compared to strains isolated from other clinical infections [20].

(d) Small colony variants (SCV): These are small, intracellular, metabolically curtailed versions of bacteria which have been described in Staphylococcal infections for more than a century. They may be identified as "dwarf" colonies on agar plates and exhibit slow growth. Studies have also described them to have downregulated some virulence genes whereas others like those associated with biofilm formation and adhesion maybe upregulated [21]. They have been reported from various chronic infections such as cystic fibrosis, prosthetic joint infections, prosthetic valve endocarditis and osteomyelitis. Of particular significance in chronic osteomyelitis, one study evaluating *S. aureus* virulence factors associated with chronic infection found that, following host cell invasion, there is a higher percentage of SCV formation [22]. Species other than *S. aureus* are also known to have SCVs and these include coagulase negative staphylococci, *Pseudomonas aeruginosa*, Enterococci, Enterobacter and *E. coli*. A recent review has detailed the significance of SCVs in chronic and persistent infections [23].

(e) New bacterial genes are being investigated for their association with infections as genetic research advances. For example, *agr* (a regulatory gene), *sasX* and the ACME genetic locus have been associated with greater pathogenicity in Staphylococcal infections [24].

(f) With reference to osteomyelitis, *S. aureus* is able to evade natural host defenses to bone infection by expressing surface proteins (adhesins) which facilitate bacterial adhesion to bone. *S. aureus* is also able to form biofilms, especially on prosthetic material, which protects the bacterial cells from host defenses and even common antibiotics.

Clinical studies have looked into the virulence factors of *S. aureus* from various infections. Kalika et al. [22] examined 41 *S. aureus* isolates and found that high host cell invasion rate, low cytotoxicity and the ability to persist and adapt within osteoblasts was a feature of chronic osteomyelitis isolates whereas those from both acute and chronic osteomyelitis strongly produced biofilm and induced high levels of host cell inflammation.

2. Coagulase negative Staphylococci (CoNS): This is a group of Gram-positive bacteria which although identical to *S. aureus* on a Gram stain differ from the latter in genetic structure, biochemical properties and virulence. Since they are similar to each other in pathogenicity and most are skin commensals, they are often referred to as a group. The classification between coagulase-positive and coagulase-negative is historical from a time when the coagulase test was used to determine the identity of *S. aureus*. Common species in this group are *Staphylococcus epidermidis* and *S. haemolyticus. S. lugdunensis,* also a CoNS, has some properties similar to *S. aureus.* Other significant CoNS include *S. capitis*, *S. hominis*, *S. simulans*, and *S. warneri.* In general CoNS are considered pathogens of low virulence which do have propensity to cause device associated infections due to their ability to biofilm and adhere to prosthetic materials. Non-prosthetic associated infections do occur in a select group of patients, examples being native valve endocarditis, bloodstream infections in premature neonates and neutropenic patients. A high proportion are methicillin resistant and resistance to glycopeptides is increasing [25].

   In microbiological studies of DFO and DFU, CoNS are commonly identified but the incidence varies with the methodology. Some laboratories do not report CoNS from superficial samples and hence concordance with deeper tissues varies. As a result, the clinical significance of CoNS is not well understood. A study comparing the differences between DFO cases where *S. aureus* or *S. epidermidis* was the sole pathogen identified found that the latter was less common in acute OM but more likely to be associated with long standing ulcers and shorter time to healing. However as the number of cases with *S. epidermidis* were low (11 cases) more studies are needed to substantiate these findings [26].
3. Streptococci: This is a large group of Gram-positive bacteria which appear arranged as chains on the Gram stain. They are further classified on the basis of haemolysis produced when cultured on blood agar into alpha, beta and gamma (non- haemolytic) Streptococci. Following recent reclassification, bacteria formerly considered *Streptococcus* have been reassigned into the genera Enterococcus and Lactococcus. Beta-haemolytic Streptococci are further classified on the basis of Lancefield group types. Although most beta-haemolytic Streptococci can cause severe infections, one of the most virulent of these is Group A Streptococcus (GAS) also known as *S. pyogenes*. It has a wide spectrum of infections ranging from superficial infections like pharyngitis to invasive infections like cellulitis, septic arthritis, pneumonia, meningitis, abscess formation, osteomyelitis, endocarditis, peritonitis and necrotizing fasciitis the last with a mortality rate up to 32%. These bacteria possess a number of virulence factors

which enable them to attach to specific tissues (adhesins, pili,) and evade host innate immune defenses (enhanced resistance to phagocytosis, complement deposition, antibody opsonization, antimicrobial peptides and neutrophil killing mechanisms). GAS can activate complement by the internal and external pathways disrupting the coagulation system. Invasive disease is hence the result of host and bacterial factors which once activated can cause severe tissue destruction, vascular leakage and an excessive inflammatory response. It is important to be aware that Group B, C, E, F and G Streptococci can also cause severe infections in the diabetic foot. Although capable of severe disease, most beta-haemolytic Streptococci (especially GAS) are some of the few bacteria still universally susceptible to Penicillin although resistance to macrolides, tetracyclines and quinolones can occur [27]

Streptococcus pneumoniae is perhaps the most virulent of the alpha haemolytic Streptococci. A classic pathogen of respiratory tract infections, it can however, cause wound infections and has been reported from diabetic feet.

4. *Pseudomonas spp*: *Pseudomonas aeruginosa* has been often reported among the top three commonly isolated organisms in diabetic wounds. Being a biofilm producer, its role in chronic wounds has an obvious association. However, it appears that there are more virulence factors in this organism which predispose its affinity to diabetic feet. When non-biofilm producing Pseudomonas mutants were tested on diabetic mice they were able to persist longer than in non-diabetic wounds. The bacterial burden in diabetic wounds was also higher than in normal wounds ($n = 18$, $p < 0.0001$) [28]. This study demonstrated that *P. aeruginosa* can establish persistent diabetic wound infection independent of its ability to form biofilms in a manner that primarily depends on its type III secretion system to inject effector proteins into host cells as part of its virulence.
5. Enterobacteriaceae: This family of Gram-negative bacteria contains some of the most frequently isolated pathogens in diabetic foot ulcers. It includes organisms in the genera *Escherichia, Klebsiella, Enterobacter, Salmonella, Proteus*, etc.

   According to a recent study, patients with culture confirmed osteomyelitis with Gram-negative bacteria in pure or mixed cultures were more likely to have osteomyelitis following traumatic wounds, and surprisingly, those with glycated haemoglobin <7%. It also reported that that these patients were likely to have more severe local signs such as fetid odor, necrosis soft tissue infections, and systemic signs such as leukocytosis at presentation [11].

   The emergence of Extended Spectrum beta-Lactamase (ESBL) and carbapenemase enzymes in Gram-negative bacteria have made therapeutic options very limited due to multidrug resistance often carried together on mobile genetic elements. One recent study from a country endemic for such bacteria reported an incidence of 31% carbapenemase producing Enterobacteriaceae (CPE) among the Gram- negative bacteria from diabetic foot ulcers [29]. CPE are resistant to carbapenem antibiotics and treatment options are often limited to colistin, aminoglycosides, fosfomycin or the new agent ceftazidime-avibactam, preferably in combination therapy. However, pan-drug resistant strains are also emerging [30, 31].

6. Fungi: In a recent study [32], a total of 384 specimens were collected from 100 diabetic foot ulcers from 100 patients and the fungal component of diabetic foot ulcers (mycobiome) was studied by sequencing the hypervariable internal transcribed spacer 1 (ITS1) region of the eukaryotic rRNA cistron. The composition of the mycobiome varied between patients and between each visit in the same patient. However, at the first visit study visit (baseline), *Ascomycota* were detected in significantly greater relative abundance ($P = 0.017$) in wounds that ultimately healed in >8 weeks compared to those that healed in <4 weeks. Also worth noting, but not unexpected, is that conventional culture yielded fungi in 5 patients as compared to in 79 patients by the molecular method. These finding suggests that there may be differences in patient outcomes linked to particular species and further work is needed to establish their true significance. A large quantity of molecular microbial data is available now but its interpretation will still require time honoured clinical correlation and follow up.
7. Anaerobes: Frequently reported among diabetic wounds, these bacteria are difficult to grow in the laboratory, requiring special incubation conditions with reduced oxygen. In a recent systematic review to determine the incidence of anaerobes in infected diabetic wounds, the authors reported an unweighted average of anaerobic pathogens in the included studies to be 11% of all isolates (weighted average 7.7%, range 0–79% median 4%) [33]. This very wide range may be because to many anaerobe species even brief exposures to air can be toxic and they can also be quite susceptible to the antibiotics commonly used to treat diabetic infections. In addition, if special anaerobic culture media are not used, then facultative anaerobes like Enterobacteriaceae may overgrow the anaerobes and the latter would then be missed. Hence the importance of proper timing and technique of sample collection, transport, medium and incubation. Of note, there do not appear to be any reports of mono-microbial anaerobic infections but again the limitations of anaerobic culture methods may have had a role to play. The authors of the review also reported that the isolation of at least one anaerobe, compared to only aerobes, increased the likelihood of lower extremity amputation (9/14 vs. 100/517; $p < 0.001$) but was not associated with the overall risk of therapeutic failure.

32.3 Laboratory Diagnosis

Sample collection: For diagnosing the etiological agents of diabetic foot infections, a variety of samples including superficial swabs, tissue, bone scrapings, bone biopsy etc. are routinely sent to microbiology labs. However, there is controversy on the correlation of swabs and deeper tissues though interpretation of results varies with the researcher and studies using stricter criteria, have reported swabs have a poor correlation with deeper tissue samples [34, 35] and with the diagnosis of osteomyelitis. Concordance

rate as low as 19% for non-bone specimens compared to a bone sample and 52% and 36% false negativity and false positivity rates respectively have been reported [36].

Diabetic foot clinicians and orthopaedic doctors often inquire how much bone sample is adequate for getting reliable results. To answer this question, it is worth remembering that most microbiology labs are not equipped to culture whole feet or even very large pieces of bone. The tools of the microbiology trade are swabs, scalpels and inoculation loops which cannot dissect large masses of human tissue especially those as hard as bone. The sample most likely to provide a useful result is that which is most representative of the infected zone. Radiologically guided percutaneous bone biopsies are ideal. However, since osteomyelitis in diabetic feet is often accompanied by ulcers or exposed bone in need of debridement, an open biopsy is often a more efficient use of resources. Hence, if a radiological image of the part has been carried out, taking this as guidance, multiple small biopsies obtained from the infected area and transported to the lab rapidly in adequate medium would have the best chance of growing significant organisms. If a large sample mixed with healthy and infected tissue is sent to the lab, the scientists would be dependent on visual identification of the infected area and may miss the area of infection. Multiple biopsies transported separately are recommended, especially if infection is associated with a prosthetic device. This is to help differentiate external contamination if only a minority of samples yield a potential environmental organism.

Timing of the sample with respect to antibiotic administration is an important consideration to get the best yield of pathogens. Where possible, antibiotics should be withheld before sampling. If antibiotics have been previously administered consideration should be given to stopping antibiotics for one-two weeks before sampling, if the clinical situation permits and a chronic osteomyelitis is suspected. Samples should be taken in duplicate and simultaneously tested for histopathology [37].

Routine laboratory testing: Culture still remains the mainstay of routine microbiological diagnosis for DFI although molecular methods are being used extensively for other infections. Guidelines recommend the inclusion of blood agar (non-selective medium for all pathogens), MacConkey's agar (selective medium for Gram-negative bacteria), anaerobic culture plate and a fungal culture medium (most commonly Sabouraud's agar) to cover the spectrum of pathogens which commonly cause infections in diabetes. Most laboratories choose to select which pathogens are reported [38]. In addition, the number of organisms likely to grow from a swab include environmental commensals colonizing the wound as well as true pathogens. Hence, to aid interpretation and make the best use of resources, only true pathogens or otherwise isolates of significance may be reported to species level from such samples. These include *Staphylococcus aureus*, beta-haemolytic Streptococci, *Streptococcus pneumoniae* and Gram-negative organisms such as pseudomonas and Enterobacteriaceae. Others such as Candida, anaerobes and coagulase negative staphylococci may be reported only to genus level. In addition, the almost universal susceptibility of anaerobes to metronidazole means that most laboratories may choose to report only this antibiotic.

For better quality samples such as deep tissue or operative bone biopsy collected after superficial debridement all microbiological growth is generally reported, identified to species level with full antimicrobial sensitivities.

32.4 Interpreting Antimicrobial Susceptibility Reports

Determining the susceptibility of bacteria to antimicrobial agents is one of the most essential functions of a microbiological laboratory. However, the tests performed are mostly classical phenotype based tests where the performance and reliability varies with the type of test, person performing it and indeed the organism itself. To complicate matters further, the phenotypic susceptibility does not always correspond to the actual resistance potential of a bacterium (presence of resistance genes) and various indicator antimicrobials are used in an attempt to deduce these complex mechanisms. For example, extended spectrum beta lactamase (ESBL) producing Gram-negative bacteria may appear susceptible to many third generation cephalosporins but their use may lead to therapeutic failure. Hence a special combination of beta lactam and beta lactam + beta lactamase inhibitor combination is used to determine if there is significant enhancement of inhibition by the latter. If such is found, the susceptibilities of relevant cephalosporins would either be suppressed or reported as resistance. Similarly, *Staphylococcus aureus* susceptibility to methicillin cannot be tested directly due the labile nature of the antibiotic. Hence oxacillin is used as a surrogate and molecular detection of mecA gene or the corresponding resistance mediating protein PBP2a may be required if in doubt. In addition, there is full or partial cross resistance between certain antibiotics (example *S. aureus* and macrolides) and others may define susceptibility for a group of antibiotics (example Penicillin and *Streptococcus pyogene*s). It is for such reasons microbiological reports require a high level of interpretive skills and selective reporting is often practised. Involving a microbiologist in patient management is likely to improve physician understanding of susceptibility results.

32.5 Development of Resistance

Resistance development to commonly used antibiotics while a patient is on treatment has been described. Detailed case reports for such instances for tigecycline and ertapenem in *Klebsiella pneumoniae* [39, 40] have examined the molecular characteristics of serial isolates and hypothesized that antimicrobial pressure in these patients was likely responsible for inducing antimicrobial resistance in the same strain. This could be induced by the use of the antimicrobial to which the organism developed resistance or other unrelated antibiotics.

Other mechanisms include the selection of resistant strains in a mixed population of susceptible and resistant strains by destruction of the former by antibiotics. The use of antimicrobials in dairy and animal farming has also been described to drive the levels of resistance [41]. Antibiotic resistance can also spread from bacteria to bacteria by genetic transfer via plasmids, transduction or transformation. Resistance strains can be transmitted over geographical areas as a result of travel, CPE and drug resistant *M. tuberculosis* being classic examples.

32.6 Modern Molecular Methods in Diagnosis and Infection Research

Traditional microbiology has been dependent on visualizing bacteria under the microscope and interpreting their characteristics after growth on agar plates. Since the incubation period required for most pathogenic bacteria to be detectable is 18–20 h, it can take on average 2–3 days before a final result is available. The emergence of molecular methods of detection, including rapid genome or proteome based tests, has considerably reduced the turn around time for microbiological identification. In addition, their use as a research tool has improved our understanding of infections in a way which was unimaginable a few decades ago. However, since molecular tests often come with an enhanced cost, their application in routine practice needs to be justified by demonstrable clinical benefit. Detailed reviews are available elsewhere [42] but some advances in technology are summarized below.

1. Target amplification by Polymerase Chain Reaction (PCR): This technique involves the detection of the presence of a fixed region of the bacterial genome. It is useful when a single or a few known pathogens are being sought. When applicable, real time PCR allows for quantification of the target pathogen in a given sample. The application in DFI can be limited due to the mixed organism profile and multitude of possible pathogens.
2. Proteomics: The identification and quantification of the total proteins in a given organism is considered a more specific marker for the metabolic characteristics than detection of the genome. This technology has been applied in Matrix Assisted Laser Desorption/ Ionization Time of Flight Mass Spectrometry (MALDI- ToF MS) allowing rapid identification of organisms based on their individual protein profiles. This has resulted in faster turn-around time in identification but still requires a culture based step before results can be reliable.
3. DNA target sequencing: The exact sequence of the DNA in a small part of the genome or indeed the entire genome can be identified by this method. It is useful in identifying unknown organisms as well as other characteristics like genotype. There have been studies applying these methods in DFI but use in routine DFI diagnostics is not yet widespread.
4. Population based studies (Microbiome and metagenomics). The term “microbiome” (in use since 2001) is used to define the collection of genes of all the micro-

bial cells harboured by an individual [43]. The ability to generate large genomic sequence at a rapid rate and cheap cost and the computation ability to interpret this data now allows us to analyse entire bacterial populations without requiring a culture based step. This process of sequencing en masse of total DNA extracted from a microbial community, is called metagenomics.

Apart from many other uses across the spectrum of medicine, this is perhaps the single most technological advance which has the potential to revolutionize the way DFI are diagnosed and change our understanding of diabetic foot microbiology. Previous culture based studies limited by bacteria being either uncultivable, difficult to culture or undetectable due to small numbers in a mixed culture can now be performed without this drawback. However, since the technology is in relative early stages and still expensive, its full impact on DFO/DFI is yet to be determined.

Summary: The microbiology of DFU is a complex science. Although a lot of research has been done, we still have many questions to answer. The polymicrobial nature of these wounds, limitations in culture based tests, chronic antimicrobial use and pathophysiology of the diabetic patient have limited our understanding of these conditions when compared to many other clinical infections. However, with advances in molecular diagnostics, knowledge is expanding. Comprehensive understanding of microorganisms and microbial ecology in the diabetic wound is now possible which accompanied by well-designed trials has the potential to improve patient outcomes.

Antibiotics and Antimicrobial Stewardship: The duration of antibiotics for the treatment of osteomyelitis in the diabetic patient has been a subject of much controversy. The NICE guidelines [1] recommend a prolonged course of antibiotics up to 6 weeks. Most authorities agree with 1–3 week course if all infected bone is resected. However, the practice on duration of antibiotics in cases where no surgical debridement has been performed is variable. The IDSA guidelines suggest a course of 3 months whereas the IWGDF suggest a maximum of 6 weeks in the absence of surgical debridement [44, 45]. Evidence is limited by the tendency of the research design to compare 3 or more months of therapy with combined medical and surgical measures. A recent small randomized controlled trial (37 patients) compared up to 3 months of antibiotic therapy alone with a combination of limited resection of bone followed by 10 days of antimicrobials and found no significant difference between wound healing, re-ulceration or other complications [46]. The patient population however was limited to those without vascular complications, necrosis or hind-foot lesions. Based on this study it appears that if patients are selected carefully, similar outcomes may result with either strategy.

Another study compared the outcome of antibiotic duration (6 weeks vs 12 weeks) in a group of carefully selected patients also without vascular and hind-foot complications who were treated without major surgical intervention and found no significant difference in the outcome measures of remission and sustained healing of the wound [47]. However, the side effects were significantly larger in the group with longer therapy though overall remission was 65%

suggesting if patients are adequately selected, there may be good outcome with shorter courses of antibiotics. However, these findings cannot be applied to the more complex group of patients with vascular disease and/or hindfoot disease who may fail antimicrobial therapy alone. Current recommendations by the IWGDF advise medical treatment alone only in patients who are either medically unsuitable, foot mechanics unstable, surgery unavailable or too costly and infection is in a small area in only the forefoot.

Antimicrobials have always been the cornerstone of managing severe infections. However, bacteria have an incredible ability to adapt and become resistant especially to frequently used antibiotics. Unfortunately, the number of new antibiotics being developed are very few. The number of multidrug resistant bacteria is rising but the ability to counteract them is not. Hence it is imperative that susceptibility to currently available antibiotics is conserved for as long as possible. Towards this end there are a number of international initiatives [48–50] which are extremely relevant especially since multidrug resistant organisms such as MRSA, CPE *Candida auris* are being increasingly reported from infected wounds in patients with diabetes [51]. The WHO has laid out five objectives [48] in its strategy published in 2015 summarised below

1. Improve awareness and understanding of antimicrobial resistance through effective communication, education and training
2. Strengthen the knowledge and evidence base through surveillance and research
3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures
4. Optimize the use of antimicrobial medicines in human and animal health.
5. Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

Although all the above points are relevant to clinical medicine, awareness, optimisation of antimicrobials and infection prevention measures are perhaps more easy to operationalise. The Classical document published by Public Health England "Start Smart then Focus" [52] lays out a plan which can be implemented at a local level (see Fig. 32.1). The application of this strategy in the management of chronic wounds and osteomyelitis in the diabetic patient can be in multiple aspects of diagnosis and treatment.

- Locally agreed guidelines for empirical management of osteomyelitis will allow the best possible broad spectrum initial therapy and guidance on collecting appropriate samples. Such guidance also serves as an easy reference tool to maintain consistency of practice.
- Appropriate samples are essential and hence a deep tissue or bone sample collected in an aseptic manner after debridement of superficial tissue ideally after a period of antimicrobial abstinence is likely to reduce the isolation of environmental contaminating bacteria to avoid overuse of antibiotics and targeting the therapy towards true pathogens.

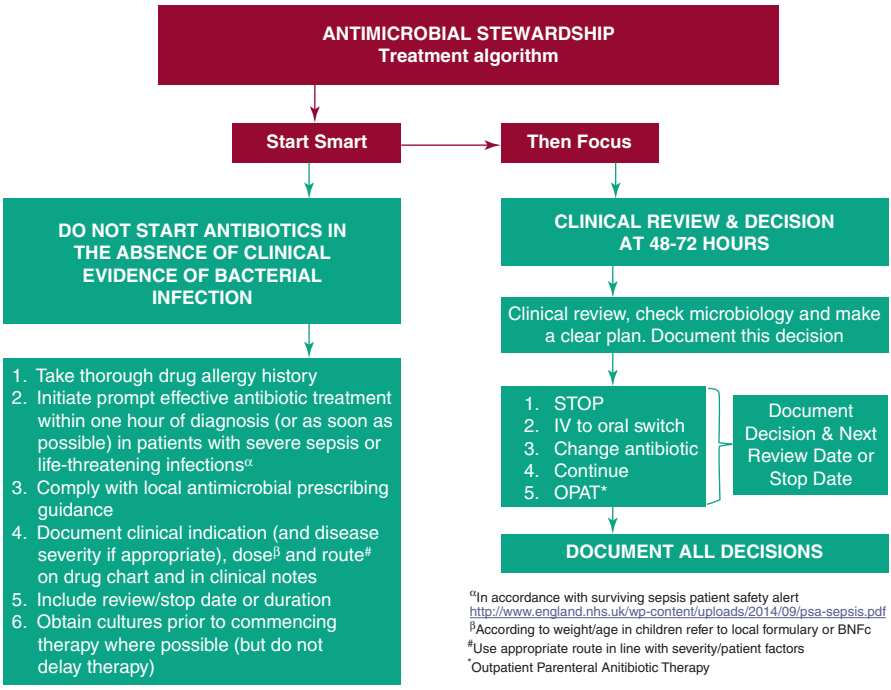

Fig. 32.1 Summary of the antimicrobial stewardship implementation plan from Start Smart then Focus [51]

- Appropriate laboratory communication and reporting of antimicrobial sensitivities is relevant in ensuring the right test is done and most appropriate antimicrobials are tested for the patient's condition. Often laboratories following a selective reporting strategy will tailor the report based on the sample and information provided (including drug allergies).
- Correct diagnosis is important to ensure the right type and duration of antibiotics. However, with respect to chronic osteomyelitis, there is a need for greater evidence and consensus on duration of antimicrobials especially if surgical management is not an option.
- Documentation of antimicrobial plans are relevant in ensuring appropriate reviews at recommended intervals and continuity of care. A key aspect of the antimicrobial stewardship is a review at 48–72 h after starting empiric antibiotics to facilitate rationalisation to the least broad spectrum antibiotic once microbiological culture results are available.
- Multidisciplinary teams comprising vascular and diabetic practitioners, podiatrists, microbiology or infectious disease physicians and pharmacists are recommended to ensure that prompt reviews of the patient's condition take place at regular intervals and specialist knowledge is available especially for difficult to treat cases. It has been recommended that infection specialists be consulted when

cultures show multidrug resistant organisms or a mixture of organisms, if there is substantial renal impairment, or response to appropriate medical or surgical therapy is not within the expected timeframe [53].

- Surgical intervention at the earliest possible opportunity is vital to prevent unnecessary long courses of antibiotics, the oversight of which unfortunately promotes the side effects of prolonged therapy including, low bacterial yield of surgical samples, vascular access device associated infections, *Clostridium difficile* infection, delayed rehabilitation and increased hospital stay.
- In the presence of concomitant wounds, similar principles as above apply. However, differentiation between superficial colonisation and true infection is paramount. Diagnosis can be more challenging due to suppression of classical signs of inflammation, hence including 'secondary' or 'intermediate' signs of wound infection, such as friable or altered granulation tissue, pocketing, unpleasant smells, and undermined ulcers may be important to observe. Diagnostic uncertainly and clinician fear of failure of therapy may lead to unnecessarily long antimicrobial courses. These are issues which may be addressed by rapid diagnostic tests, development of reliable biomarkers along with clinician and patient education [54].

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Chapter 33
Presentation of Infection

Michael E. Edmonds, Elizabeth Pendry, Ian Alejandro, and Ines Reichert

33.1 Introduction

All health care professionals looking after diabetic patients should understand that infection is one of the great threats to the diabetic foot and uncontrolled infection is the main destroyer of tissue in the diabetic patient especially in the lower limb. Nevertheless, if infection is diagnosed early and treated actively, such tissue destruction can be prevented. This is the great challenge for health care professionals who care for diabetic patients.

This chapter will discuss the impact of infection, the susceptibility of diabetic patients to infection and the presentation of infection.

33.2 Impact of Infection

The diabetic foot is highly susceptible to infection which can spread rapidly leading to overwhelming tissue destruction and this may result in the need for amputation. Diabetic foot infections are one of the most frequent reasons for diabetic patients to be admitted to hospital in the United States, accounting for 20% of all hospital admissions [1]. Readmission rates for patients with diabetic foot infections are approximately 40% and nearly one in six patients die within 1 year of their infection [2].

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33.3 Predisposition to Infection

Two of the great pathologies that afflict the lower limb of the diabetic patient, neuropathy and ischaemia, render it susceptible to the third pathology namely infection, which is an important complication of the neuropathic foot and the Charcot foot. Also, diabetic patients who present with infection often have peripheral arterial disease and the combination of infection and ischaemia can lead to a high amputation rate.

The Eurodiale study demonstrated a significant interaction between peripheral arterial disease and infection in the diabetic ischaemic foot. A consortium of 14 European centres carried out a prospective data collection study, in which patients with a diabetic foot ulcer were followed until healing. Data was obtained on 1229 consecutive patients with diabetes and a new foot ulcer [3]. Within 1-year follow-up, 77% of the 1088 patients healed, 5% underwent a major amputation, 6% died and 11% remained unhealed. After categorising patients according to the presence or absence of both peripheral arterial disease and infection, significantly worse outcomes were noted in patients with both peripheral arterial disease and infection [4]. Thus the combination of ischaemia and infection had a major impact on both healing and major amputation and indicated the existence of a significant interaction between peripheral arterial disease and infection.

The underlying susceptibility to infection results from an immunopathy which causes both a reduced local and systemic response to infection. A central pillar of immune function is effective neutrophil microbial action which depends on the generation of several oxygen-derived free radicals. These toxic species, which include the superoxide anion, are formed during the respiratory burst which is activated after chemotaxis and phagocytosis. In diabetes, especially if it is poorly controlled, there are deficiencies in neutrophil chemotaxis, phagocytosis, superoxide production, respiratory burst activity and intracellular killing [5]. Neutrophil phagocytosis is significantly reduced in patients with poorly controlled diabetes, and improvement of microbiocidal rates has been directly related to correction of hyperglycaemia [6]. Local signs of infection may often be markedly diminished or absent due to neuropathy and reduced blood supply to the lower limb. Also, there is a diminished systemic response to infection in diabetes. This manifests itself by a failure to produce a neutrophil leucocytosis and also by an absence of fever in response to infection [7]. Only 50% of episodes of severe infection will trigger a fever or leucocytosis and white blood count and body temperature may be normal even in severe infections.

It is important to diagnose infection early in diabetic patients. Classical symptoms and signs of infection are often absent because their expression is dependent on an intact peripheral nervous system. There must be a meticulous examination to elicit subtle symptoms and signs which are clues to infection. All practitioners looking after diabetic feet should understand this and appreciate how neuropathy makes the diagnosis of infection difficult.

33.4 Presentation of Infection

Every diabetic patient with a foot ulcer should be assessed for the presence of infection. The most common manifestation is cellulitis, which is defined as an infection of the skin and subcutaneous tissue and presents as redness or erythema.

Clinically, three distinct stages of diabetic foot infection may be recognised:

- Infection of the ulcer itself, namely local infection with cellulitis less than 2 cm from the ulcer
- Infection with cellulitis spreading more than 2 cm from the ulcer, referred to as spreading infection
- Infection extending into the subcutaneous tissues such as fascia, bone and joint which is called deep tissue infection.

These stages of infection can be recognised in the neuropathic foot, the Charcot foot and the ischaemic foot. Each of these presentations may be complicated by osteomyelitis. The severity of infection should be properly assessed after debridement of callus and necrotic tissue, and should relate to its extent and depth and the presence of any systemic findings.

All patients presenting with clinical signs of infection should have an X-ray of the foot to detect possible

- Osteomyelitis
- Gas in the deep tissues
- Foreign body

It is usually possible to make an accurate diagnosis of infection after clinical assessment and X-rays. Further investigations may be necessary. Grey- scale ultrasound may be useful to image soft tissue infections and collections of fluids and magnetic resonance imaging (MRI) may be helpful to detect anatomical location and extent of infection.

33.4.1 Localised Ulcer Infection

This refers to infection in the ulcer bed and the immediate surrounding skin. This may present with purulent discharge and surrounding erythema. Local signs that an ulcer has become infected include:

- Purulent discharge
- Unpleasant smell
- Ulcer becomes painful
- Sinuses develop in the ulcer
- Edges may become undermined
- Bone or tendon becomes exposed

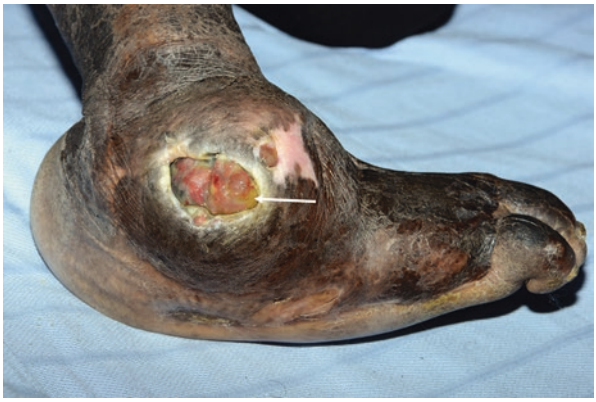

Fig. 33.1 Ulcer in a Charcot foot showing areas of yellowish discharge suggestive of infection (arrow)

However, the classical features of infection namely redness, heat, pain and loss of function may not be evident. Signs of infection may be very subtle and early warning signs should be sought in all diabetic patients especially in those with breaks in the skin. The base of the ulcer may simply change from healthy pink granulation to yellowish or grey tissue and becomes moist (Fig. 33.1).

Moist, green or yellow slough indicates infection. Pain associated with a neuroischaemic ulcer may be due to the ischaemia itself or to infection. The degree of pain will depend on the severity of concomitant neuropathy. Oedema around an ulcer is usually suggestive of infection but may be related to ischaemia. Diffuse redness of the surrounding tissues may indicate infection, especially if this is associated with oedema and purulent discharge.

33.4.1.1 Tenderness

This should be elicited by gentle palpation and may be due either to infection or to ischaemia.

33.4.1.2 Odour

Any odour associated with an ulcer is suggestive of infection.

33.4.2 Spreading Infection

In this stage, bacterial invasion has progressed to give signs of spreading infection at least 2 cm from the ulcer such as diffuse extending erythema (Fig. 33.2), oedema, lymphangitis (Fig. 33.3) and lymphadenitis in addition to local signs of infection. Systemic symptoms and signs may be present when the foot has extensive diffuse

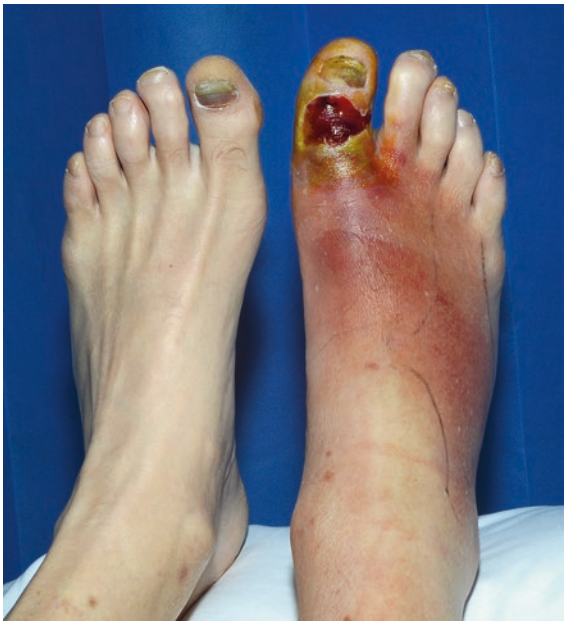

Fig. 33.2 Diffuse spreading erythema from infected right first toe. Lines demarcate extent of cellultis

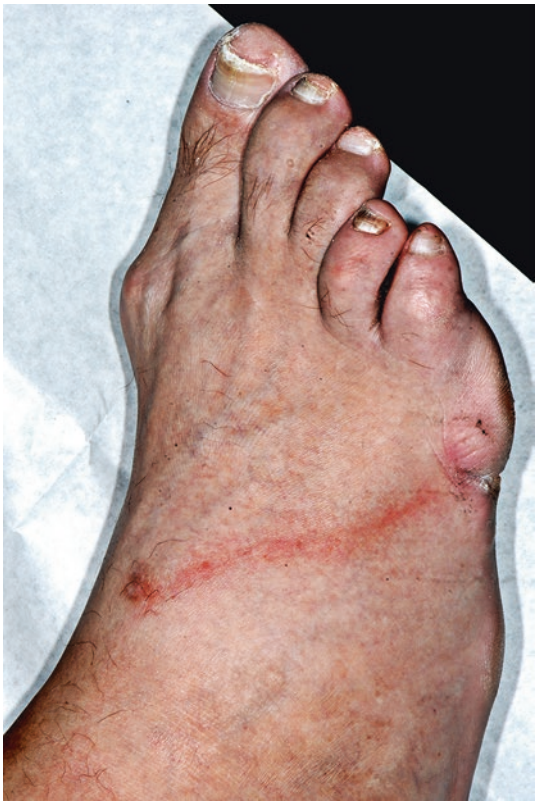

Fig. 33.3 Lymphangitis (shown as a red line) spreading over dorsum of foot from skin breakdown on lateral foot

cellulitis although there is often a reduced systemic response to infection in the diabetic patient. The portal of entry of infection may be a corn, callus, blister, fissure or any other skin breakdown. Puncture wounds may be complicated by cellulitis. Bacteria are inoculated at the base of the puncture wound and then track back towards the surface of the skin, with infection eventually manifesting itself as a cellulitis.

It is important to note that in the pigmented (e.g. Afro-Caribbean) foot, cellulitis can be difficult to detect, but careful comparison with the other foot may reveal a tawny hue. In the neuroischaemic foot, it may be difficult to differentiate between the erythema of cellulitis and the redness of ischaemia. However, the redness of ischaemia is usually associated with a cold foot, although not always so, and is most marked on dependency, while the erythema of inflammation is warm and not affected by position. Erythema also occurs in response to traumas, including insect stings. Erythematous inflammation of the feet may also be present in eczema, which is characterised by crusting and scaling. This is not seen in cellulitis.

33.4.3 Deep Tissue Infection

This refers to extensive deep soft tissue infection complicating an ulcer. In the presence of neuropathy, pain and throbbing may not be appreciated but if present, this is a danger sign, indicating serious infection within the tissues. Palpation may disclose fluctuance, suggesting abscess formation but development of a classical discrete abscess is rare in the diabetic foot because poor white cell function cannot localise the infection to produce an abscess. Many practitioners are unaware of this and feel that the only indication for operation is fluctuance with abscess formation. However, surgery is indicated for generalised sloughing of the ulcer and surrounding subcutaneous tissues which eventually liquefy and disintegrate and need removal by surgical debridement (Fig. 33.4).

Severe infection can also present as a bluish-purple discoloration caused by inadequate supply of oxygen to the soft tissues (Fig. 33.5). This results from increased metabolic demands of infection and a decrease of blood flow to the skin, as a result of a septic vasculitis of the cutaneous circulation. Blue discolouration can occur in either the neuropathic or the ischaemic foot, particularly in the toes, and in the ischaemic foot should not be inevitably attributed to worsening ischaemia due to large vessel disease. Severe infection leading to a septic vasculitis can result in bulla formation and wet digital necrosis. (Fig. 33.6 a, b) In severe cases of infection, bluish–purplish discolouration of the skin often appears as purple blebs indicating subcutaneous necrosis. Severe subcutaneous infection by Gram-negative and anaerobic organisms produces gas, which can be detected by palpating crepitus and which can be seen on X-ray (Fig. 33.7). In extreme cases there is widespread destruction of tissues with bullae formation indicative of a necrotising fasciitis (Fig. 33.8).

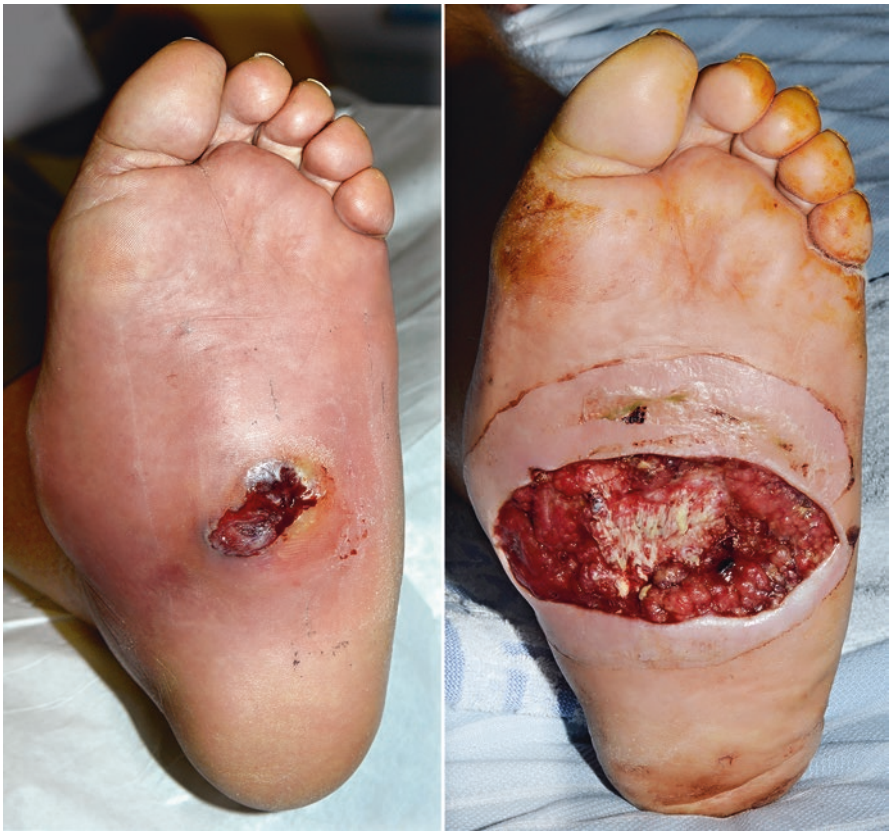

Fig. 33.4 Ulcer and necrosis on rocker bottom deformity with sloughing of the surrounding subcutaneous tissues and appearance after surgical debridement

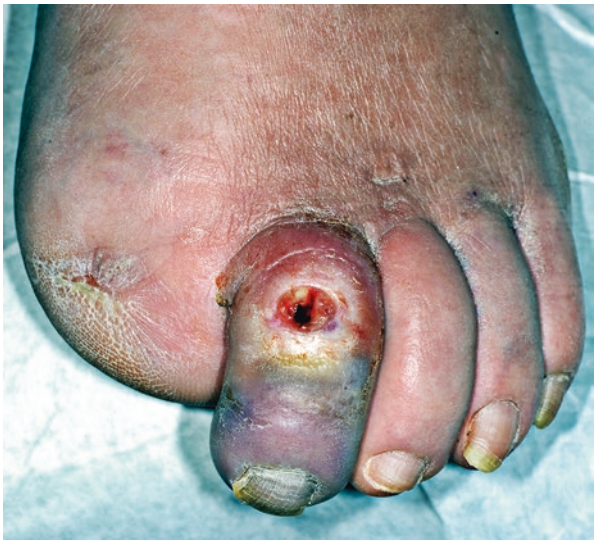

Fig. 33.5 Bluish discoloration of distal part of second toe secondary to infection complicating dorsal ulcer of the toe

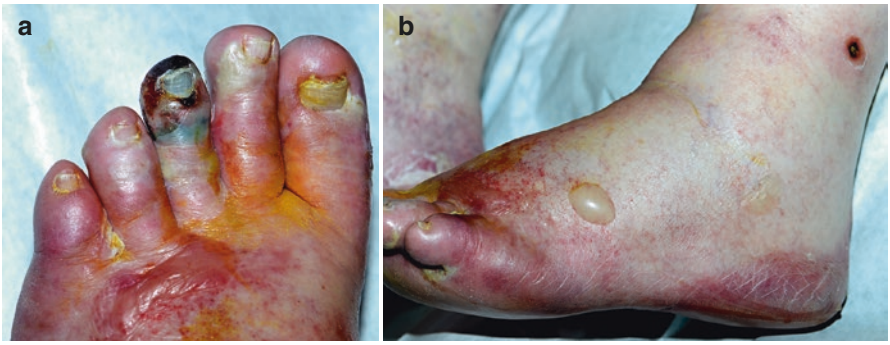

Fig. 33.6 (**a**) Wet digital necrosis secondary to severe infection with bulla formation. (**b**) Lateral aspect of same foot with further bulla formation

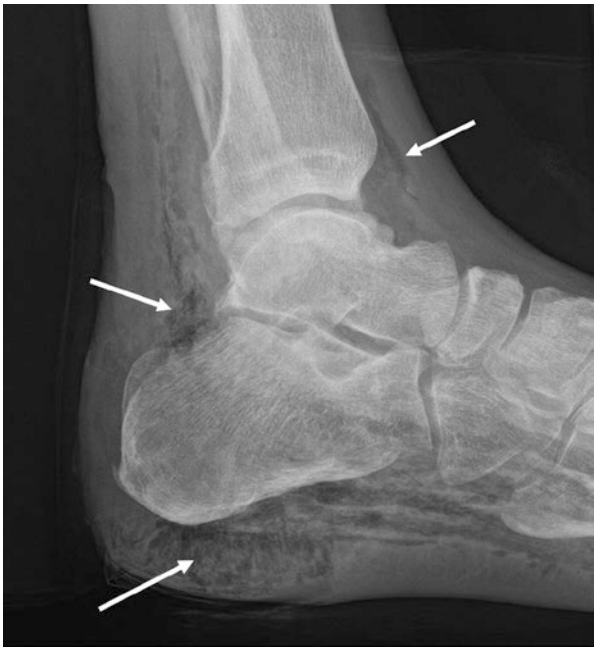

Fig. 33.7 Extensive gas in soft tissues of hind foot (arrows)

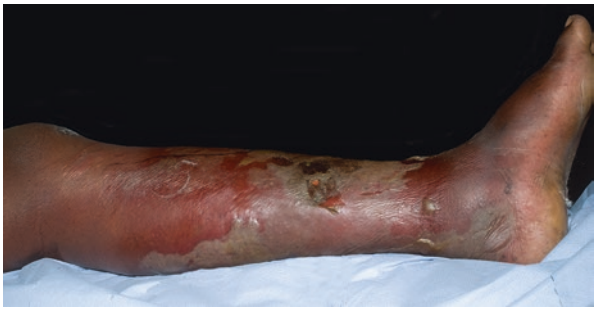

Fig. 33.8 Necrotising fasciitis with bullae formation

This stage may also be associated with bacteraemia, with the patient presenting with hypotension and organ failure. However, systemic signs and symptoms are often absent in many severe infections of the diabetic foot [7].

33.4.4 Systemic Infection

All stages of infection, local, spreading and deep tissue may also be associated with a bacteraemia, leading to systemic signs of infection. Signs of systemic infection include drowsiness, shivering, tachycardia, reduced body temperature (<35 °C) or raised body temperature (>37 °C) and hypotension. A body temperature that is raised above 37 °C is significant in a diabetic patient. However, systemic signs and symptoms are notoriously absent in many severe infections of the diabetic foot. When a fever is present it usually indicates a severe infection which has tracked into the deep spaces of the foot. Among patients hospitalised for late infections, only 12–35% have significant fever and only 50% of episodes of severe cellulitis will provoke a fever or leucocytosis. Serum CRP is a more reliable indicator of systemic infection, although it reflects inflammatory systemic activity over the previous 24 hours and may not mirror the true extent of inflammation at the time the blood is taken. Nevertheless, serum C-reactive protein (CRP) is a good indicator of the extent of infection and tissue destruction. Levels of CRP above 200 mmol/L usually indicate the need for surgical debridement. A subsequent fall in its level during treatment is a useful indication of the resolution of infection.

33.4.5 Osteomyelitis

Osteomyelitis can complicate any of the above infective presentations [8]. Infection often associated with ulceration can lead to osteomyelitis by contiguous spread to bone Osteomyelitis may be suspected clinically when a sterile probe inserted into the base of the ulcer penetrates down to bone. This may happen in an apparently clean, uninfected ulcer, but osteomyelitis must still be suspected.

Probing reveals the presence of:

- Undermined edges where the probe can be passed from the ulcer under surrounding intact skin
- Sinuses when the probe can be inserted deeper than in other areas of the ulcer bed and may reach tendon or bone. A sinus may not be immediately apparent, but may be revealed by probing areas of the ulcer, which are a different colour to the remainder of the ulcer bed. These areas may also be less firm and resilient.

When probing, the practitioner should determine the following:

- The depth and breadth of the ulcer

- The depth and direction of any sinus
- Does the probe reach bone? If so, this suggests osteomyelitis

Previously it was thought that probing to bone was a useful indicator of osteomyelitis, particularly in a group of patients who actually present with significant soft tissue limb threatening infection. However, in a recent study of a population of outpatient diabetic patients, in whom osteomyelitis was found in only 12% of diabetic foot wounds, probing to bone had a low positive predictive value of 0.57. However, it was concluded that a negative test could exclude the diagnosis of osteomyelitis [9].

Chronic osteomyelitis of a toe has a swollen, red, sausage-like appearance. It is most commonly diagnosed on X-ray. However, in the initial stages, X-ray may be normal. Loss of cortex, fragmentation and bony destruction are signs of osteomyelitis on X-ray but these changes may take 10–14 days to develop (Fig. 33.9). MRI scanning may detect early changes and can demonstrate oedema and abscesses in bone. However bone oedema may also be present in the Charcot foot. MRI, radiolabeled white blood cell (WBC) scintigraphy (either with ^{99m}Tc-hexamethylpropylene amine oxime [HMPAO] or ^{111}In-oxine), and [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}F-FDG–PET)/ computed tomography} have been used to detect osteomyelitis [10]. The various modalities have similar sensitivity, but 18F-FDG–PET and ^{99m}Tc-HMPAO–labeled WBC scintigraphy offer the highest specificity. A sign that an underlying joint is infected is the drainage of viscous, "bubbly" synovial fluid which is clear and sometimes has a yellowish tinge.

Bone biopsy may be valuable in establishing the diagnosis of osteomyelitis, for defining the pathogenic organism(s), and for determining the antibiotic susceptibilities of such organisms. Osteomyelitis may be confirmed by a positive bone culture or bone biopsy showing bone death, inflammation and repair. When bone biopsy is not possible, then the diagnosis should be made on clinical and radiological grounds.

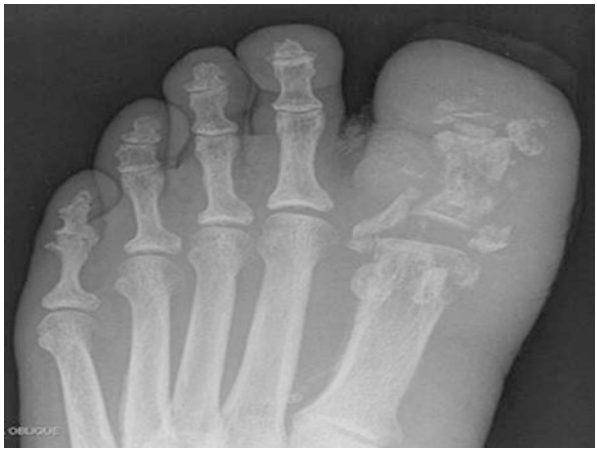

Fig. 33.9 Osteomyelitis of hallux with destruction of distal phalanx and fragmentation of proximal phalanx

Leucocytosis is a poor indicator of acute osteomyelitis of the foot in diabetic mellitus. Only 50% of episodes of osteomyelitis result in a fever or leucocytosis [7].

33.5 Conclusion

All health care professionals looking after diabetic patients should understand that infection is one of the great destroyers of body tissues in the diabetic patient. However, if infection is diagnosed early and treated actively then such tissue destruction can be prevented. Classical features of infection may be absent because of neuropathy. Nevertheless, it is important to be aware of its possible presentations and to make as early a diagnosis of infection as possible.

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Chapter 34
Osteomyelitis

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34.1 Background

In patients with diabetes mellitus, it is estimated that up to 25% will develop a foot ulcer within their lifetime [1]. Of those with diabetic foot ulcers, up to 60% can go on to develop diabetic foot infection, which complicates ulcer treatment while increasing risk of developing osteomyelitis and amputation [2, 3]. There has been an increase in the incidence of osteomyelitis of the foot and ankle, partly due to the increase in predisposing conditions such as diabetes mellitus and peripheral vascular disease. The increase in availability and use of sensitive imaging tests, such as magnetic resonance imaging (MRI) and bone scintigraphy, has also improved its diagnostic accuracy. Osteomyelitis in the diabetic foot behaves very differently from osteomyelitis in the foot of patients without diabetes. The diabetic foot is different because three great pathologies come together in this disease process. The combination of neuropathy, ischemia, and immunopathy can present significant challenges. It makes the natural history of osteomyelitis in the diabetic foot rapidly progressive as well as chronic. The aim of this chapter is to give an overview of the pathophysiology, diagnosis and management.

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34.2 Pathophysiology

Osteomyelitis is an infection of the bone that, when progressive, can cause destruction of the bone [4]. In patients with diabetic foot infections, osteomyelitis is generally caused by contiguous spread from infected skin and soft tissue in the setting of an ulceration, infected wound following surgery, or a contaminated open fracture (Fig. 34.1). Hematogenous spread of bacterial organisms resulting in osteomyelitis of the diabetic foot is relatively uncommon.

In contiguous osteomyelitis, bacteria can gain access to bone by direct inoculation or by extension to bone from contaminated soft tissue that is adjacent to the bone [5]. Foreign bodies, trauma, deep pressure ulcers and ischemia may all cause osteomyelitis in the diabetic foot. Figure 34.2 depicts a patient who presented with a right heel diabetic foot ulcer. In patients with diabetes mellitus or peripheral vascular disease, osteomyelitis due to a contiguous focus of infection is often associated with vascular insufficiency and may go under-recognized in the setting of peripheral neuropathy [5]. Acute osteomyelitis, particularly if inadequately treated, may progress to a chronic infection. Sequestrum, or dead bone, is common in the setting of chronic osteomyelitis [4]. Patients with chronic osteomyelitis also have chronic bone loss and involucrum (reactive bony encasement of the sequestrum).

There are several components involved in the pathogenesis of osteomyelitis in the diabetic foot. Important factors to consider are the causative organism, location and vascular status of the bone and whether or not the host is immunocompromised [6]. The most common cause of osteomyelitis is *Staphylococcus aureus*. This organism is a cause of contiguous and hematogenous osteomyelitis and produces many cell-associated and extracellular virulence factors that promote bone destruction. This destruction is achieved through proteolytic activity, resistance to host defense mechanisms and by promoting bacterial adherence [6]. Other common bacteria include anaerobic bacteria, Gram-negative enteric organisms, and streptococci [7].

Since normal, healthy bone is highly resistant to infection, a large amount of bacterial burden is found in cases of osteomyelitis [8]. Adhesins are proteins that facilitate bacterial attachment to the bone and formation of biofilm, which is the layer that protects bacteria from antimicrobial agents [4, 6]. The immune response of the host can also result in bone destruction. Cytokines have osteolytic properties, and phagocytes also produce proteolytic enzymes and toxic oxygen radicals that can destroy host cells. This inflammation causes an increase in intraosseous pressure, which lim-

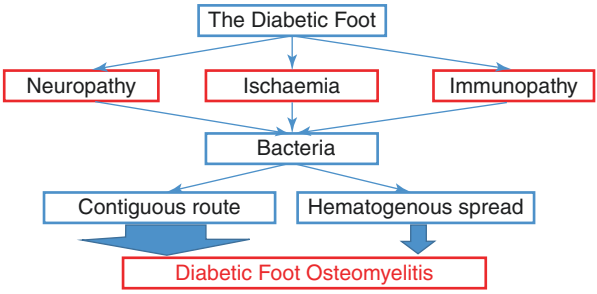

Fig. 34.1 Pathophysiology of osteomyelitis in the diabetic foot

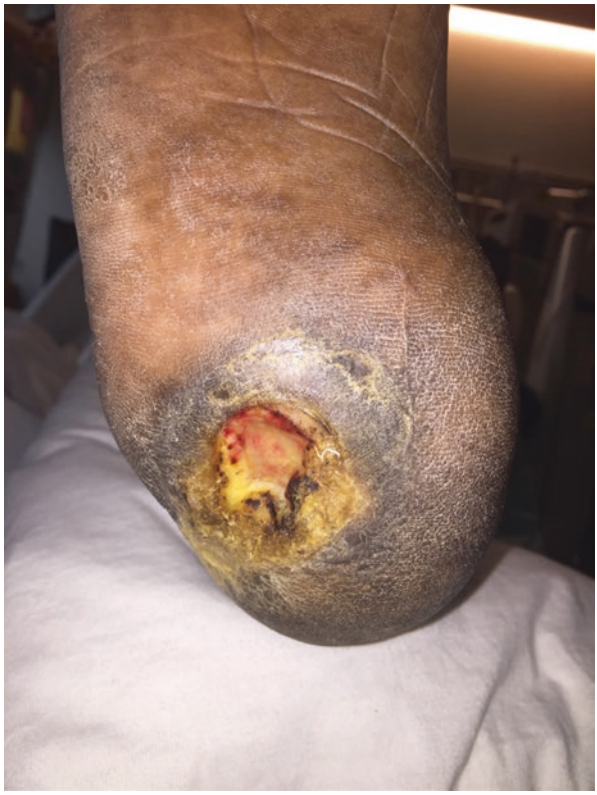

Fig. 34.2 Right heel diabetic foot ulcer

its blood flow and can lead to necrosis of the bone. This necrosis is known as sequestrum, which is susceptible to attachment of biofilm [9]. Specifically, IL-1β[beta] is a proinflammatory cytokine that has a role in bone destruction in osteomyelitis [10]. Additionally, chronically poor blood flow as seen in peripheral arterial disease also makes it more difficult for antimicrobial agents to be effective [9].

Osteomyelitis is very common in the foot, and the risk of its development increases when patients have ulcers that are 2 cm or greater or have exposed bone or joint in the ulcer [11]. The forefoot is the most common site, with up to 90% of cases involving the weight bearing bones of the foot (first metatarsal head, calcaneum, and fifth metatarsal head). The midfoot and hindfoot comprise about 10% of infections [12].

Immunocompromised patients are at higher risk for osteomyelitis, likely related to the inadequate immunological response to infection at a more superficial level.

34.3 Histological Appearance

Histopathological signs that are seen in acute osteomyelitis include acute inflammatory cells with edema, small vessel thrombosis, and vascular congestion [6]. Initially,

in early disease, the infection extends to the soft tissue surrounding the bone, and therefore the vascular supply to the bone is reduced [6]. If sequestrum is formed, surrounded by ischemic and necrotic tissue, bacteria can be difficult to eradicate by antimicrobial therapy alone. Acute and chronic osteomyelitis have similar histologic pictures [6]. Chronic osteomyelitis includes necrotic bone, the formation of new bone, and exudates with large numbers of lymphocytes, histiocytes, and some plasma cells. Osteomyelitis is also characterized by tissue necrosis. Granulation tissue at the surface of dead bone is absorbed and granulation tissue can completely destroy the bone and cause a cavity in the area [6]. Trabecular bone in localized osteomyelitis is usually absorbed, and often parts of the dead cortical bone are detached from the healthy residual bone to form sequestra.

In osteomyelitis, there is also new bone formation, which can be formed around the dead bone, though it may be of poor quality. This is known as involucrum. It is irregular and often osteoporotic, and may have areas of perforation where there may be purulence [6]. Even after removal of the sequestrum, a cavity may still be present which can fill with fibrous tissue and connect with the skin through a sinus tract.

34.4 Diagnostic Testing

Establishing a diagnosis of osteomyelitis in the diabetic foot can be difficult. Physicians should have a high clinical suspicion for underlying osteomyelitis in the setting of a chronic non-healing ulcer with poor vascular supply overlying a bony prominence [13]. There is no one test that aids in diagnosis, rather a combination of laboratory tests, imaging and bone biopsy with culture can be used in diagnosing osteomyelitis in the appropriate history and clinical examination.

34.4.1 Laboratory Testing

Among currently available laboratory tests, the erythrocyte sedimentation rate (ESR) appears to be most useful in diagnosing osteomyelitis [13–15]. In patients with suspected diabetic foot infections, an ESR $\geq$ 70 mm/h has a sensitivity of 83–89% and specificity of 77–100% in diagnosing osteomyelitis [14, 16]. Combining the use of tests like ulcer depth and C-reactive protein (CRP) or ESR has been shown to improve the sensitivity of the diagnosis of osteomyelitis to 100% [17]. The use of procalcitonin (PCT) level has also been studied in the diagnosis of osteomyelitis and one study reported a sensitivity and specificity of 0.81 and 0.71, respectively [18]. The role of PCT level is still unclear as another study found no statistical difference in levels to help distinguish osteomyelitis from soft tissue infection [19]. Another common test obtained is a serum white blood cell count; however this is usually not helpful as it can be normal in almost half of patients with bone infections [15]. Blood glucose monitoring is important as hyperglycemia can increase risk of

complications and mortality in patients with diabetes undergoing surgery [20]. One study found that among patients admitted with diabetic foot osteomyelitis, a predictive factor for amputation was perioperative hyperglycemia [21].

34.4.2 Probe to Bone Test

A probe-to-bone (PTB) test is a commonly used clinical test for diagnosing osteomyelitis, especially in the setting of diabetic foot ulcer and suspicion of infection. Given that the etiology of diabetic foot osteomyelitis is usually via contiguous spread from surrounding tissue, bacteria can easily access bone. Therefore, a PTB test suggests that if a probe can reach bone, bacteria can as well [22]. A sterile, blunt metal surgical probe is used when performing a PTB test and is considered positive if a hard surface is palpated with a grinding sensation when moving the probe over the surface. Although there have been prior small literature reviews of the PTB test, its applicability has been questioned, especially in settings with low pretest probability of osteomyelitis [23, 24]. A recent systematic review was performed to help delineate the diagnostic accuracy of the PTB test in detecting osteomyelitis in the diabetic foot. This review found that the pooled sensitivity and specificity for the PTB test was 87% and 83%, respectively [22]. In high-risk patients with a high pretest probability, the PTB test can support a diagnosis of diabetic foot osteomyelitis, while ruling out osteomyelitis in low-risk patients.

34.4.3 Bone Biopsy

A combination of microbiological culture and histopathological bone examination is considered the gold standard in the diagnosis of osteomyelitis [25–27]. Identifying responsible pathogens and antibiotic susceptibility testing of organisms cultured from surgically obtained bone is helpful in guiding antibiotic therapy. Superficial cultures are often not useful as they often grow numerous microorganisms that may not correlate with deeper bone culture [28]. Less than 50% concordance has been seen when comparing bone culture to superficial culture of a wound [29]. Culture of surgically obtained bone may not be performed in all patients. The use of an anticoagulant, severe ischemia, or very small bone involvement are some examples of possible clinical reasons why a surgical bone specimen may not be obtained. Receipt of antibiotics prior to obtaining a bone specimen for microbiological culture may decrease the ability to grow organisms from the specimen. Prior to obtaining a surgical bone specimen for microbiological culture, antibiotics should be held or discontinued, if feasible, to help maximize the culture yield [30, 31]. A bone biopsy may be less useful in patients who will undergo extensive debridement or amputation. However, when surgical resection and/or amputation is performed, the proximal margin should be obtained for culture and to assess for residual infected bone based on histopathological evaluation.

34.5 Imaging

34.5.1 Plain Radiography

Radiographic imaging is of high importance in establishing the diagnosis of osteomyelitis of the diabetic foot. Both the Infectious Diseases Society of America (IDSA) and the National Institute for Health and Clinical Excellence (NICE (UK), recommend plain radiographs as initial evaluation for all diabetic foot ulcers [26, 32]. Plain radiographs are helpful in identifying the presence of foreign bodies, arterial calcifications and bony deformities [33]. Some key characteristic features of osteomyelitis on plain radiography include periosteal elevation, bony erosion, marrow radiolucency and new bone formation, which is often surrounded by soft tissue swelling [13]. A significant loss of bone mineral content of 30–50% is necessary to produce visible changes on plain radiographs [34]. There has been a broad range of the sensitivity and specificity of radiography reported in the literature. One study among 27 diabetic patients with suspected foot infection reported a sensitivity and specificity of 22% and 94%, respectively in diagnosing osteomyelitis [35]. The NICE (UK) guidelines performed a significant literature review and found that plain radiographs had a sensitivity ranging from 22% to 75% and specificity of 17–94% among published studies [32]. Sequential imaging of the foot over time may be more likely to predict the presence of osteomyelitis than a single image. Poor specificity of radiographs is likely due to difficulty differentiating patients with bony destruction secondary to Charcot neuropathic osteoarthropathy [13]. Figure 34.3 shows a right foot X-ray in a diabetic patient with suspected osteomyelitis of the second toe. Table 34.1 illustrates the sensitivity and specificity of various imaging techniques in diagnosing osteomyelitis in diabetic foot infections from selected studies.

Of the current imaging techniques available to aid in diagnosing osteomyelitis, magnetic resonance imaging (MRI) with gadolinium contrast is usually considered the most optimal. One study among 29 diabetic patients with suspected foot infections found that MRI was 100% sensitive and 63% specific in diagnosing osteomyelitis [36]. In a more recent meta-analysis evaluating MRI for diagnosing foot osteomyelitis in which the vast majority of patients were diabetic, the pooled sensitivity was reported as 77–100% and the pooled specificity ranged from 40–100% [33]. Some characteristic features of osteomyelitis on MRI include low focal signal intensity on T1-weighted images and high focal signal on T2-weighted images [13]. MRI scans are able to accurately outline the extent of inflammation and more precisely define the anatomic location in the foot, which is a significant advantage compared to radionuclide bone scans. Unfortunately, MRI is not feasible in all circumstances due to availability or patient contraindications. When MRI is unavailable, an alternative approach based on IDSA guidelines consists of combined radionuclide bone scan and a labeled white blood cell scan [26]. The IDSA does not recommend any other type of nuclear medicine imaging. Alternatively, the NICE (UK) guidelines recommend the use of a labeled white blood scan alone when MRI

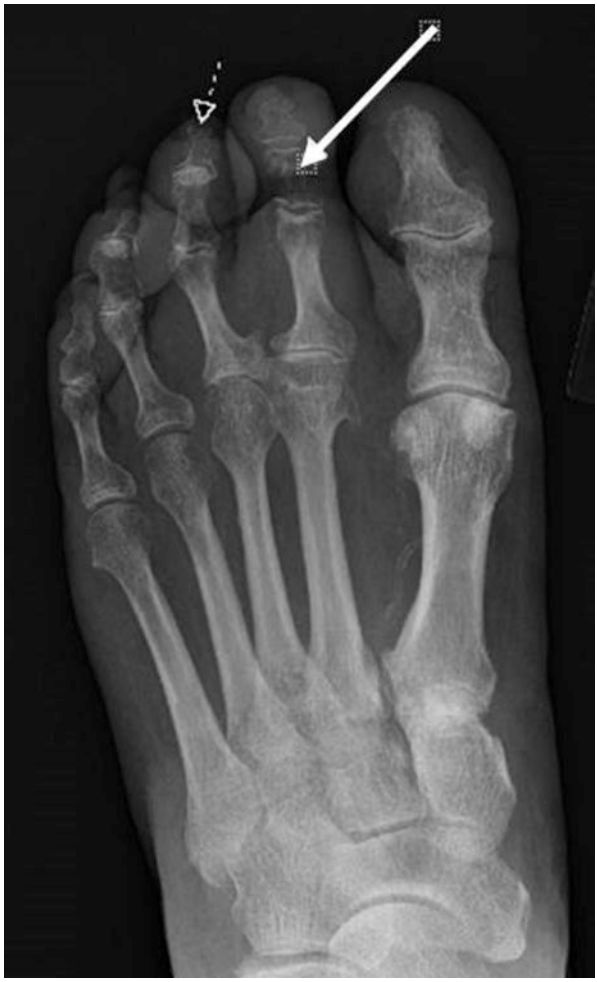

Fig. 34.3 Right foot X-ray revealing destruction of the second toe middle phalanx (unbroken arrow) and possible cortical erosion of the distal third toe (broken arrow)

Table 34.1 Sensitivity and specificity among various imaging modalities from selected studies in diagnosing osteomyelitis in diabetic foot infections

Study [year]	Imaging modality	No. of patients	Sensitivity (%)	Specificity (%)
Croll et al. [35] [1996]	Plain radiography	27	22	94
	MRI	27	89	100
	Technetium bone scan	22	50	50
	Indium leukocyte scan	19	33	69
Ertugrul et al. [37] [2006]	Technetium bone scan and labeled leukocyte scan	26	91	67
	MRI	28	78	60
Al-Khawari et al. [36] [2005]	MRI	29	100	63

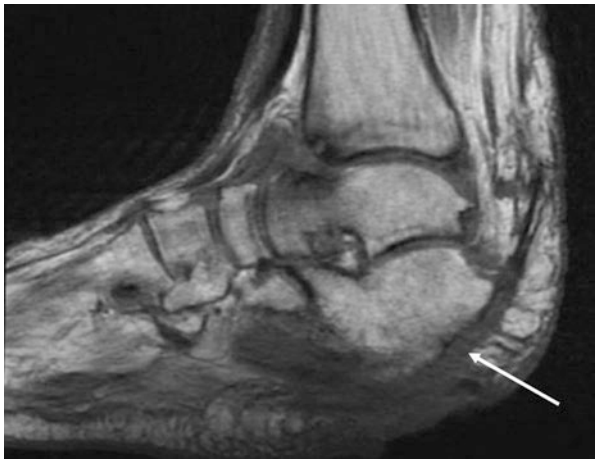

Fig. 34.4 Right foot MRI with contrast revealing loss of the normal dark T1 cortex with effacement of the normal T1 bright marrow fat along the posterior and lateral aspects of the calcaneus (arrow)

is unavailable or contraindicated and advises against the use of other nuclear medicine scans [32]. Figure 34.4 is a right foot MRI showing evidence of calcaneal osteomyelitis in a patient with an underlying diabetic foot ulcer.

34.5.2 Nuclear Medicine

There are several nuclear medicine techniques available for diagnosing diabetic foot infections. One such technique includes bone scans, which are commonly performed using ^{99m}Tc-methylene diphosphate and findings of abnormally increased intensity localized to bone are suggestive of osteomyelitis [23]. One study found that technetium bone scanning alone had sensitivity and specificity each of 50% [35]. A more recent study combined the use of labeled leukocyte scanning and technetium bone scans with a reported sensitivity and specificity of 91% and 67%, respectively [37]. Therefore, bone scans are more useful when negative as it can reliably rule out osteomyelitis; however there appears to be increased sensitivity and specificity when used in combination with a labeled leukocyte scan.

34.6 Management

There is a widely varied approach to the management of diabetic foot osteomyelitis. A combined surgical and medical approach is most frequently utilized, though in some cases surgery, often amputation, may be curative while select cases may be treated with medical therapy alone. Little data exists to help support clinical decision making with respect to the optimal route of antibiotic delivery or duration of therapy in either soft tissue infection or osteomyelitis in the diabetic foot [13, 26, 27, 38].

Initial antibiotic regimens usually consist of empiric, broad-spectrum parenteral therapy, especially in severe infections. Once microbiological data is available, the goal in most scenarios is to use the most narrow-spectrum antibiotics based on culture and sensitivity, and switch to oral therapy, when appropriate and feasible [26].

Antibiotic penetration to the site of infection in the diabetic foot is an important aspect of antibiotic selection. Beta-lactam antibiotics (penicillins, cephalosporins, and carbapenems) have been shown to penetrate bone at levels up to 20% of those in serum [39]. When given parenterally, these antibiotics reach high serum levels and therefore absolute bone levels likely surpass minimum inhibitory concentrations (MICs) of most organisms. Oral dosing of beta-lactam agents, however, is unlikely to achieve necessary bone concentration due to very low serum concentration [39].

Some antibiotics with high oral bioavailability have been shown to achieve adequate bone penetration. High oral bioavailability and bone concentrations at about 50% of serum has been reported when using fluoroquinolones, linezolid, and trimethoprim [13, 38–41]. Clindamycin also reliably penetrates into bone and necrotic tissue [13, 42, 43]. An oral treatment option in anaerobic osteomyelitis is metronidazole, as this reaches similar concentrations in bone as in serum [39, 44].

Decisions regarding initial empiric antibiotic therapy are patient specific, depending on suspected organisms of concern and the severity of infection. Some examples of initial broad-spectrum empiric therapy include ertapenem, levofloxacin, ceftriaxone or ampicillin-sulbactam [26, 32, 39]. It is important to treat Gram-positive cocci, specifically streptococci and staphylococci, as these are the most common pathogens in diabetic foot infections, and in severe infections, to consider empiric therapy treating Gram-negative organisms [26, 32]. In certain individuals, such as those with a prior history of methicillin-resistant *Staphylococcus aureus* (MRSA) or where the local prevalence of MRSA is high, it is reasonable to initiate therapy active against MRSA. Some examples of agents with activity against MRSA include vancomycin, linezolid, and daptomycin [26, 39]. Antipseudomonal therapy must be considered in special circumstances but this is often unnecessary in many cases. In areas of high local prevalence or frequent exposure of the foot to water, should prompt consideration for antipseudomonal therapy [26]. Multidrug-resistant Gram-negative organisms, with resistance to beta-lactams and fluoroquinolones are a growing concern, and should be considered when selecting empiric therapy for a patient with risk factors for these organisms, including prior treatment with broad-spectrum antibiotics.

34.6.1 Duration of Treatment

The optimal duration of antimicrobial therapy in diabetic foot osteomyelitis is still unclear [27, 38, 39, 45]. In a systematic review, the mean antibiotic duration ranged from 6 to 28 days [45]. The degree of debridement or resection performed does affect the duration of treatment. Aggressive surgical debridement and proximal amputation to the site of osteomyelitis are usually considered sufficient to consider

shortening treatment to 2–5 days [26]. When infected bone remains or surgical resection is not possible, treatment should consist of at least 4 weeks of targeted intravenous therapy or high bioavailability oral antibiotics with good bone penetration [13, 26, 39]. To date there are no tests proven to correlate with long-term resolution of osteomyelitis. The consensus guidelines concluded that the following were suggestive of a response: a decrease in inflammatory markers (especially the ESR); healing of any wound; resolution of superimposed soft tissue infection; and radiographic changes that suggest healing [26]. PCT levels are likely less helpful during long-term follow-up as one study found that PCT values return to near-normal within approximately 1 week [18].

34.7 Summary

A high clinical suspicion is necessary in diagnosing osteomyelitis in the diabetic foot, which can be supported by histopathology, microbiologic culture and radiographic imaging. Combining exam findings with results from imaging studies and inflammatory markers will increase the accuracy and reliability of diagnosing osteomyelitis. An individualized approach to treatment is necessary, preferably utilizing a multidisciplinary approach.

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Chapter 35
Infected Neuropathic Foot: Investigation

Shelly D. Sedberry, Michael I. Gazes, and Peter A. Blume

35.1 The Clinical Problem

Peripheral neuropathy is the most common etiology of foot ulcerations. Diabetes mellitus is the most common cause of neuropathy [1]. Other etiologies of neuropathy include metabolic causes (diabetes, hypothyroidism, alcoholism, vitamin deficiency), toxins (heavy metals, organic compounds, drug intoxication), infections (human immunodeficiency virus, cytomegalovirus, Lyme disease, hepatitis), Immune or inflammatory disease (Systemic Lupus Erythematosus, Rheumatoid Arthritis, demyelinating disease), ischemia, and genetics (Charcot-Marie Tooth Syndrome, Roussy-Levy Syndrome). Neuropathy is present in 42% of patients that have had diabetes for over 20 years [2]. The annual incidence of foot ulceration in all patients with diabetes is slightly more than 2% [3]. This percentage increases to 5.0% (type II) and 7.5% (Type I and II combined) in patients with peripheral neuropathy [4]. Infection often develops in patients with foot ulcerations, resulting in adverse outcomes [5, 6]. Patients with diabetes have a 15% lifelong incidence of developing foot ulcers, which result in over 50% of non-traumatic lower limb amputations [7–11]. Additionally, patients with diabetes are also prone to Charcot neuroarthropathy [12]. Abnormal perfusion to foot bones causes fractures and joint collapse resulting in the foot taking on an abnormal shape or "rocker bottom" foot [12, 13]. These deformities are prone to tissue breakdown and ulceration [12, 13].

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35.2 Pathophysiology of Neuropathy

Loss of sensation due to peripheral neuropathy is the leading risk factor in both foot ulcers and amputations [4–6, 14, 15]. The pathogenesis of neuropathy in patients with diabetes is not well understood. Peripheral neuropathy in this population is thought to be a result of abnormalities in metabolic pathways [16, 17]. Chronic hyperglycemia results in abnormal activation of polyol pathway resulting in a deficiency in sorbitol metabolism, non-enzymatic glycation of protein elements, and accumulation of vasoactive substances which manifest in both somatic and autonomic fibers [16, 17]. Type A sensory fibers are heavily myelinated and are high velocity fibers responding to acute pain, temperature, touch, pressure, proprioception, and somatic efferent fibers. Type B sensory fibers are less heavily myelinated and are moderate velocity fibers responding to visceral afferents and preganglionic autonomics. Type C sensory fibers are unmyelinated and respond to painful stimuli, noxious stimuli, and temperature. Loss of sensory fibers result in diminished sensation in a "glove and stocking" distribution. This loss of sensation predisposes patients to ulcerations and infection as the patient is unable to detect pain (Fig. 35.1) [5, 7].

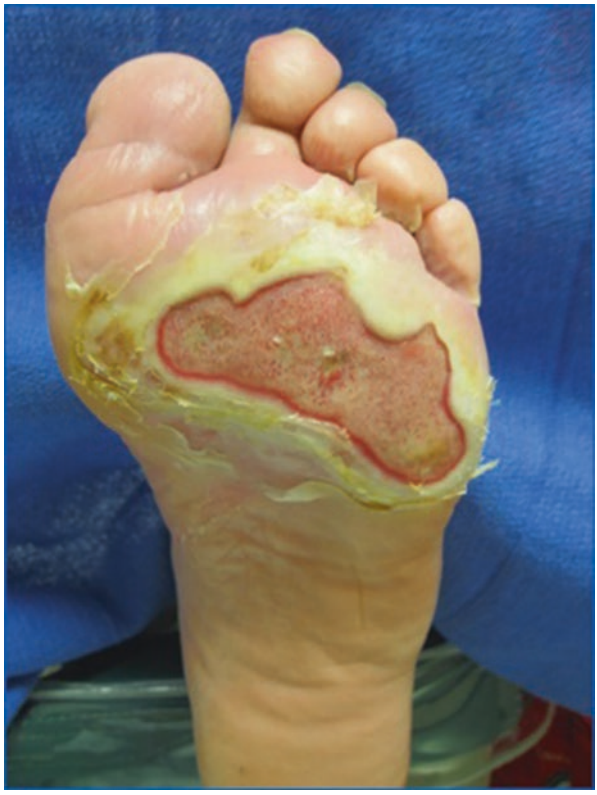

Fig. 35.1 Neuropathic diabetic foot ulceration

Motor neuropathy results in structural changes from ligamentous laxity and muscle atrophy to intrinsic muscles of the foot thus resulting in collapse of the arch, prominence of metatarsal heads, crowding of toes, metatarsophalangeal joint instability, and subluxation of metatarsal heads which may result in callus and formation of ulcers [7, 12, 18]. Bauman et al showed that even slight pressure applied to a bony deformity can lead to ischemic necrosis and ulceration [19]. In a meta-analysis including 8 studies, Fernando et al found that overall mean peak plantar pressure was higher in diabetics with peripheral neuropathy with a history of foot ulcerations than those without a history of foot ulcerations [20]. Extrinsic muscles overcompensate, thus leading to digital contractures, ankle equinus, and varus hindfoot [21]. In a prospective study of 248 individuals, Casselli et al. showed that the forefoot to rearfoot plantar pressure ratio is increased in patients with severe neuropathy [22]. Areas of high load during gait goes undetected due to loss of protective sensation and therefore gait patterns remain the same eventually leading to tissue breakdown and ulceration. Furthermore, autonomic involvement results in impairment of microvascular thermoregulation. This impairment leads to dry and brittle skin due to the inability for the foot to sweat and moisturize the skin, leading to fissuring and cracking. Autonomic involvement also causes arteriovenous shunting in the subcutaneous and dermal levels resulting in tissue breakdown secondary to diminished delivery of nutrients and oxygen [1].

35.3 Diagnosis of Peripheral Neuropathy

Screening for diabetic peripheral neuropathy can be used to make an early diagnosis in at high risk patients in order to prevent future ulcerations and amputations [23, 24]. While nerve conduction studies are the gold standard for diagnosis of peripheral neuropathy, a screening for peripheral neuropathy can be performed through the use of inexpensive, simple, rapid, and painless methods. Peripheral neuropathy can be detected by testing sensation with a 5.07 monofilament. Several studies have shown a strong association between elevated cutaneous pressure thresholds and foot ulcerations. There is a seven fold risk of ulceration in patients insensitive to 5.07 monofilament [25]. In a systematic review, Feng et al suggested that the optimal method to use the 5.07/10 g monofilament is to test the plantar aspect of the hallux, third, and fifth metatarsal heads [26]. If one or more sites are unable to be detected, then the patient should be considered to be at risk for neuropathy with a sensitivity of 90% [26]. Other tests to screen for peripheral neuropathy include a 128-Hz tuning fork, a pinprick test, ankle reflexes, or a biothesiometer, which provides a semiquantitative assessment of vibration perception threshold (VPT) [4, 7]. A VPT greater than 25 V is a predictor of future development of ulcers [7]. In a 4 year prospective study, Young et al showed that a VPT of greater than 25 V was 7 times more likely to develop foot ulcers [27]. Additionally, composite scores including the modified neuropathy disability score can be employed, which involves testing of vibration threshold, temperature sensation, pinprick sensation, and Achilles reflex [3].

35.4 Mechanism of Ulceration

77% of all ulcer pathways include trauma with common components of foot ulcerations. Common components of foot ulcerations include peripheral neuropathy, deformity, minor trauma, peripheral ischemia, callus, and peripheral edema [9]. Neuropathic ulcerations occur by three different mechanisms: [21]

- A quick traumatic event such as stepping on a sharp object that pierces the skin.
- Chronic low grade pressure such as ill-fitting shoes.
- Repetitive and moderate pressures.

Areas of increased pressure can be identified by the presence of callus formation.

35.5 Infection of the Diabetic Foot

Patients with diabetes are more prone to infections than patients without diabetes [28]. Infection is usually a consequence of foot ulceration and can cause a delay in healing with deterioration of the surrounding tissue [29]. Factors that predispose diabetic patients to lower extremity infections include neuropathy, vascular impairment, and decreased resistance to infection [14, 29–31].

Diabetic foot infections are categorized as either life or limb threatening or non-limb-threatening. Non-limb-threatening infections are mild infections with less than 2 cm of cellulitis and no systemic signs of infection. They typically consist of superficial ulcers with an average of 2.1 pathogens present [32, 33]. Aerobic gram-positive cocci are the only pathogens found in 42% of non-limb threatening diabetic foot infections [32, 33]. The most common organisms in non-limb threatening infections are Staphylococcus aureus, coagulase-negative Staphylococcus, and Streptococci. Treatment for mild infections are typically oral antibiotics. Life or limb threatening infections are considered severe and are usually polymicrobial in nature. Ulcerations are deeper or consist of an abscess, gangrene, or necrotizing fasciitis [21]. Cellulitis of greater than 2 cm, lymphangitis, edema, and systemic signs of infection may be present in severe diabetic foot infections. Gram-positive and gram-negative aerobic and anaerobic organisms are often seen in these severe infections. The most common organisms include Staphylococcus aureus, coagulase-negative Staphylococcus, group B Streptococcus, Proteus, Escherichia coli, Pseudomonas, Bacteroides, and increasingly Methicillin-Resistant Staphylococcus aureus (MRSA) [28, 34, 35]. Anaerobic infections with Clostridium also occur.

Bacteria, including normal flora, will be present in all wounds, essentially making swab cultures inadequate for determining infection. Diagnosis of infection is therefore based on clinical evaluation [33, 34]. Clinical diagnosis includes the presence of systemic signs of infection (fever, leukocytosis, increased heart rate), purulence, or two or more local signs of infection (redness, warmth, induration, pain, or

tenderness) [29]. Systemic signs of infection may be absent in patients with diabetes [11, 35]. A clinical diagnosis can be supported with imaging, deep tissue or bone cultures, and laboratory results. Recalcitrant hyperglycemia may also be an indicator of infection.

35.6 Osteomyelitis

Ramsey reported that 15% of patients with diabetic foot ulcers developed osteomyelitis [36]. Ulcers that probe to bone are strongly correlated to the presence of osteomyelitis [37]. In a study of 75 diabetic patients, Grayson et al reported a 66% sensitivity, 85% specificity, 89% positive predictive value, and 56% negative predictive value for osteomyelitis when ulcerations were positive for probing to bone. In a study of 132 patients, the probe to bone test had a 98% sensitivity, 78% specificity, 95% positive predictive value and a 91% negative predictive value [38]. Positive probe to bone has a higher positive predictive value than imaging. Laboratory testing is non-specific to osteomyelitis. Leukocytosis may be present in acute osteomyelitis, but is not always elevated in chronic osteomyelitis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are inflammatory markers used to evaluate for the presence of osteomyelitis. In a retrospective study that compared patients with cellulitis to those with osteomyelitis, an ESR greater than 70 mm/h had a sensitivity of 0.89 and a specificity of 1.00 in the diagnosis of osteomyelitis [39].

Bone biopsy is considered the gold standard for diagnosis of osteomyelitis [40]. Superficial wound swabs do not correlate with infection that is present within the bone [41–43]. Senneville et al demonstrated the concordance between superficial swab culture and bone cultures to be only 22.5% [41]. When surgical debridement is required, bone samples should be obtained and sent for gram stain, culture, and hisotopathology [44]. Percutaneous needle biopsy can be obtained when an open biopsy is not ideal; however results from these cultures are less reliable. An evaluation comparing needle puncture biopsies to transcutaneous bone biopsies found a 23.9% correlation between the microbiological results [41]. If percutaneous biopsy is performed, the biopsy should be obtained through tissue that is not inflamed or ulcerated. Histopathological features of osteomyelitis include osteonecrosis and infiltration of leukocytes or chronic inflammatory cells [45].

35.7 Imaging for Osteomyelitis

Several imaging modalities are available to evaluate an infected foot. There is no single imaging study that is ideal in every situation. Factors such as time of onset, site of foot infection, severity and progression of infection, previous surgeries, and comorbidities factor into the choice for diagnostic imaging [46].

If osteomyelitis is suspected and the patient has clinical symptoms for 2 weeks or longer, plain radiographs should be obtained. Plain radiographs are not adequate for early detection of osteomyelitis, as approximately 50% of the bone must be destroyed prior to having consistent findings on plain film. Findings for osteomyelitis include osseous destruction, periosteal elevation, involucrum, sequestration, cortical lucency, osteoporosis, sinus tracts, and soft-tissue swelling [44, 47, 48]. Radiographic findings unique to chronic osteomyelitis include reactive sclerosis, sequestra, and involucrum [47]. Plain films may not be sufficient to distinguish osteomyelitis from Charcot arthropathy and fracture [49].

Magnetic resonance imaging (MRI) is the imaging modality with the greatest sensitivity for diagnosis of osteomyelitis and can detect osteomyelitis as early as 3–5 days after infection [45]. MRI has a high sensitivity and negative predictive value that is superior to both plain radiography and nuclear modalities [45, 50]. In a meta-analysis of sixteen studies, MRI was shown to be superior to technetium Tc 99m bone scanning, plain radiography, and white cell studies [50]. A low signal intensity of T-1 weighted images and high signal intensity on T-2 weighted images is consistent with osteomyelitis [45]. MRI is useful in evaluating the extent of cortical destruction, soft tissue inflammation, and inflammation of the bone marrow [51]. Gadolinium contrast enhances the visualization of sinus tracts, fistulas and necrotic tissue, but it is not required to diagnose osteomyelitis. MRI has nearly 100% negative predictive value for excluding osteomyelitis. The positive predictive value for osteomyelitis ranges from 70% to 80% due to its inability to differentiate between other causes of abnormal marrow signal intensity, including Charcot foot [52]. Contraindications to MRI include ferromagnetic metal in body, pacemakers, claustrophobia, and surgical metal implants in the area of interest.

Computer tomography (CT) is useful for evaluation of osseous sequestra and involucrum [53]. It is more sensitive than plain radiography. CT provides excellent cortical bony detail. However, CT is considered to be an inferior approach to magnetic resonance imaging (MRI). MRI provides better visualization of soft tissue and eliminates the exposure to high levels of ionizing radiation.

Nuclear imaging relies on specific isotopes, either alone or linked to white cells, and is useful in individuals with contraindication to MRI or surgical hardware in the area of concern. Several agents have been studied, including technetium-99m–labeled methylene diphosphonate (^{99m}Tc-MDP), gallium-67 citrate, and indium-111–labeled white blood cells.

The phosphonate in ^{99m}Tc-MDP attaches to hydroxyapatite crystals and results in increased uptake to areas of new bone formation.[54] ^{99m}Tc-MDP can detect osteomyelitis days to weeks before osseous changes are seen on plain radiographs. The bone scan involves three phases: angiographic/flow, blood pool, and delayed. The angiographic phase, or flow study, is a dynamic study of the area of interest. The blood pool phase represents intravascular and extravascular activity, as the radioisotope will pool in areas of inflammation. At this time, resolution between bone and soft tissue can be visualized. The third phase demonstrates the osseous involvement. It has a high sensitivity for detecting inflammation, making it a better option for evaluation of acute infection than chronic infection. Disadvantages include a delay in

obtaining the results and low specificity. Oloff reports a specificity of 27.3%, as other diseases involving osteoblastic activity, such as fractures and previous surgery, will result in a positive bone scan result [54, 55].

Radiogallium attaches to transferrin produced by leukocytes. Gallium scintigraphy is often performed with radionuclide bone imaging. In patients with osteomyelitis, gallium will accumulate in areas of infection. It is difficult to distinguish between bone and soft tissue inflammation. Sensitivity for gallium scan is 25% to 80%, with a specificity of 67% [54, 56, 57].

Combining the three phase bone scan with labelled white blood cells increases the specificity and sensitivity of the scan to infection [58]. White blood cell scans done with indium-111 tagged leukocytes or 99mTc-hexamethyl-propyleneamine oxime (HMPAO)-labeled white cells provides greater specificity than with bone scans [54].

Kagna et al. investigated fluorodeoxyglucose positron emission tomography for diagnosing osteomyelitis in the diabetic foot and found the FDG PET/CT sensitivity, specificity, and accuracy of 100%, 92%, and 95% [59]. Acute infections can be precisely localized with PET/CT, allowing differentiation between osteomyelitis and soft-tissue infection. However, FDG PET/CT specificity with respect to distinguishing between acute infection and sterile inflammatory processes is limited [60]. In the context of acute post-surgical or post-traumatic infection, FDG PET/CT is limited.

35.8 Charcot Osteoarthropathy and Infection

Charcot osteoarthropathy and osteomyelitis often occur in the same foot. Of all patients with diabetes, 0.1–7.5% have Charcot osteoarthropathy. 29% of patients with diabetes and peripheral neuropathy have Charcot osteoarthropathy [61, 62]. It most commonly affects the midfoot, but may occur anywhere in the foot or ankle.

Acute Charcot osteoarthropathy presents as a red, hot, swollen foot or ankle. Infection may also be present if there is fever and elevated ESR, CRP, or WBC [63]. However, infection cannot be excluded in the absence of systemic signs of infection and laboratory results. In a study of 24 patients with Charcot osteoarthropathy, Chantelau reported that 80% were misdiagnosed as having a sprain, osteomyelitis, Sudeck's atrophy, deep vein thrombosis, cellulitis, or rheumatoid arthritis [64]. In the acute phase of Charcot, pain may or may not be present, skin temperature of the affected foot is typically 2–6 degrees Celsius warmer than the contralateral side. The acute phase lasts for days to years [65]. The transition to chronic Charcot results in irreversible deformity [62].

Eichenholtz [66] described three stages of Charcot: Stage one—bone dissolution, Stage 2 -bone coalescence, and stage 3—bone remodeling. Clinically, stages I and II are characterized by inflammation. Charcot foot Stage 0 has been added to the stages of Charcot and is characterized by inflammatory foot edema, but with no radiographic bony abnormalities [64, 67–69].

Plain radiographs should be obtained at initial presentation and will show subchondral and periarticular changes in the midfoot with polyarticular distribution [64]. Plain radiographs have a less than 50% sensitivity and specificity in detection of acute Charcot osteartropathy [62, 64, 70].

MRI is the most sensitive modality in the detection of acute Charcot. MRI will show evidence of soft tissue edema and early stages of joint disruption, joint effusions, and subchondral bone marrow edema of involved joints [70–72]. Misinterpretation of signals in the marrow and cortex may occur in the presence of osteomyelitis or fractures related to Charcot [73]. Charcot osteoarthropathy usually has multiple bones and joints involved while osteomyelitis usually affects a focal area and does not cause deformity.

Technetium-99m methylene diphosphonate bone scan provides an increased uptake in all three phases with both Charcot and osteomyelitis. Labeled white cell scans usually do not accumulate at sites of new bone formation without infection. However, WBC scan can be falsely positive without any infection due to an increased uptake at radiographically invisible periarticular microfractures [74].

35.9 Medical Management of Neuropathic Infection

Infection of an ulcer site is a significant risk factor for lower extremity amputation [9, 10]. Management of an infected neuropathic foot include ridding the foot of infection, removal of pressure from the ulcer site, appropriate wound care, and prevention of recurrence.

Control of infection: A clinically infected foot requires antibiotics guided by cultures. Initial antibiotics should provide coverage of suspected pathogens. For severe infections, intravenous antibiotics with polymicrobial coverage including gram-negative and gram-positive aerobes and anaerobes should be used [75]. As deep wound cultures become available, antibiotic coverage can be focused to determined pathogens and sensitivities. Mild soft tissue infections typically require 2 weeks of therapy [21]. Deep soft tissue infections may require longer courses of antibiotics of up to 2 months [21]. Osteomyelitis requires 6 weeks or longer of antibiotic therapy in addition to surgical debridement of the infected bone [76]. Ulcers over an osseous prominence that fail to heal with offloading should be evaluated for osteomyelitis.

Wound care and debridement: Inappropriate footwear it the most common cause of neuropathic ulcerations in a diabetic patient [77]. A biomechanical exam and offloading is essential to remove abnormally high pressure areas in a neuropathic patient. Techniques for offloading, such as accommodative inserts, Controlled Ankle Motion (CAM)-walkers, CROW boots, total contact casting, or use of felt, may be effective at preventing or healing an ulcer. Armstrong et al demonstrated that a total contact cast resulted in quicker healing of ulcers compared to removable casts and half shoes [78]. Increased healing in these patients is likely due to an increase in compliance. In a study by Armstrong et al, patients that were given a removable cast only wore it for 28% of steps taken [79]. Piaggesi et al. showed that patient with total contact casts have better healing as demonstrated histologically with evidence

of angiogenesis and formation of granular tissue as opposed to patient treated with debridement alone [80]. Contraindications to non-removable casts include infection or ischemic wounds. Offloading via surgical procedures, such as exostectomies, Achilles tendon lengthening for forefoot ulcers, realignment arthrodesis, osteotomies, tendon transfers, or amputations may be necessary for adequate offloading and wound prevention. Computerized gait analysis is effective at assessing areas of high pressure, allowing improved customization and use of orthotic devices.

Superficial sharp debridement of ulcerations can be performed in the clinical or surgical settings in order to remove hyperkeratosis, necrotic tissue and foreign material, potentially exposing a healthy granular base within the wound [76]. Deep ulcer debridements may be warranted in advanced ulcers. Sharp debridement of the ulcer site allows for a thorough removal of bacteria and necrotic tissue while increasing healing potential [81]. Sharp debridement should include the removal of all necrotic bone and soft tissue, devascularized structures, and a small segment of uninvolved bone for histopathology evaluation. Larger wounds may require multiple debridements in order to obtain healthy granular wound beds. Once infection has been eradicated, ulcer excision with primary closure, local or free flaps can be used for wound coverage.

Clostridial collagenase can be used as a chemical debridement and has reduced the mean wound area when compared to sharp debridement [82]. Hydrocolloid and hydrogel dressings facilitate autolysis of necrotic tissue. Contraindications for hydrocolloid and hydrogel dressings include infection.

Several choices for dressings are available, and selection is specific to wound etiology and patient characteristics. While moist to dry dressings are common, newer dressings are available that provide a moist environment without tissue destruction. Dressings available include collagen-protease or cellulose and hyaluronan matrix replacements. Treatment of local edema in addition to wound bed management should be utilized. Armstrong and Nguyen demonstrated that edema reduction via the use of a pneumatic pump in addition to debridement improved healing as compared to sharp debridement alone at 12 weeks [83].

Negative pressure wound therapy (NPWT) can be used to stimulate angiogenesis and the formation of granular tissue, resulting in a significantly reduced healing time [84, 85]. NPWT achieved wound closure in 43% of patients compared to 29% when treated by advanced moist wound therapy [86]. Once a healthy granular tissue is achieved, split thickness skin grafts can be applied to provide an effective method of covering larger areas of skin defects and granular tissue beds [86, 87].

Revascularization: In a prospective study of 70 patients, Prakash et al found that the presence of neuropathy increases the risk of foot ulcerations and the presence of ischemia worsens the presentation [88, 89]. Peripheral vascular disease in diabetes typically involves occlusive lesions involving the femoral-popliteal segment and the tibial arteries below the knee [89]. Chronic hyperglycemia leads to endothelial cell dysfunction resulting in an increase in thromboxane A2 and a decrease in vasodilators, resulting in a hypercoagulation state and vasoconstriction respectively [90].

Vascular assessment includes Doppler ultrasound, ankle-brachial index (ABI), toe-brachial index (TBI), duplex ultrasound, and angiography (Fig. 35.2) [87, 91]. In patients with peripheral arterial disease, grafts and bypasses may be indicated. If

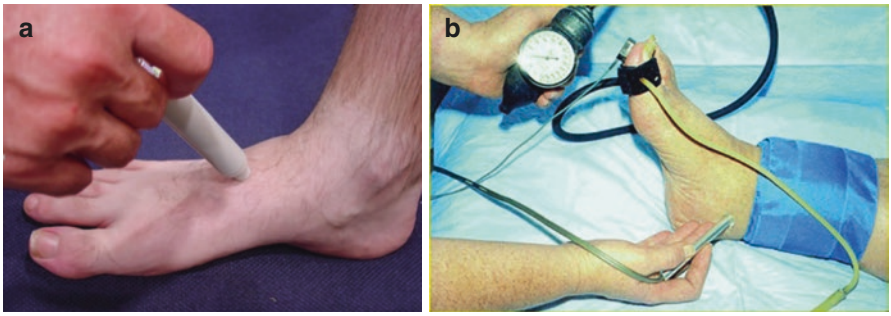

Fig. 35.2 Vascular assessment; (**a**) Doppler ultrasound for the dorsalis pedis artery; (**b**) ankle-brachial index/toe-brachial index

vascular interventions are indicated, the procedures should be performed as soon as possible. In situations that vascular interventions are not feasible, amputation of the limb may be warranted [1].

Management of comorbidities: Strict glucose control in patients with diabetes can help delay or prevent neuropathy. Chronic hyperglycemia impairs leukocyte function [14, 92]. Increased T lymphocyte apoptosis inhibits healing in patients with diabetic foot ulcers [93]. Lowering hemoglobin A1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of diabetes [94]. Patients should be advised to stop smoking. Incisional wound infections are higher in smokers than in nonsmokers and former smokers [95].

35.10 Conclusion

Early diagnosis and management of diabetes and neuropathy can aid in the prevention of ulcerations and amputations. Care is best delivered through a multidisciplinary approach. High risk patients should be identified during routine foot exams. Routine foot examinations should be performed on all patients with diabetes to achieve early diagnosis and prevention of foot ulcerations. Clinical diagnosis and valuable imaging modalities can assist with diagnosing infection, which should be treated appropriately and timely to achieve the most successful outcomes. Effective preventative interventions to avoid infection should include strict glycemic control, smoking cessation and vascular health, intensive podiatric care, offloading of high pressure locations, and debridement of wounds and calluses.

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Chapter 36
Surgical Management of the Infected Diabetic Foot

Shane J. Reynolds, Michael I. Gazes, and Peter A. Blume

36.1 Introduction

The diabetic foot is a personal, socioeconomic, and medical issue that remains prominent despite multiple medical improvements over the last few decades. Foot ulcerations occur in a sizable subset of all patients with diabetes and are a very costly. Diagnosing infections in these patients is more difficult than in healthy individuals, which leads to more serious complications. Infection management varies. Some of these infections can be treated with outpatient antibiotic management, whereas others are much more complex in nature. These more serious infections can be classified into skin and soft tissue infections, bony infections, and surgical emergencies, all of which require surgical intervention to permit the patient to progress to an uninfected state. The degree of and timing of intervention differs with each level of infection in the diabetic foot.

The term diabetic foot infection comprises many different entities that span a wide range of infectious processes. Diabetic foot infections range from local fungal infections of the toenails to necrotizing limb- or life-threatening infections. With the combination of immune dysfunction, diabetic neuropathy, vascular compromise, and delayed detection, cellulitis and other minor infections may rapidly progress. In addition, laboratory and clinical markers of infection, such as elevated white blood cell (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fevers may not manifest until the infection is advanced secondary to impairment of a patient's immune system.

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In the face of the innumerate advancements in medical and surgical care during the last few decades, foot complications remain a prominent public health issue and are the single most common reason for hospitalization of diabetic patients with diabetes. Patients with diabetes have a 15% chance of developing a foot ulcerations over their lifespans. Of these ulcerations, a subsequent/overlying infection is a frequent complication (40–80%) [1]. This often leads to some form of surgical intervention. 15% of diabetics who develop ulcerations develop osteomyelitis. 15% of foot ulcers result in amputations.

Despite the fact that people with diabetes comprise only 6.3% of the U.S. population [2], it is noted that they account for more than half of all non-traumatic lower extremity amputations. Additionally, they have only a 40% 5-year survival after amputation. Diabetic foot ulcerations are the cause of 20% of all diabetic hospital admissions and cost more than $4500 to treat per episode [3]. Other than the clear psychological ramifications, diabetic foot complications result in large individual costs and a sizable economic burden.

36.2 Diabetic Foot Infections

Diabetes causes impairment in the functioning of polymorphonuclear (PMN) leukocytes, which can manifest as a decrease in migration, phagocytosis, and intracellular activity [4, 5]. Additionally, hyperglycemia seems to be a compounding factor with evidence that shows some of the defects appearing to improve with control of hyperglycemia [6], which highlights the need for a well monitored and consistent control of blood sugar values. Furthermore, the presence of peripheral arterial disease (PAD), diabetic peripheral neuropathy, and/or decreased cellular immune response leads to reduced local inflammatory responses and the standard clinical signs and symptoms of local infection, making the diagnosis of a diabetic foot infection less apparent [7, 8]. Therefore, undetected and uninfected foot ulcers often have a high likelihood to convert to acute infections. Most of these infections involve soft tissues of the foot, but about 15–20% of the patients develop further more serious infections [1].

Early detection, assessment, and timely surgical intervention are imperative. The aim of most interventions is to salvage as much tissue as possible while still removing all non-viable tissue and bone, potentially leading to eradication of infection. Additionally, the surgeon must take into consideration the post-operative functionality of the patient's foot. Residual foot deformities may lead to abnormal osseous prominences, possibly leading to re-ulceration [9] and further complications. Additionally, vascular compromise leads to poor healing and involvement of a team that can perform revascularization procedures is paramount. The surgeon treating diabetic foot infections needs to have an extensive knowledge of the pedal anatomy and function to allow the patient to heal effectively.

Diabetic foot infections can be classified into skin and soft tissue infections, bony infections, and limb- or life-threatening infections. The non-limb-threatening

diabetic foot infections are often mild-to-moderate infections associated with a diabetic foot ulcer. They often have less surrounding cellulitis and demonstrate no signs of systemic compromise. The more serious infections need urgent surgical management to allow for a better prognosis.

36.2.1 Skin and Soft Tissue Infections

Skin and soft tissue infections of the foot typically begin with local infectious symptomology and can eventually spread to a systemic level. Knowledge of the common bacterial infectious agents, a timely diagnosis, and early management allows for successful control of these infections in most circumstances. However, there are cases where surgical debridement is imminent. These instances require an astute surgeon to take notice and intervene in a timely fashion. It is widely accepted that deep skin and soft tissue infections need to be treated both with adequate surgical debridement and effective initial broad spectrum antibiosis, which is then narrowed via guidance by operative cultures.

36.2.2 Infected Ulcerations/Cellulitis

The diabetic patient has a 15% chance of developing an ulcer over the span of their lifetime [10]. If the patient does not present for routine foot evaluations, these ulcerations, most often secondary to complications with peripheral neuropathy, often remain undetected until they are infected. They become acutely problematic, sometimes in need of urgent debridement so they do not progress to even further limb- or life-threatening infections. Clinical diagnosis of infection is based on the presence of a combination of purulent discharge from the ulcer, associated cellulitis, calor, and signs of systemic toxicity. Furthermore, multiple imaging modalities assist in diagnosing the anatomical level of infection involvement to guide surgical intervention. The more extensive the involvement of the skin and soft tissues, the more extensive the debridement.

Once a patient with diabetes is diagnosed with an infected ulceration, prompt intervention and antibiosis is necessary to decrease progression to deeper or more proximal tissue and/or bone. Surgical debridement of all involved tissues with removal of all non-viable tissue to healthy wound margins is imperative. Devitalized tissue in a wound can delay healing, predispose the patient to further infection, and interfere with adequate assessment of the severity of the wound. [11] Surgical debridement of non-viable tissue exposes the healthy tissue, which in turn restarts the wound healing process (Fig. 36.1). Furthermore, debridement decreases the risk of further infection by removing the microbial contaminants. Patients should be informed that after debridement, the wound will appear larger and bleeding is likely

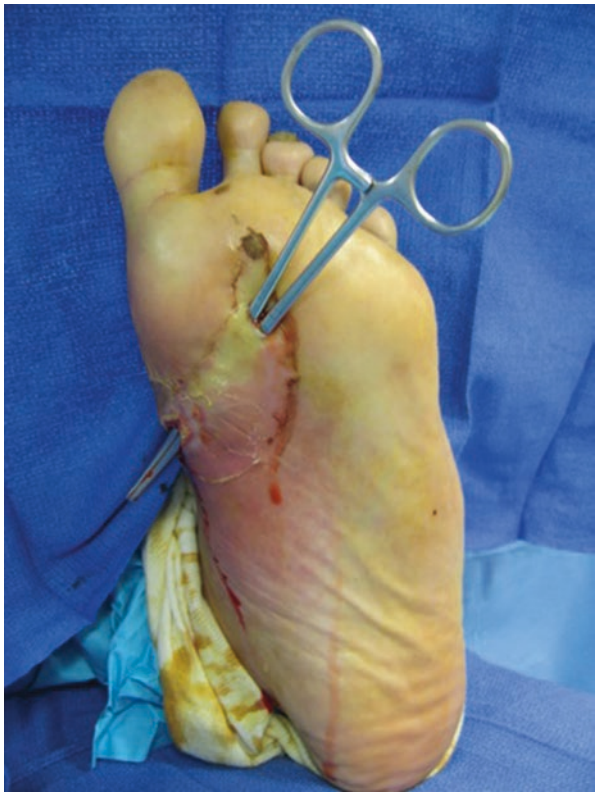

Fig. 36.1 Infected diabetic foot infection with tunneling

pending vascular status. Surgical wounds will remain open post-operatively to heal by secondary intention, further local wound care, or staged intervention (Fig. 36.2).

Proper microbiologic and pathologic examination is also of paramount importance. Taking specimens from infected sites and having specimens evaluated microbiologically and pathologically is necessary to guide the patient's post-operative antibiosis selection and duration. This is especially important for diabetic foot infections, as most are polymicrobial in nature. These infections typically have 3–5 species of microorganisms present, including aerobic gram-positive cocci, gram-negative rods, and obligate anaerobes [12]. Whenever possible, the laboratory will culture material from a deep curettage of a debrided ulcer or a deep tissue biopsy to guide therapy [13], rather than that of a superficial swab. However, concurrence between a swab and deep biopsy specimen, while not perfect, has been shown to be adequate [14]. Thus, samples should be obtained prior to and post-debridement to accurately assess the microorganisms causing the infection and to assure eradication of the infection post intervention. If an infective process is still identified, another surgical debridement is the mainstay of treatment, repeating the process until infection is no longer present.

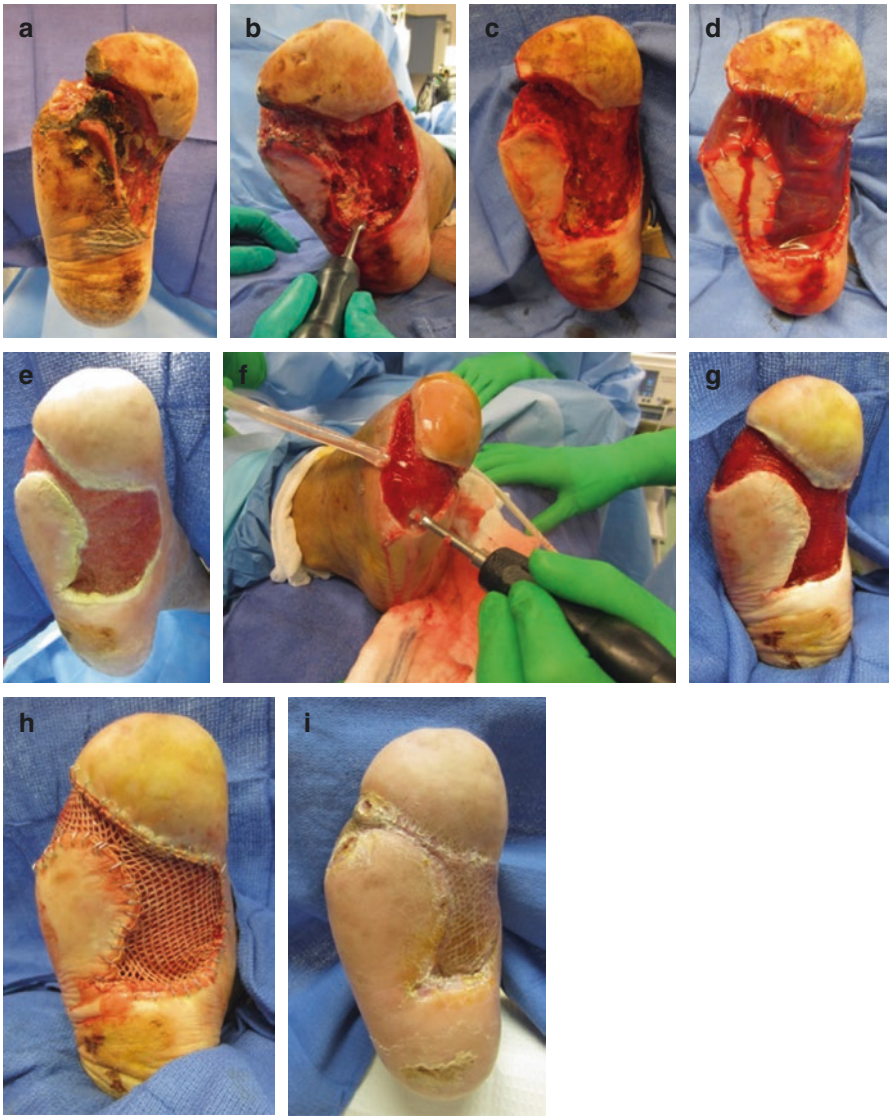

Fig. 36.2 Staged intervention, (**a**) Right foot wound post infection debridement, (**b**, **c**) Initial ultrasonic debridement staged procedure, (**d**)Application of collagen allograft skin substitute, (**e**) Appearance of foot after allograft take, pre-ultrasonic debridement in staged procedure for STSG application, (**f**, **g**), Ultrasonic debridement and wound appearance, (**h**) Application of STSG, (**i**) Wound closure

36.2.3 Abscesses

Deeper infections occur frequently in diabetic patients, often secondary to delayed diagnosis. These infections are especially troubling in diabetics, as these patients may not notice pain, swelling, and erythema, which would lead to a quick diagnosis in an otherwise healthy patient. Secondary to neuropathy and decreased immune responses, diabetic patients do not have as clear of a clinical picture. Diabetic patients may initially present with soft tissue fullness and slight erythema without any pain associated with the area [15]. Thus, an astute clinician must recognize clinical signs without subjective pain and not rule out an abscess diagnosis. Untreated, these infections could eventually lead to lymphangitis, fever and chills, leukocytosis, and other systemic symptomology [1, 16]. Therefore, if the clinician believes an abscess to be present, magnetic resonance imaging or ultrasound should be obtained to determine the etiology of the soft tissue fullness.

Once diagnosed with a diabetic foot abscess, prompt intervention is required so the infection does not progressively worsen. The physician should start pre-operative antibiotics of an empiric regimen to broadly cover the patient until microbiologic data has been obtained intra-operatively [8]. Next, a timely incision and drainage of the area with removal of all purulence and non-viable soft tissue is imperative. During this intervention, the surgeon should obtain intra-operative cultures of both the fluid and the soft tissue surrounding the abscess for adequate microbiologic evaluation. Care must be taken during the procedure to removal all abscess tissue to decrease rates of recurrence. Once all associated abscess tissue has been removed and the area is surgically irrigated, the surgical wound should be packed open to allow for further drainage to exit the site and healing via secondary intention. Post-operatively the patient should continue with antibiosis for 1–2 weeks [8].

36.2.4 Diabetic Foot Infections with Osteomyelitis

Osteomyelitis (OM) is a highly destructive complication of diabetic foot infections. It is often associated with diabetic foot ulcerations, as bone infections are present in up to 60% of infected diabetic ulcers. It often requires aggressive, early, well-planned surgical intervention pending vascular status. In situations with vascular compromise, a revascularization procedure may be needed prior to amputation/debridement. There are multiple ways to classify osteomyelitis; hematogenous vs direct extension, cortical vs medullary, acute vs chronic.

When soft tissue infection progresses into deeper structures, or if bone is exposed, microorganisms begin colonizing local and surrounding tissues. Bacteria attach to osseous surfaces via high-affinity receptors for bone matrix proteins, such as fibronectin [17], and penetrate cortical bone, eventually gaining access to the central marrow canal. Once the bacteria have established themselves in the bone marrow,

they can evade host immune responses and antibiotics by hiding intracellularly, slowing metabolic rates, or forming glycocalyx biofilms [19]. These bacterial antigens stimulate inflammatory cells to generate soluble factors, such as interleukin-1 and tumor necrosis factor, which stimulate osteoclast-mediated osteolysis [20]. On radiographic evaluation, this feature is seen as periosteal reaction.

Clinically diagnosing osteomyelitis requires a thoroughly evaluation. Physical examination, imaging, lab work, and biopsies are all tools that should be utilized. On physical examination, the presence of bony exposure in the wound, or a positive "probe-to-bone" test, has a specificity of 85% and positive predictive value of 89%. However, sensitivity is only 66% [5]. Furthermore, lab work such as ESR (>70 mm/h) and elevated CRP help identify osteomyelitis. The presence of leukocytosis may aid in diagnosis, but is frequently absent secondary to impaired diabetic immune responses. Multiple imaging modalities exist to identify osteomyelitis. Plain films demonstrate periosteal reaction followed by focal erosion of cortical or medullary bone. Unfortunately, these changes are generally not evident on plain films until 40–70% of the bone has been resorbed, reducing the sensitivity in the first 2–4 weeks of infection [19]. Three phase bone scans demonstrate increased bone uptake in all three phases, yet the specificity of this test is poor, averaging less than 50% [21, 22]. MRI sensitivity is high, generally reported to be between 90% and 100%, whereas specificity ranges between 80% and 100% in most studies [23, 24]. Furthermore, MRI offers excellent anatomic detail versus other imaging modalities. This allows for improved evaluation of the extent of bone and soft tissue involvement, which is especially useful in operative planning. Bone biopsies, often used as the gold standard for diagnosing osteomyelitis can be completed prior to operative intervention to assure an accurate diagnosis when the other clinical signs are questionable.

Each patient is different, and thus no one operative management is fully encompassing for osteomyelitis. However, it is imperative to have a multidisciplinary approach for these patients. A primary care team, podiatric surgeon, vascular surgeon, infectious disease team, and other specialists give the patient a well-balanced management with the strongest likelihood for healing. Adequate blood flow, appropriate antibiosis, and early, aggressive debridement are imperative to allow the patient to heal properly.

The average 5-year survival rate after a diabetic foot amputation is approximately 39%. When planning for operative debridement, the entire care team needs to adequately assess the patient [25]. The primary plan should be to eradicate the infection. However, a secondary consideration of needing to salvage as much of the foot as possible to allow for efficient, low-energy, functional ambulation is also imperative. The more proximal the amputation, the higher the stress placed on the patient's body and the more likely the patient is to develop further complications.

An "oncologic approach," with radical debridement and an end plan for a functional foot should be carried out [26, 27]. First, the patient's vascular status should be evaluated if the osteomyelitis is not causing a life-threatening infection. Thus prior to any non-acute osteomyelitis, the blood flow should be assessed and revas-

cularization should be performed if necessary. Next, all infected bone with adequate margins, infected soft tissue, and bone marrow should be removed with the site copiously irrigated [28]. The size of the defect produced by the procedure is not a primary consideration [29], as the aim is to completely eradicate the infection. During resection, samples for culture and pathology should be obtained of the infected sites and of the clean margins post lavage. Next, the surgeon should evaluate how extensive the resection was and manage the newly created "dead space." [29] Implantation of antibiotic beads, spacers with or without antibiotics, packing strips, or a wound VAC are frequently utilized (Fig. 36.3). Moreover, depending on the situation, septic joint arthrodesis can occur with management (Fig. 36.4). These modalities provide a decreased likelihood of a new infection forming in the "dead space". If a surgical cure has been achieved, such as in cases of digital amputations with infections only involving the distal phalanges, then primary closure can be completed. On the contrary, if the surgeon is concerned with any possibility of remaining infection, then the surgical site should remain at least partially open for drainage to occur until pathology and microbiology tests have resulted. If clinical examination and blood tests show the infection effectively eradicated, then either a definitive soft tissue delayed primary closure is carried out 4–8 days later, or the area is allowed to heal via secondary intention. If the results are positive for remaining bony infection, then either antibiotics, typically a 6-week duration, or another surgical intervention with further debridement occurs. After surgical eradication of the infection has been completed, reconstructive efforts can then be attempted for foot stability and functionality.

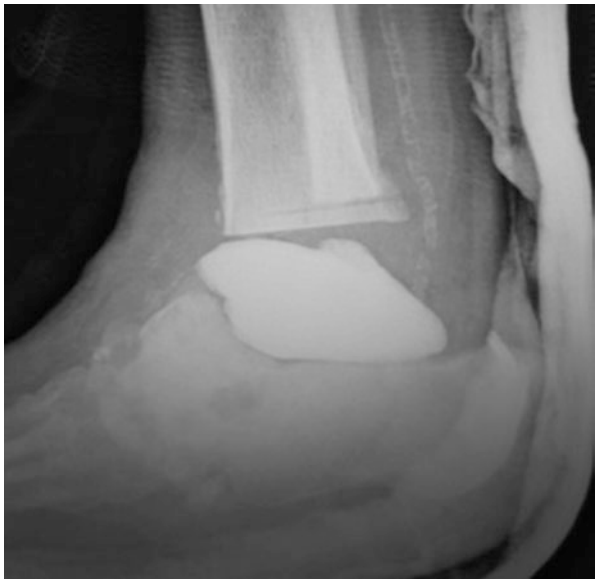

Fig. 36.3 Antibiotic spacer in the ankle joint

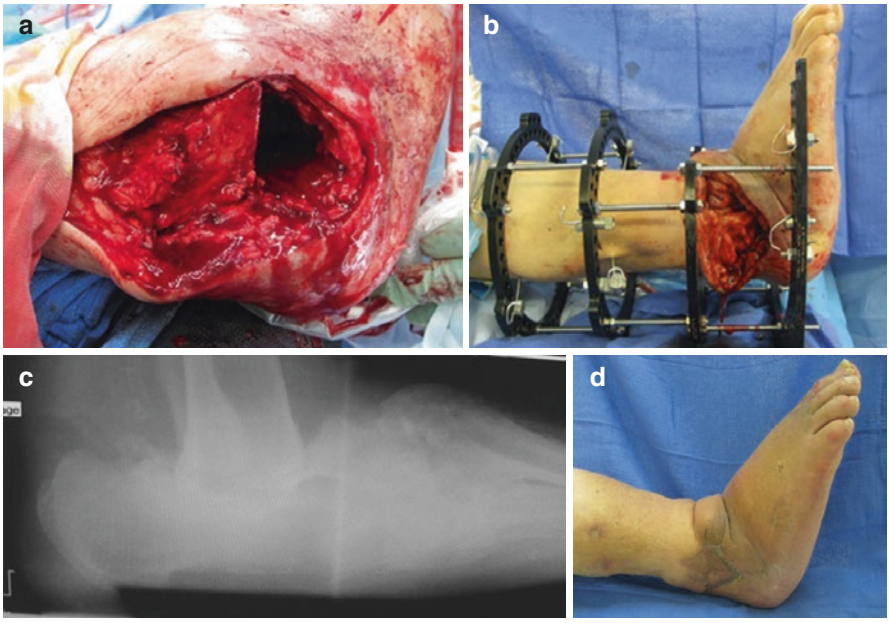

Fig. 36.4 Septic fusion utilizing external fixation, (**a**) Joint preparation, (**b**) Application of external fixation with no internal fixation utilized, (**c**) Post removal of external fixation, (**d**) Plantigrade foot

36.3 Surgical Emergencies

The most worrisome of the diabetic foot infections are those that are considered surgical emergencies. These include gas gangrene, necrotizing fasciitis, and septic joints. These infections can spread rapidly, leading to a need for extensive debridement with focus on "damage control." Similar to the treatment plans for osteomyelitis, the aforementioned surgical emergencies are focused on eradication of the infection then secondarily directed at a reconstruction opportunity if needed.

Gas Gangrene and Necrotizing Fasciitis. These infections, are rapidly progressing and possibly life-threatening form of tissue death. They are associated with a high mortality rate (20–80%) [30, 31], often necessitating amputation in order to control the infection [32]. The most common bacteria causing these types of infections are classically primarily the Clostridia species with gas gangrene and Group A Strep with necrotizing fasciitis. Nevertheless, polymicrobial infections occur with the aforementioned bacteria in addition to Bacteroides, Enterobacteriaceae, Proteus, among others [33, 34]. The patient often presents with fever, pain, skin discoloration, reversed temperature gradient, and an erythematous foot with streaking up the foot/leg. Edema and crepitus are usually present; however, in as many as 50% of cases there may not be any discernable crepitus or gas on radiographs upon the initial presentation [35].

These patients should be imaged emergently. Often subcutaneous emphysema will be present on plain film imaging. However, if plain radiographs do not demon-

strate gas, then a computed tomography (CT) scan could be conducted, as it has a higher sensitivity for subcutaneous, gas. The absence of gas on plain films does not rule out gas gangrene.

Once diagnosed, prompt initiation of broad antimicrobial treatment is critical. The decision becomes whether the limb is possible to save via intervention, or if primary amputation should be performed. If possible, in depth discussion should be had with the patient, with comprehension of potential surgical outcomes if intra-operative findings of infection call for primary amputation. Limb salvage may require multiple surgical interventions, in staged format, can lead to chronic pain, and require multiple hospital admissions. In the end, these interventions may still not lead to a functional foot [36, 37]. Early amputation and prosthetic fitting has been associated with decreased morbidity, fewer operations, shorter hospital course, decreased hospital costs, and shorter rehabilitation in cases of traumatic limb injury; however this may have psychological effects and lead to different complications depending on patient compliance [36]. In either case, the patient requires prompt intervention to prevent further spread of the infection. The patient typically requires radical debridement with removal of all non-viable tissue and bone. Urgent surgical drainage must always be done before any revascularization procedure takes place. The revascularization procedure must be done, however, as soon as possible after the drainage procedure if it is deemed necessary [38]. During the surgical intervention, cultures should be obtained to guide therapy. If multiple toes or heel necrosis presents, a limb-salvage procedure is less likely to be successful, and may be a threat, to the patient and require amputation.

36.4 Conclusion

Different types of infection occur in the diabetic foot. Mild skin and soft tissue infections can typically be treated with outpatient management. Moderate to severe infections, infected ulcers, and osteomyelitis typically require effective work-up and surgical intervention, with an end goal of an uninfected and functional foot. Emergencies, including gas gangrene and necrotizing fasciitis, require urgent and emergent surgical intervention, where the limb is not always salvageable. Patient selection based on co-morbidities and patient preference should always be taken into account for surgical planning; however, in instances where infection is too great for appropriate medical and surgical reconstructive management, primary amputation should be considered.

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Chapter 37
Infected Charcot Foot: Surgical Management

Venu Kavarthapu

37.1 Infected Acute (Active) Charcot Foot

Acute (active) CN can progress much more quickly in some patients if the foot is not protected optimally, resulting in rapid bone disorganisation and destruction. This leads to marked foot swelling, often due to fragmentation of the involved bones and associated haematoma formation. This sometimes presents as a 'bag of bones' on palpation of the foot, due to the presence of bone fragments bathed in liquefied haematoma. The resulting progressive deformity and instability makes the foot vulnerable to develop skin rubs and ulceration over the bony prominences. An uncommon source of infection in an active Charcot foot is haematogenous seeding. Whichever the source of bacterial seeding, the haematoma can provide an excellent medium for infection to flourish, resulting in rapid dissemination. In general, osteomyelitis without skin breakdown is extremely rare.

Treatment of the infected active Charcot foot can be divided into three parts: treatment of the infection, off-loading treatment of the active Charcot foot to convert to an inactive foot and management of deformity.

37.1.1 Treatment of Infection

Infection may manifest as a localised infected ulcer, an infected ulcer with superficial spreading infection or with deep tissue infection (Chap. 33). Occasionally, such infection leads to local tissue necrosis with spread of infection along the tissue

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planes. This is frequently noted along the tendon sheaths and this route of spread is often coined as along the 'super highways'. This manifests as a large area of spreading cellulitis proximal and distal to the ulcer and also as a systemic response to infection. Such aggressive infection is called a 'foot attack' [1] (Fig. 37.1). The risk factors for such rapidly spreading infections with tissue necrosis include the history of the presence of previous ulcer, previous amputation, neuropathy, peripheral arterial disease and deformity.

The infected active Charcot foot is best managed in a multidisciplinary set-up using a structured emergency pathway [2]. The underlying principles are to diagnose infection rapidly, culture the bacteria responsible, treat aggressively with antibiotic therapy and consider the need for debridement and surgery. The patients are initially seen in the diabetic foot clinic, bacterial cultures taken, commenced on intravenous antibiotics and a decision taken as to the need for surgical debridement.

The principles of management of infected active Charcot foot with deep tissue infection thus include the following:

1. Rapid diagnosis of the infection is achieved by performing thorough clinical examination, including vascular assessment. The blood investigations include serum C-reactive protein levels, as this is often elevated to greater than 100 mg/L in acute severe infections. The leucocyte count is, however, a poor indicator of infection. MR imaging is useful in identifying the presence of osteomyelitis and soft tissue collections. In such infections, 'time is tissue', so it is recommended not to delay the treatment by performing extensive imaging studies.
2. Specimens for microbiological cultures are collected prior to starting intravenous antibiotics. This is achieved by taking deep tissue specimens from the base of the ulcer if present and sending them for both aerobic and anaerobic culture. Ultrasound guided aspiration is performed if there is any clinical or MRI evidence of deep collection.
3. Empirical intravenous antibiotic therapy is commenced soon after obtaining the microbiological samples. The antibiotics are changed as per the microbiological sensitivities of the bacteria responsible for infection [2].

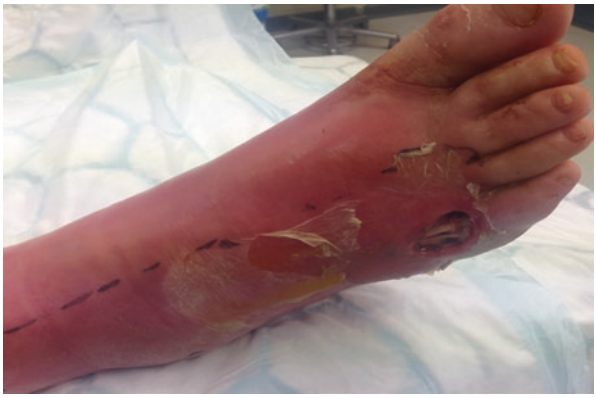

Fig. 37.1 Foot attack demonstrating a large area of spreading cellulitis proximal and distal to the ulcer and local tissue necrosis

4. In the presence of tissue necrosis or deep tissue collection, an urgent aggressive surgical debridement is performed and the wound is left open. Repeat debridement is performed as required (Figs. 37.2, 37.3, and 37.4). Negative pressure wound therapy (NPWT) is commenced as soon as practical to promote wound healing and clearance of residual collection. The foot is meanwhile stabilised either in a total contact cast which is "windowed" for small wounds or a bivalve cast for larger tissue defects. The antibiotic treatment is continued until the infection is completely cleared as noted by clinical parameters and serological markers. Skin grafting or a similar form of plastic surgical procedure is performed to achieve soft tissue coverage of the wound.
5. After initial debridement, these patients should be kept under close clinical, biochemical and microbiological surveillance with deep swabs and surgical tissue specimens. High levels of serum CRP, or a clinical failure to respond to antibiotics may require repeated surgical intervention or a change in antimicrobial therapy.

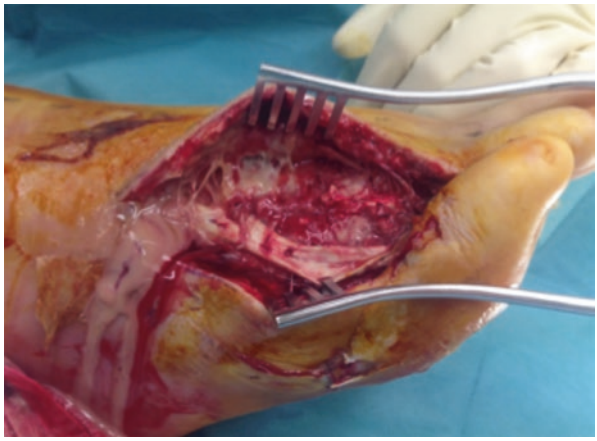

Fig. 37.2 Foot attack demonstrating a large pus collection with tissue necrosis and evidence of spread of infection along the tendon sheaths

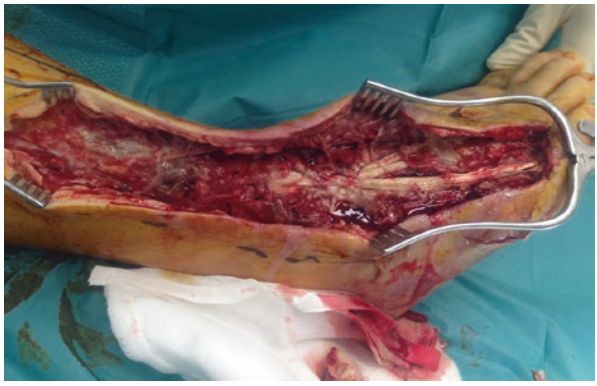

Fig. 37.3 Adequate aggressive sharp surgical debridement has been performed

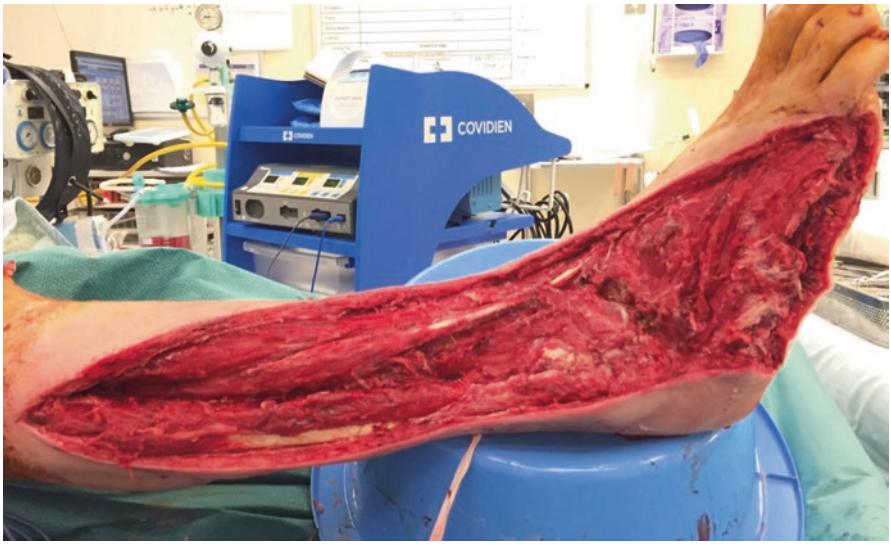

Fig. 37.4 Repeat sharp surgical debridement after 48 h showed healthy healing tissue with no evidence of residual infection

37.1.2 Off-loading Treatment of the Active Charcot Foot

After achieving complete eradication of infection, the offloading of the foot is continued in a total contact cast progressing to a removable walker or Charcot restraint orthotic walker (CROW) and then on to an ankle–foot orthosis (AFO) with bespoke footwear until the Charcot process has resolved (Eichenholtz stage 3).

37.1.3 Management of Deformity

In the presence of significant deformity and / or instability not amenable to offloading, surgical reconstruction can be considered following resolution of the Charcot process. (Chap. 14).

37.2 Infected Chronic (or Inactive) Charcot Foot

The infected chronic Charcot foot is a more frequent presentation than the infected acute Charcot foot. It is commonly due to the skin breaking down leading to ulceration in a deformed but inactive “burnt out” Charcot foot. Most of these deformities can usually be effectively accommodated in an ankle foot orthosis and bespoke footwear so that abnormal foot pressures from altered foot shape or exostosis can be

reduced. However, severe deformity and /or instability make it difficult to prevent point loading despite advanced offloading measures, resulting in a chronic ulceration. It is important to have a high index of suspicion of infection in patients with established Charcot feet who then develop new signs of inflammation, especially when there is an associated break in the skin. The ulcers can often be complicated by secondary deep infection. The infection frequently spreads to the bone prominence and as a result leads to chronic osteomyelitis. Without deformity correction, the infected ulcer often fails to heal with antibiotic treatment alone and repeat exacerbations of infection lead to progressive bone involvement and a higher risk of amputation.

37.2.1 Assessment

The initial approach to the management of the infected chronic Charcot foot with ulceration is a clinical examination followed by investigations, including imaging and blood inflammatory markers. Detailed examination of the foot deformity, presence of mechanical instability, the ulcer, tight Achilles tendon and vascular status are performed. The ulcers can be categorized as predominantly of mechanical type when they are related to bony prominence and abnormal pressure area. In the absence of such features, the ulcer origin could predominantly be vascular or infective in origin. C-reactive protein is often a useful marker in diagnosing complicating infection in a foot ulcer. However, leucocyte count is often very unreliable.

Imaging studies include plain radiographs of the foot and ankle. Whenever possible, weight bearing anterior–posterior, oblique and lateral views are performed as these can provide information about the mechanical origin of the ulcer. MR imaging should also be performed but it is often difficult to differentiate chronic Charcot changes from osteomyelitis. If the MRI is non-conclusive, SPECT / CT (single-photon emission computed tomography/ computed tomography) or FDG PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography)could be considered, but the diagnostic accuracy of these imaging methods is yet to be fully established. If any deep fluid collection is present, ultrasound-guided aspiration can confirm the diagnosis of deep infection and isolate the organisms. If there has not been a skin breach and infection parameters are normal, a red and swollen foot in a diabetic patient is probably an acute active stage of CN rather than an infection. Furthermore, vascular compromise in a chronic Charcot is not that uncommon and this can also contribute to the non-healing of the ulcer. Vascular lower limb studies should also be carried out.

37.2.2 Management

Staged surgical reconstruction is required, particularly in those that develop ulceration despite effective offloading measures. One stage reconstruction of an actively infected Charcot foot carries a significant risk of recurrence of infection. This could

be due to the risk of inadequate or incomplete bone debridement, retention of biofilm in the previously infected areas, reactivation of infection that flourishes in the dead space left over following bone resection or administration of post-operative antibiotics that do not match the microbiological sensitivities from the intra-operative samples. In the presence of an active foot infection, including infected ulceration and osteomyelitis, a staged surgical approach reduces the risk of recurrence of infection significantly.

37.3 Two Stage Reconstruction of Infected Charcot Foot

37.3.1 First Stage- Eradication of Infection Prior to Definitive Reconstruction

Microbiological culture and sensitivities are the most crucial in the management of infected Charcot foot [2]. Deep tissue specimens from the floor of the foot ulcer taken during bedside debridement are helpful. However, if osteomyelitis is suspected, bone biopsies should be performed to confirm the presence of deep infection and isolate the organisms. The biopsy can be performed in the outpatient setup and does not routinely require administration of local anaesthetic block in this group of patients, as they often present with marked sensory neuropathy. The biopsy is done by inserting the bone harvest trochar through the healthy skin adjacent to the ulcer to adequate depth aiming for the targeted bone part and the specimens are taken from the suspected area of involvement for microbiological cultures and histological examination. Whenever possible, the antibiotic administration is not commenced until deep tissue specimen or bone biopsy has been obtained. If the patient is already on antibiotic therapy and if the clinical situation permits, these are stopped for two weeks prior to the bone biopsy procedure to improve the diagnostic accuracy.

Aggressive and radical debridement of all infected tissues, incorporating the ulcer is essential for eradication of the infection during the first stage of this staged reconstruction. Chronic non-healing ulcer usually has three zones of tissues in its vicinity. Zone 1 (red) represents the infected and necrotic tissue that can be clearly identified (Fig. 37.5). Zone 2 (amber) surrounds the red zone and represents the reactive and scar tissue (Fig. 37.6). This tissue often harbours areas of infection and is often left behind if the quality of debridement is inadequate. Zone 3 (green) represents healthy tissue that has not been affected in the infection process (Fig. 37.7). This red/amber/green (RAG) zone concept facilitates adequate ulcer debridement. It is essential that the wide excision of the ulcer extends into the green zone in all directions (Figs. 37.8, 37.9, and 37.10). Deep tissue specimens are obtained during the debridement for microbiological cultures. Specimens are taken of infected and necrotic tissue but also from the margins of the tissues remaining after debridement. It is important that each specimen is handled with uncontaminated separate set of instruments. Culture-specific parenteral antibiotics are administered and optimal offloading is provided post-operatively. Additional local antibiotic impregnated calcium sulphate or antibiotic loaded

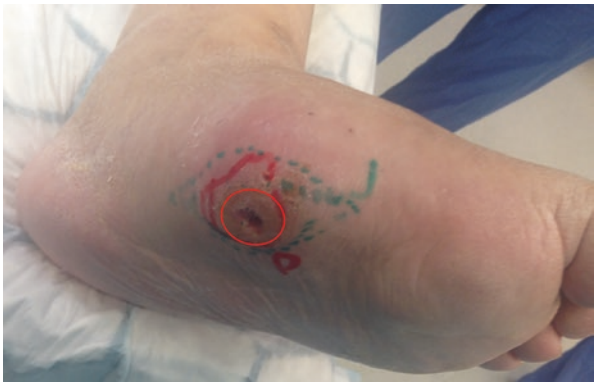

Fig. 37.5 Zone 1 (red) represents the infected and necrotic tissue

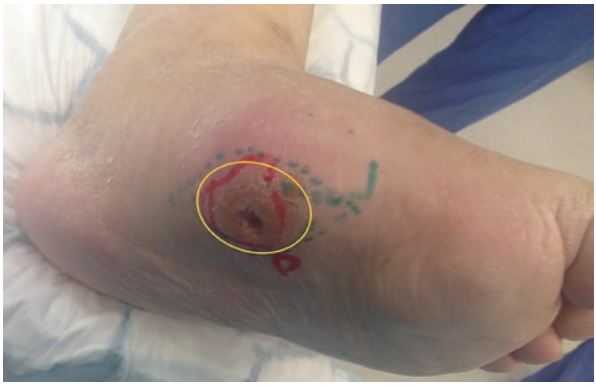

Fig. 37.6 Zone 2 (amber) surrounds the red zone and represents the reactive and scar tissue

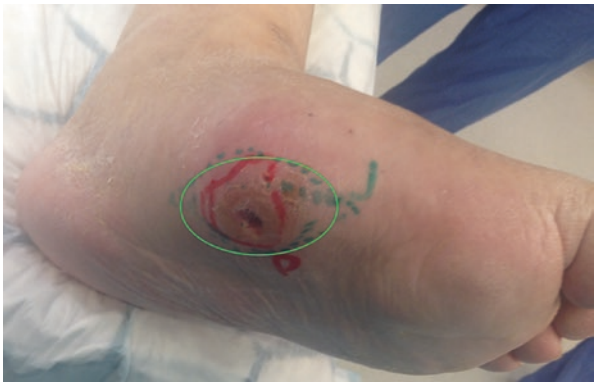

Fig. 37.7 Zone 3 (green) represents healthy tissue that has not been affected in the infection process

calcium sulphate+hydroxyapatite biocomposite can be implanted in the defect at the time of surgical debridement to improve infection clearance. The choice of the antibiotic component for local antibiotic delivery preparation depends upon the sensitivities from previous microbiological cultures. Large soft tissue defects resulting from aggressive ulcer and deep tissue debridement can be treated with NPWT.

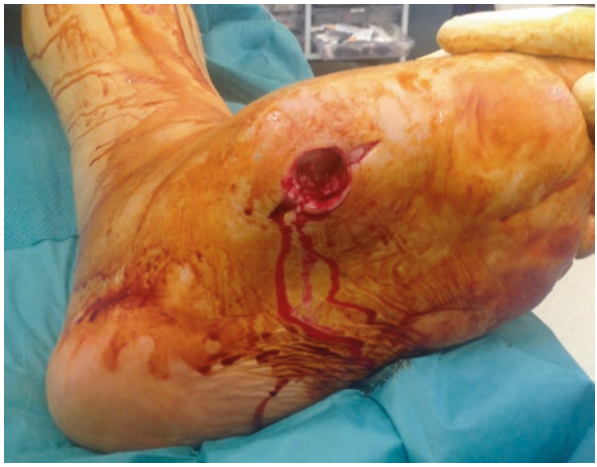

Fig. 37.8 Surgical debridement of the ulcer necrotic tissue (red zone) leaves possible residual infected area in the reactive zone

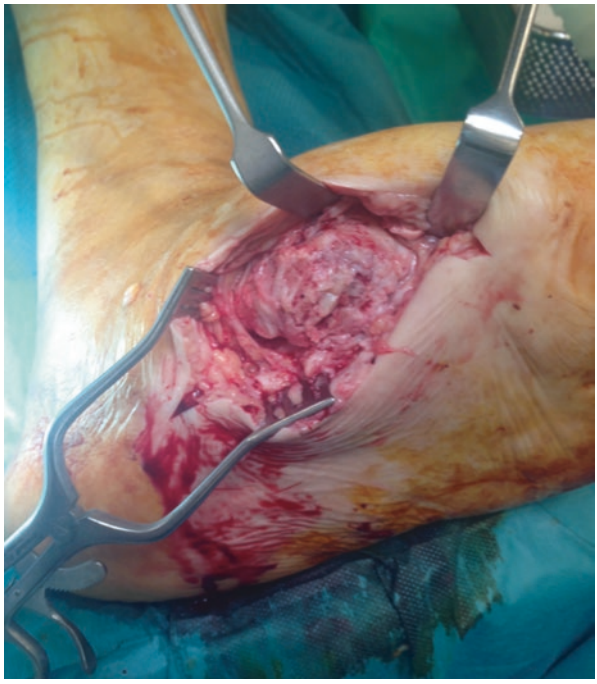

Fig. 37.9 Extension of the surgical debridement into the reactive zone revealed further pockets of necrosis and possible infective areas (amber zone)

During the first stage, aggressive debridement of the infected bone and soft tissues may result in instability due to the need for large bone resections. This instability can interfere with tissue healing, reduce the ability to eradicate infection and make it more challenging to apply the NPWT dressings. In the presence of minor instability, we recommend the use of 2–4 threaded wires (2–3 mm diameter) that are either buried in the subcutaneous plane or left protruding through the skin

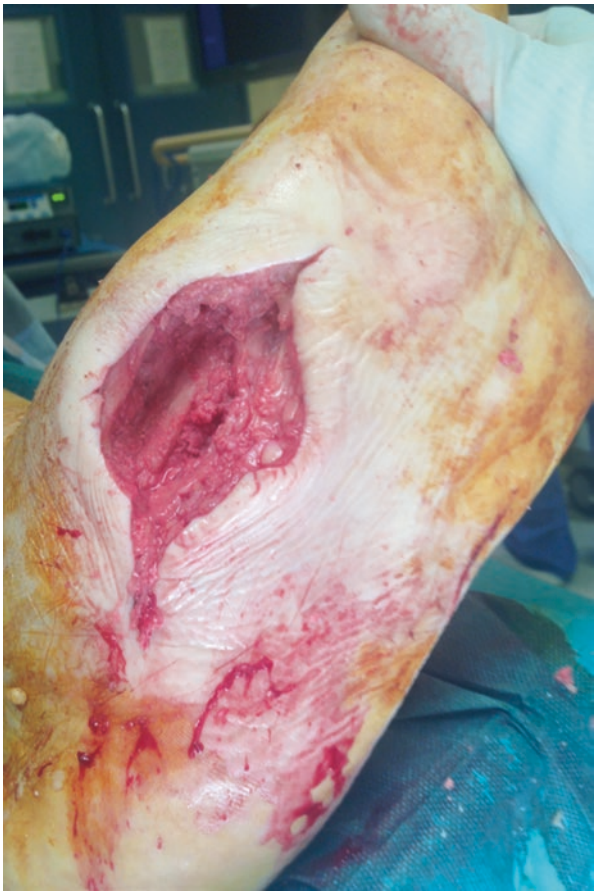

Fig. 37.10 Excision of reactive zone revealed the healthy looking normal tissue, indicating complete excision of all infected areas

for easy removal, for temporary stabilisation of the foot and ankle in an optimal alignment. In the presence of a major instability, we use a temporary external fixator to facilitate wound healing and infection clearance (Figs. 37.11, 37.12, 37.13 and 37.14). The pin-sites of the fixator need to be closely monitored for any possibility of development of local infection.

Perioperative intravenous antibiotic treatment is chosen according to the culture sensitivities from deep tissue specimens. Regular clinical and serological assessments are performed to monitor the response to the antibiotic therapy. The progression of wound healing in the presence of large soft tissue defects that are managed with NPWT is also a good sign of infection control. When there is clinical and radiological evidence of complete infection clearance, the second stage reconstruction can be performed. However, if there is concern about residual infection, a repeat surgical debridement can be carried out to achieve infection eradication before considering the reconstruction procedure. The ulcer healing may not be achieved in the presence of severe deformity even with adequate offloading. The

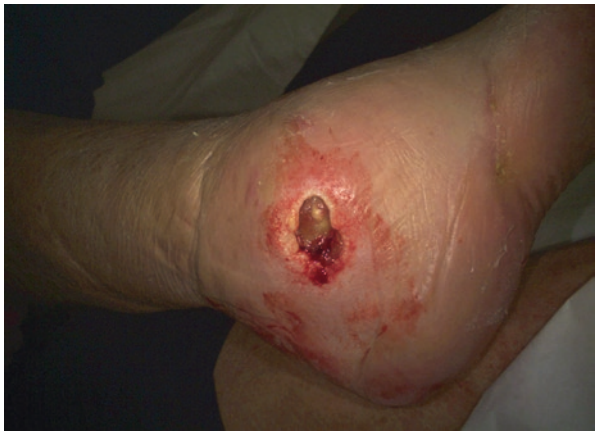

Fig. 37.11 Clinical photograph of infected Charcot foot with lateral ankle ulceration and deep tissue involvement

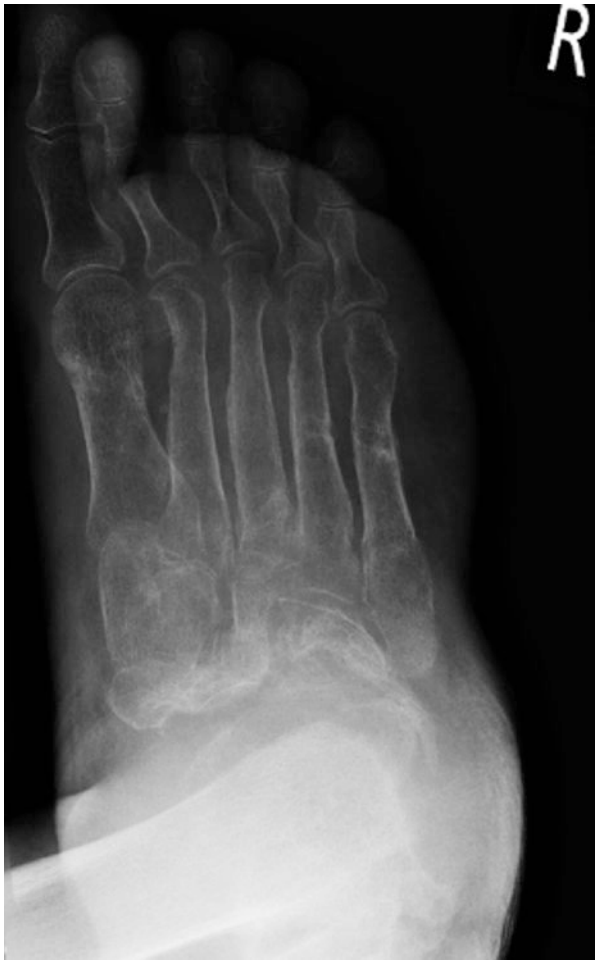

Fig. 37.12 Radiograph of the infected Charcot foot showing disruption of the right midfoot and hindfoot

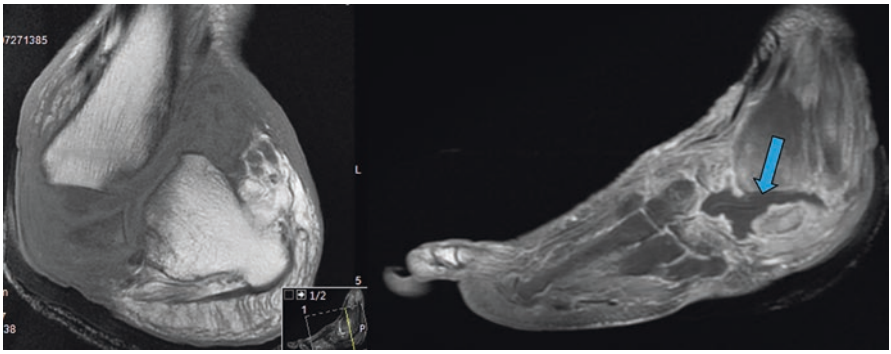

Fig. 37.13 Coronal T1 MRI imaging of ankle and sagittal T1 FAT SATURATED post-contrast imaging of foot showing the degree of deformity, bone loss and fluid collection (arrow)

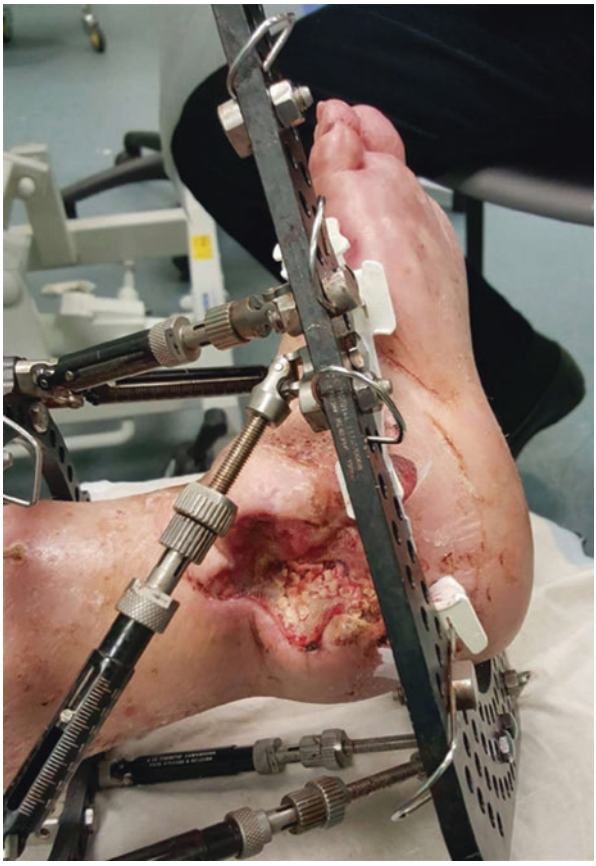

Fig. 37.14 Following radical ulcer and deep tissue debridement including, bone resections, the resulting major instability is managed with an external fixation in good alignment. In this example, antibiotic eluting calcium sulphate preparation is used, that is visible through the lateral ankle wound

aim is to eradicate infection with or without ulcer healing prior to the planned surgical reconstruction. The ulcer often heals predictably once the deformity is corrected during the second stage.

In those deformities that present with healed ulcers, it is still important to exclude any possible residual deep infection by performing bone biopsies prior to the reconstructive procedure. The biopsy is done through healthy skin adjacent to the area of healed ulcer and the specimens are taken from the suspected area of bone involvement. If the samples show positive results, the reconstruction may be performed as a two stage procedure if required.

37.3.2 Second Stage-Stabilisation

The choices of fixation include external stabilization, internal stabilization and combination of both. There are advantages and disadvantages to each method and the surgical decision-making should come down to the quality of bone and soft tissues and the surgeon's experience or preference [3].

37.3.2.1 External Stabilisation

External stabilisation method is currently the most commonly used technique during the second stage of treatment of infected Charcot foot. External fixation has been suggested to offer some advantages over internal fixation, as this can allow stable fixation, while permitting access to open wounds and potentially allow weight bearing at an earlier stage, although the findings from most published series did not show significant difference [3–5]. The pin site infection rate and patient's compliance remain the main concern with the external fixation option. Detailed surgical techniques of external stabilization in Charcot foot reconstruction are discussed in Chap. 15.

37.3.2.2 Internal Stabilisation

Internal fixation in the presence of bone and soft tissue infection is always a concern. However, recent published studies showed higher rates of limb salvage using the internal fixation technique for reconstruction of infected Charcot foot [6, 7]. The internal fixation techniques also have the advantage of better patient and surgeon acceptance over the external fixation option. The intramedullary nail serves as a rigid load-sharing device and can resist large forces across the ankle especially with the long lever arm that the foot exerts on this area. Some studies have reported high limb salvage rates in patients treated with internal fixation for hindfoot reconstruction. Siebachmeyer et al. [6] had a 100% limb salvage, Pinzur et al. [8] reported a salvage rate of 95.2%, Richman et al. [9] observed a salvage rate of 93.75% and Vasukutty [10] observed a salvage rate of 100%.

The second stage part of the reconstruction using internal stabilisation follows the same principles as one stage procedure (Chap. 14). If external fixation has been used for temporary stabilisation in the first stage procedure, the fixator is removed once the infection is cleared, based on the clinical and serological markers, about 2 weeks before the planned second stage of reconstruction. This allows a 'pin-site holiday' and promotes complete healing of the pin sites. This also minimises the risk of secondary infection from pin-track colonisation of microorganisms. Following multidisciplinary assessment, parenteral antibiotics can be stopped about 2 weeks before the second stage procedure, provided these have been administered for about 6 weeks.

If an ulcer is present, it is thoroughly debrided at the beginning of the second stage procedure. Further bone resections are done to remove any residual avascular or possible infected bone parts. Intra-operative bone and deep soft tissue samples are taken from all areas of debridement for microbiological cultures. It is important that each specimen is handled with uncontaminated separate set of instruments. These specimens are sent for microbiological cultures and histological examination. The instruments used are disposed of and the foot is washed out and re-draped.

The choice of surgical approach for the reconstruction part depends on the type of hindfoot and midfoot deformities. Wedge bone resections are performed as appropriate for correction of the deformity. Internal fixation is completed using the standard long-segment rigid fixation principles, with optimal bone opposition across the fusion site. Injectable antibiotic impregnated calcium sulphate + calcium hydroxyapatite preparation is used to fill in all bone voids in the fusion area. The calcium hydroxyapatite component of this preparation can act as the bone graft substitute. This antibiotic elution helps eradicate any possible remaining microorganisms and reduces the risk of postoperative infection. Primary wound closure without soft tissue tension is usually possible. However, this is occasionally not feasible, necessitating partial wound closure aiming for metalwork coverage and a NPWT dressing [5]. A well-padded below knee splint is applied (Figs. 37.15 and 37.16).

Parenteral antibiotics are commenced at the second stage procedure based on the microbiological culture sensitivities of the first stage debridement until the sensitivities become available from the second stage. Appropriate change of antibiotics is considered if these are different the from the previous culture sensitivities. However, in our experience, this is rarely needed.

The post-operative care is discussed in detail in Chap. 14. Management of the infected Charcot foot is very complicated and it is extremely important that this care is provided in a specialist diabetic foot unit by a multidisciplinary team.

37.3.2.3 Infection Around Internal Stabilisation Hardware

Successful reconstruction of the deformed Charcot foot results in a much improved ambulatory state of the patient. The metal work used for internal stabilisation is however prone to develop secondary infection in the long term, especially from

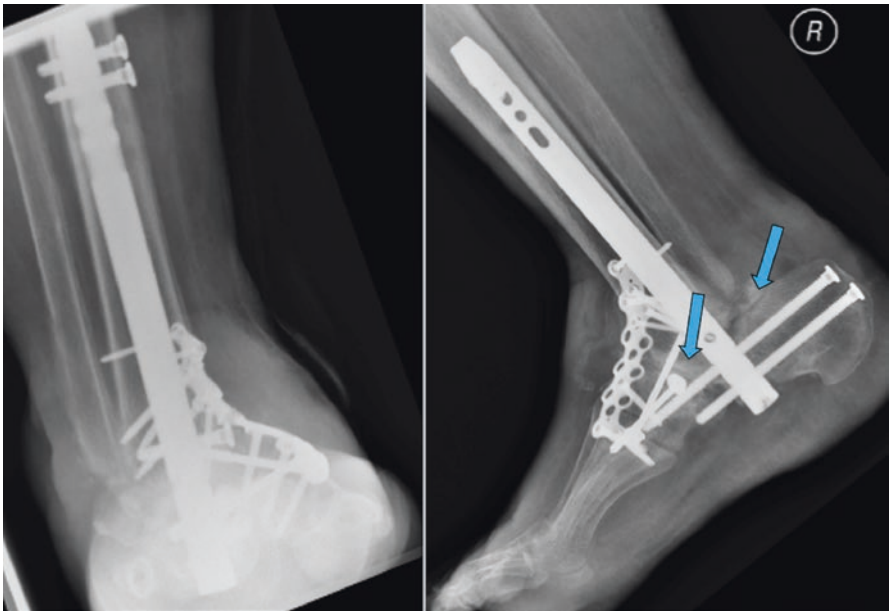

Fig. 37.15 Post-operative AP and lateral radiographs of foot and ankle showing the internal fixation construct has provided good deformity correction, secure fixation and optimal bone opposition. Injectable antibiotic eluding calcium sulphate and hydroxyapatite preparation (arrows) is used to fill in the bone voids

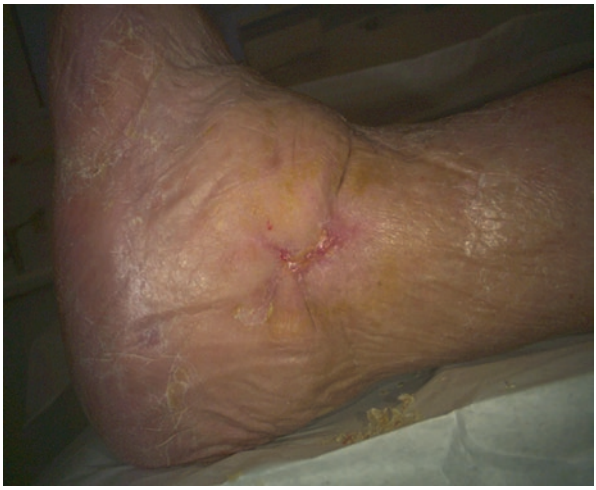

Fig. 37.16 Clinical photograph taken at 10-week follow-up showing complete healing of lateral ankle ulcer by secondary healing

haematogenous seeding of microorganisms. Custom made foot wear is provided for these patients to ensure that the foot is not subjected to abnormal loads. It is essential that the patients are adequately counselled and encouraged to attend the multidisciplinary unit if they develop any signs of local infection.

37.3.2.4 Combined Reconstruction Using Intramedullary Nail Coated with Antibiotic-Containing Cement Combined with Ring Fixation

A recent report indicates that severely deformed, infected, neuroarthropathic ankles have been treated in single-stage reconstruction arthrodesis with an interlocked intramedullary nail coated with antibiotic-containing cement combined with ring fixation [11] .Taylor Spatial Frame™ technology was used when the deformity was not amenable to acute correction. Overall, a functional and clinically stable salvaged lower limb was achieved for most patients. A further report indicated that antibiotic-coated nails have been applied to treat infected ankle nonunions and infected distal tibial fractures in Charcot patients leading to successful bony union, fusion, and eradication of infection [12].

37.4 Conclusion

Infection in a foot affected by Charcot neuroarthropathy (CN) is one of the most difficult conditions to manage and requires a specialist multidisciplinary approach to prevent the risk of foot amputation. It is useful to divide the presentation of infection into infection in the acute or active Charcot foot and infection in the chronic or inactive Charcot foot. Treatment of the infected active Charcot foot consists of treatment of the infection, off -loading treatment of the active Charcot foot to convert to an inactive foot and management of deformity. Treatment of the infected chronic Charcot foot usually requires a two stage reconstruction: first stage- comprising eradication of infection prior to a secondary stage of definitive reconstruction and stabilization.

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Chapter 38
Infected Ischemic Foot: Investigation

Samuel M. Miller, Brandon J. Sumpio, and Bauer E. Sumpio

The diabetic patient with an infected foot will often also describe a history of foot ischemia. In the absence of abnormalities in leg perfusion, the presence of neuropathy is likely and this scenario is covered elsewhere in the book. Ischemia, and the accompanying tissue hypoxia, impairs the foot's ability to heal. As the leg becomes more ischemic, the ability to fight and eliminate infection decreases, and the patient becomes more prone to ulceration. Thus, the presence of ulcers is often indicative of advanced peripheral vascular insufficiency. What starts as a simple break in the dermal barrier from the shear force of walking does not heal, and evolves into erosion of the underlying subcutaneous tissue. The patient's healing capacity is related directly to the perfusion to the affected segment of the foot.

The workup and investigation of the ischemic infected foot follows the same outline as that of many other conditions. A focused history and physical exam should provide the information necessary to triage the patient. Depending on the extent of disease, both noninvasive and invasive vascular assessments will help to determine whether the patient is a surgical candidate. These assessments consist of imaging studies, pressure recordings and laboratory testing.

38.1 History

There are a number of patient characteristics that correlate with the presence of arterial insufficiency. Non-modifiable risk factors include old age and being male [1].

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Higher rates of peripheral artery disease are also seen in those who smoke and those who have diabetes mellitus, hypertension, hyperlipidemia or are obese [1]. These comorbidities, as well as others that should be considered in the patient with the infected ischemic foot, are summarized in Table 38.1. Peripheral vascular disease may also present initially with impotence associated with aorto-iliac disease [1]. It is also not unusual that patients will report a history of recurrent ulcers that may or may not have required surgical intervention.

If the patient has pain, he or she should be asked to describe it specific location. Ischemic pain is often localized to the forefoot and toes [2]. These are the most distal areas of the foot and, as such, are the first to be affected by inadequate perfusion. Provoking factors include limb elevation and lying in bed while pain is often alleviated by hanging feet over a bed or simply by walking. This pain is often refractory to analgesics.

One of the more important aspects of the history is to determine the presence of other atherosclerotic conditions. 10% of patients with lower extremity arterial disease will have cerebrovascular disease and 28% will have coronary artery disease [3]. With this in mind, it is possible that the presenting patient will have a cardiac condition that should be treated before his or her foot infection. Patients should be stratified based on the guidelines from the ACC (American College of Cardiology) and the AHA (American Heart Association) into low-, intermediate- or high-risk groups (Table 38.2) [4, 5]. After clinical evaluation, roughly 10% of patients will be considered to be at high-risk for cardiac complications [6]. Of those who are considered low- or intermediate-risk and who will undergo vascular surgery, about 10% will be reclassified as high-risk by non-invasive testing [6]. Exercise electrocardiography is considered the test of choice to assess an intermediate- or high-risk patient's candidacy for surgery [6]. Ultimately, these patients should obtain clearance from a heart specialist prior to undergoing surgery.

Table 38.1 Comorbidities associated with peripheral vascular disease

Medical history	Implications for management
Hyperlipidemia	Increased atherosclerosis
Diabetes mellitus	Increased infection risk, impaired wound healing, increased atherosclerosis
Congestive heart failure	Worsened peripheral perfusion, lower extremity edema, increased cardiac risk
Atrial fibrillation	Peripheral embolism, need to reverse anticoagulation for procedures
Valve replacement	Valve vegetations, need to reverse anticoagulation for procedures
COPD	Ventilator dependency
Renal insufficiency	IV Contrast nephropathy, challenging fluid management
Hypertension	Increased risk of post-op bleeding from anastomoses
Obesity	Impaired wound healing, difficulty with ambulation
Stroke	Difficulty with ambulation, bleeding
Myocardial revascularization	Decreased availability of conduit for revascularization

Table 38.2 Summary of ACC/AHA guidelines on perioperative cardiac assessment for noncardiac surgery

Low risk	Intermediate risk	High risk
• Advanced age • Abnormal ECG • Low functional capacity • History of stroke • Uncontrolled hypertension	• Prior MI • Diabetes Mellitus • Compensated or prior CHF • Mild angina pectoris	• Recent MI • Unstable or severe angina • Decompensated CHF • Significant arrhythmia – High grade AV block – Symptomatic arrhythmias in the presence of underlying heart disease – Supraventricular arrhythmias with uncontrolled ventricular rate • Severe valvular disease

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The patient's diabetes history should also be addressed. Management of the current infection and prevention of recurrence is contingent upon achieving appropriate long and short term control of the patient's glucose levels. Episodes of urinary frequency and of dizziness, lightheadedness and passing out should be recorded. If available, the patient's glucose log and recent HbA1c values should be evaluated to gain insight into the success or failure of past management strategies. Medications should be reconciled with precise dosages noted. Patients on medication, especially steroids, should be asked about stress dosing and whether they have adjusted their medication doses in the midst of their foot infections [7].

38.2 Physical Exam

The entirety of the physical exam should take place with the patient in an examination gown. Vital signs offer insight into the infectious status of the patient. A temperature of over 38 °C (100.4 °F) may indicate an active infection, at the foot or elsewhere [1, 2]. Both tachypnea (respiratory rate > 20 breaths/min) and tachycardia (heart rate > 100 beats/min) are also suggestive of infection [1, 3]. Blood pressure readings should be recorded at bilateral biceps and calves to establish baseline measures as well as to identify potential perfusion differences between limbs.

The patient should lie supine on the exam table to allow for visual inspection of the lower extremities. Ulcer location, size, depth and appearance should all be noted at the initial evaluation to allow for comparison with each follow up examination. Odor should also be considered, as it may indicate the presence of anaerobic bacteria responsible for tissue degradation [8].

Ischemic ulcers are typically at the "end of the line" and are often found on the marginal surfaces of the foot and toes or in between digits (Fig. 38.1) [3]. Humans place the majority of their weight on the first and fifth toes while walking and thus,

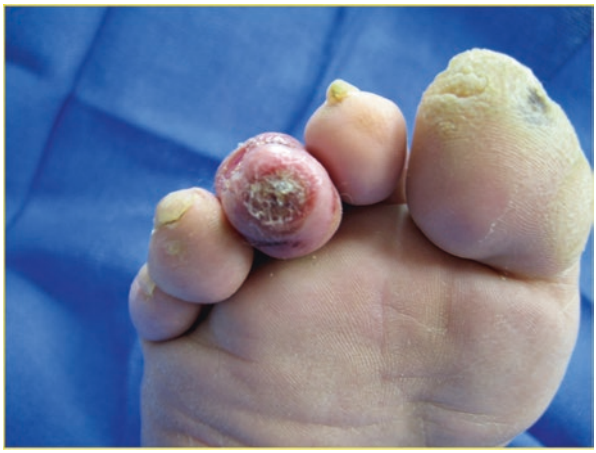

Fig. 38.1 Toe ulcer in a patient with diabetes and hammer-toe deformity

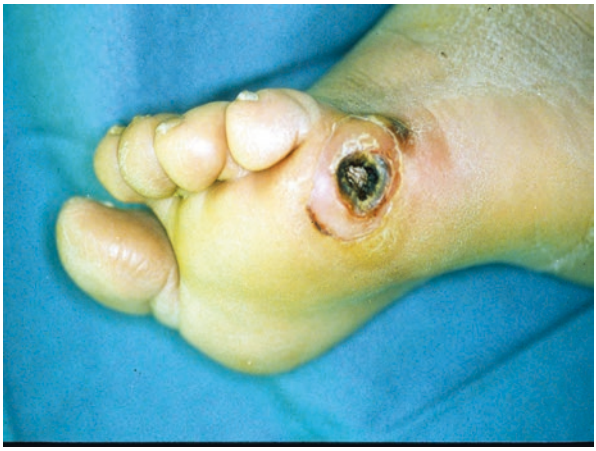

Fig. 38.2 Ischemic ulcer on lateral plantar aspect of a patient with diabetes

ulcers are more common in these digits (Fig. 38.2) [2]. Ischemic ulcers in patients without a foot deformity are less on the dorsum of the foot as pressure to this area is generally less sustained and perfusion is better [2]. These lesions often appear punched out and may be painful and/or bleeding.

Ulcers with other etiologies are more common in other parts of the foot (Table 38.3). Venous ulceration generally occurs at the medial aspect of the ankle where venous pressures are highest [3]. They are associated with induration of the skin as well as brown pigmentation and scaling of the surrounding skin. Neuropathic ulcers often present at the heel or over the metatarsal heads on the plantar surface (mal perforans ulcer) of the foot (Fig. 38.3) [1, 2]. Trauma may lead to neuropathic ulcers at less characteristic locations. Patients with a Charcot foot will have a typical "rocker bottom" appearance with mid-foot plantar ulceration (Fig. 38.4) [9].

The skin surrounding the ulcer should then be inspected. Skin color will often change with positioning of the foot and leg, and therefore, the exam should begin

Table 38.3 Ulcer characteristics

Ulcer type	Localization	Surrounding skin appearance	Ulcer appearance	Pain	Other findings
Venous	– Lower 1/3 part of leg below the knee – Malleolar area	– Edema – Hemosiderin – Pigmentation – Dermatitis eczema	– "Weeping" surface – Irregular borders	– Painful	– Varicose veins – Lymphedema – "Bottle leg " – ABI normal
Arterial	– Most distal areas – Toes – Pressure sites	– Thin – Atrophic – Dry – "Shiny" – Hair loss	– Round – Regular – No bleeding – Dry base	– Very painful	– Weak/absent peripheral ulcers – Poor capillary refill – ABI < 0.8
Diabetes neuro-pathic	– Pressure sites – Heel	– Cellulitis	– Round – Deep – Fistula – Purulent discharge	– Painless	– Sensory deficits – ABI often >2

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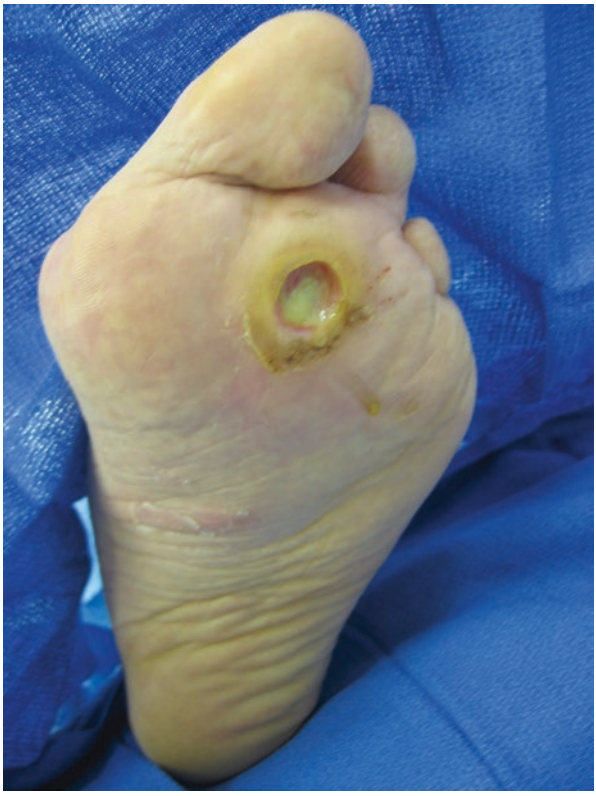

Fig. 38.3 Neuropathic ulcer overlying the third metatarsal head. Note the foot deformity and the amputated second toe

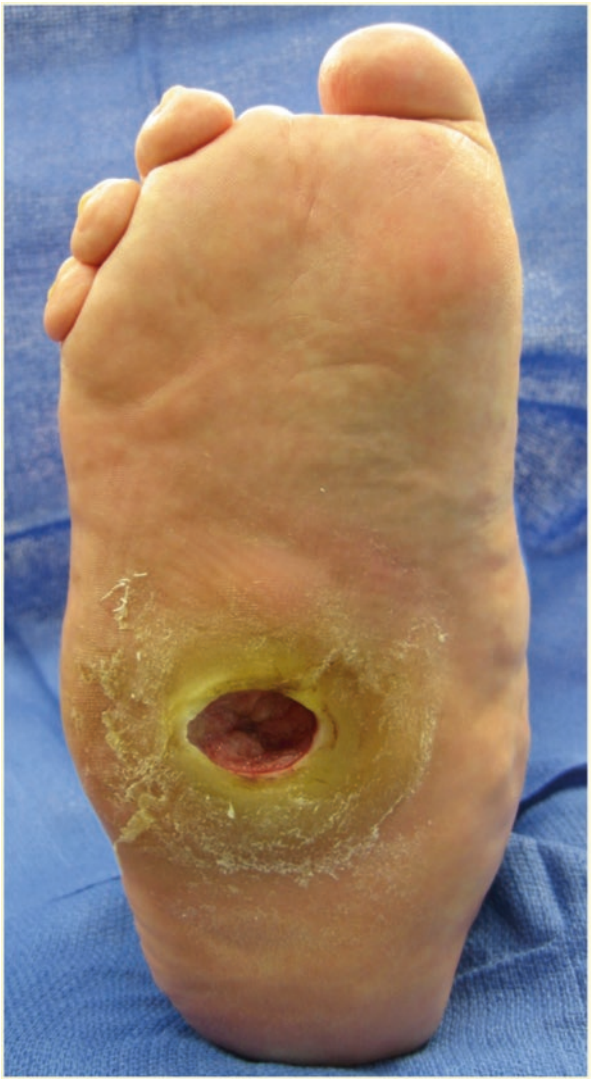

Fig. 38.4 A diabetic patient with a Charcot foot. There is a collapse of the bones of the mid-foot resulting in the characteristic deformity. This leads to increased pressure that predisposes to plantar ulceration

with the patient laying supine with feet resting on the exam table. Ischemia resulting from vascular insufficiency allows for pooling of blood in the venules, causing the skin to appear red in the cold and blue in the heat [2, 3]. An infected foot may present with similar changes in skin color and thus, the rubor associated with vascular insufficiency must be differentiated from that due to infection. Cellulitic color changes will remain with elevation of the foot and lower extremity while those due simply to compromised vasculature will resolve with elevation, as pooled venous blood will drain from the foot [2, 3]. In fact, ischemic limbs often become pale with elevation, as arterial flow is not strong enough to overcome gravity.

Inadequate perfusion will cause thinning and functional loss of dermal appendages in the setting of decreased nutritional supply. Skin may appear dry, shiny and hairless while nails will become brittle and ridged [3]. Skin temperature should be examined by lightly palpating the skin with the back of the hand. Temperature should be compared on similar sites of one extremity to the other. Ischemic limbs will be cooler and demarcation of temperature change can give a rough indication of the level of the occlusion [3]. Obviously, temperature comparison between limbs will be confounded if both limbs are affected by ischemia.

After visual inspection of the ulcer and the surrounding skin, the ulcer should be gently probed with a cotton-tipped probe to identify the presence of sinus tracts, establish ulcer margins and evaluate the extent of tissue destruction [10]. It may be helpful to trace these sinus tracts and ulcer margins on the skin with a marker to allow for a photograph that will be used to track progression of the ulcer. Ulcer area can be determined by multiplying the longest and widest diameters of the ulcer [11]. Extension of the ulcer to tendon, bone or joint should be sought. A positive probe-to-bone finding has a high predictive value for osteomyelitis (discussed further in Chap. 33) [10].

Peripheral pulses should be palpated at the brachial, radial, femoral, dorsalis pedis and posterior tibial arteries. Pulses may be absent due to coexistent arterial disease, medial calcinosis, or swelling of the surrounding tissue. Diabetic patients show an increased rate of atherosclerotic vascular disease and medial calcinosis than the general public [3, 9, 12]. Thus, it may be more difficult to palpate peripheral pulses in the diabetic patient and in these cases, the affected vessels should be evaluated with a handheld continuous wave Doppler.

A full neurologic assessment should be performed on both the affected and unaffected lower extremity [13]. The baseline neurologic status offers a point of comparison for future exams and should include both motor and sensory testing. Sensory loss and progressive motor weakness in the setting of acute arterial occlusion suggest the need for prompt intervention. Vibratory, proprioceptive and protective sensation should also be assessed. Loss of protective sensation due to peripheral neuropathy is the most common cause of ulceration in diabetics [1, 2, 14]. Monofilament gauges (Semmes-Weinstein) can be used to assess protective sensation by determining the smallest monofilament that the patient can detect [15]. A patient is considered to have normal sensation if he or she can feel a 4.17 monofilament. Protective sensation is considered absent when the patient cannot feel a 5.07 monofilament when it buckles [16, 17]. Foot ulceration is strongly correlated with elevated cutaneous pressure perception thresholds [15].

38.3 Vascular Assessment

The primary purpose of the vascular assessment is to determine whether the affected foot and leg are viable, threatened or unsalvageable. Viable limbs may have areas of tissue loss, but the provider is afforded more time to complete additional studies to

further qualify and quantify the injuries. Threatened limbs may require immediate intervention without the luxury of extensive testing. Unsalvageable limbs deserve an assessment of the necessary amputation level based on clinical examination or with non-invasive techniques. This non-invasive assessment allows for verification of vascular etiology, localization of the level of obstruction and evaluation of healing potential based on tissue perfusion.

Non-invasive testing often begins with the calculation of ABIs (ankle brachial indices) (Table 38.4) [18]. A blood pressure cuff is placed just above the ankle and

Table 38.4 Overview of global perfusion studies

Modality	Description	Benefits	Limitations
Doppler (physiological)	Continuous wave Doppler transmits and receives sound waves to evaluate rate of blood flow in vessels	• Fast, noninvasive, cost effective • Office/clinic application	• Limited by user skill and patient body habitus • Cannot localize location of obstruction
ABI/segmental pressure (physiological)	Measuring the difference in blood pressure between the brachial and ankle arteries with segmental pressures displaying a gradient if there is PAD	• Fast, noninvasive, cost effective • Office/clinic application	Can be false elevated secondary to arterial calcinosis in DM and renal disease
Plethysmography/ PVR (physiological)	Evaluates and records variations in the volume or blood flow through an extremity as well as arterial pulsatility	• Fast, noninvasive, cost effective • Office/clinic application	Must be combined with PVR and Segmental pressures to provide a relevant and significant clinical information
Ultrasound (anatomical)	Sonography to visualize vessel caliber, obstruction, flow, and characterize plaque lesions	• Fast, noninvasive, cost effective • Office/clinic application	• Limited by user skill • Difficulty assessing perfusion in distal and smaller size vessels in lower leg and foot
CTA (anatomical)	CT—cross-sectional imaging to provide 360 reconstruction of vasculature	• Fast and noninvasive • More cost effective vs traditional angiography	• Iodinated contrast is nephrotoxic • Imaging obscured by vessel calcification
MRA (anatomical)	MR—cross-sectional imaging to provide 360 reconstruction of vasculature	• Noninvasive • Not obscured by vessel calcification	• Length and cost of study • Gadolinium is nephrotoxic • Imaging obscured by venous artifact

ABI, ankle-brachial index; CTA, computed tomography angiography; DM, diabetes mellitus, MRA, magnetic resonance angiography; PVR, pulse volume recording

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insufflated to a pressure above which the audible Doppler signal in either the dorsalis pedis or posterior tibial artery disappears. The cuff is then slowly deflated until the pressure at which the signal returns is realized and recorded. The ABI is then calculated by dividing this pressure by the highest systolic pressure measured at the brachial artery. Normal ABI values are between 0.9 and 1.2. The patient with an ABI <0.6 will experience claudication while those with ABIs <0.3 will have pain at rest. Patients with tissue loss will have ABIs <0.5 [3].

Segmental limb pressures are an extension of ABIs. They are used to localize occlusive disease by comparing pressures at successive levels of the affected extremity. Four blood pressure cuffs are placed at the proximal thigh, above knee, below knee and ankle positions. The dorsalis pedis or posterior tibial arterial Doppler signal is obtained with a continuous wave Doppler. The pressure at which each cuff occludes the pedal signal is measured similarly to the ABI. Each cuff is inflated until the Doppler signal is no longer present and then deflated until the signal reappears. The pressure at each level is divided by the highest systolic brachial pressure to obtain an index for each level [3]. A 20 mmHg pressure gradient between successive levels on the same extremity is considered a significant pressure drop and correlates with flow limiting vascular lesions. Decreases at successive levels are indicative of multi-level disease. Comparison of the unaffected and affected limbs is a good indicator of the severity of the process; the systolic pressures measured at the same level in both legs should not differ by more than 20 mmHg in the normal patient [3]. Diabetics show higher rates of arterial calcification [12] and as such, their vasculature is less compressible than that of the general population. This leads to falsely elevated pressures required to obscure the pulse at the ankle and these patients often have non-occlusive pressures with ABI's greater than 1.3, limiting the utility of ankle or segmental pressures in the evaluation of peripheral vascular disease in patients with diabetes [3]. In addition, pressure gradients may be increased in the hypertensive patient and decreased in low cardiac output states.

The TBI (toe-brachial index) is particularly useful in diabetic patients in the absence of ABIs. Arteries in the toes rarely exhibit medial calcification [19] and thus, TBIs are more reliable in the diabetic patient [20]. A pneumatic cuff is placed on the digit and a photoelectrode placed on the end of the digit to obtain a photoplethysmographic (PPG) arterial waveform. An infrared light is transmitted into the superficial layers of the skin and the reflected portion is received by a phototransistor within the plethysmographic sensor. The resulting signal is proportional to the quantity of red blood cells in the cutaneous circulation [21]. The toe cuff is then inflated until the waveform flattens and is then progressively deflated. The systolic pressure is recorded at the point where the normal waveform is re-established. The ratio of the recorded systolic pressure to the highest of the two brachial pressures gives the TBI.

Pulse volume recordings (PVRs) are also frequently used in the evaluation of the diabetic patient [22, 23]. Sequential blood pressure cuffs are applied to the legs with an air plethysmographic technique. Each cuff is inflated to 10–65 mmHg and variations in blood volume of the tissue beneath can be assessed by interpreting the alterations in pressure transmitted through the cuff into a pressure transducer [21].

In a less sophisticated fashion, these pressure changes can be visualized with the aid of a standard sphygmomanometer applied to the upper arm. As the cuff is inflated to the brachial occlusion point, the dial begins to bob up and down with the cardiac cycle. The dial varies with the pressure change in the arm cuff because of capillary bed volume changes in the arm beneath the cuff. Conversion of this pressure signal to an appropriately calibrated electrical signal permits production of an analog tracing which can be examined and interpreted. The normal PVR waveform has a sharp upstroke and peak with a reflected wave present before returning to baseline. With mild obstruction, the reflected wave is lost, the upstroke delayed and the peak blunted. Moderate to severe obstruction produces a bowing of the downstroke away from the baseline. A flat PVR is irregular with low amplitude and indicates severe obstruction [22].

Transcutaneous oxygen measurements provide supplemental information regarding tissue perfusion and skin oxygenation. In doing so, they help to gauge the healing potential of lower-extremity ulcers. Platinum oxygen electrodes are placed on the chest wall and feet. The provider can choose to evaluate either the absolute value of the oxygen tension at the foot, or a ratio of this value to that at the chest wall [3]. A normal value at the foot is 60 mmHg and a normal chest/foot ratio is 0.9 [23]. Controversy exists regarding the optimal level for tissue healing. It is generally accepted that wounds are likely to heal if oxygen tension is greater than 40 mmHg (foot/chest ratio > 0.5) and that healing is not likely to occur with a value less than 20 mmHg. A higher value must be achieved for healing of an ulcer in the diabetic foot. The accuracy of the value obtained is limited by local edema, skin temperature, emotional state (sympathetic vasoconstriction) and pharmacologic agents [24].

38.4 Infected Wound Assessment

Laboratory testing is crucial in the evaluation of the infected foot. Bloodwork should consist of a complete blood count to identify possible leukocytosis. Glucose, HbA1c and urinalysis will allow for an evaluation of glycemic control and will offer insight into healing capability. Electrolytes and a basic metabolic profile will allow for an assessment of glycemic control and potential acid-base abnormalities. ESR and CRP can be useful in gauging a patient's response to therapy and thus, baseline values should be established with initial bloodwork.

Cultures should not be performed in all patients presenting with a possible infection of an ischemic foot [25]. Bacteria are likely to be present in lower extremity wounds regardless of infection and therefore, their presence does not confirm the presence of infection. In order to simply determine the utility of cultures, patients should be stratified based on the following parameters. Wounds are considered to be 'uninfected' if they lack purulent discharge or inflammation [25]. These patients do not need cultures. 'Mild' infection is considered in the presence of at least two indications of inflammation (purulence, erythema, pain, tenderness, warmth or induration) but when any cellulitis or erythema extends less than 2 cm around the ulcer [25].

In those with these 'mild' infections, the likelihood of their wound being colonized by resistant organisms should be considered in the decision to take cultures [25]. For example, patients who have recently taken antibiotics are more likely to have resistant bacteria and should therefore have cultures collected [25]. A 'moderate' infection is one in which the patient is systemically well and metabolically stable but has one or more of the following symptoms: cellulitis extending more than 2 cm from the ulcer, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene or involvement of the muscle, tendon, joint or bone [25]. 'Severe' infection is classified as a patient with systemic toxicity or metabolic instability [25]. Patients with moderate or severe infections should have cultures collected as well [25]. These cultures should be obtained during the time of debridement and should be sent for aerobic and anaerobic bacterial cultures [25].

Superficial infections are often due to aerobic gram-positive cocci, among them Staphylococcus aureus, Staphylococcus agalactiae, Streptococcus pyogenes and coagulase-negative staphylococci [26]. These single-organism infections are less common in diabetics, who tend to have polymicrobial infections. Diabetic foot infections are often polymicrobial, and include the previously mentioned bacteria, as well as enterococci [26, 27]. Anaerobic pathogens should be considered in wounds with extensive inflammation, necrosis or malodorous discharge. Common organisms in these settings include anaerobic streptococci or Bacteroides or Clostridium species [26].

38.5 Radiologic Studies and Vascular Testing

After the initial, preliminary assessment of the patient with an infected ischemic foot, further radiologic studies may be needed to confirm, localize and grade the foot lesions. Many of the imaging modalities that are important in the evaluation of ischemia are also helpful in the assessment of wound infection. Non-invasive tests such as ultrasound, plain radiography, MRI, and MRA (MR angiography) CTA (CT angiography) and nuclear imaging can all be helpful to the patient with an infected ischemic foot (Table 38.4) [3, 18, 28].

Plain radiography can be used to rule out bony lesions as the cause of pain as well as to determine the presence of absence of osteomyelitis beneath an ulcerated lesion (discussed further in Chap. 33) [29]. Plain radiography is also helpful in assessing the degree of vascular wall calcification that is present in a given vessel and identifying soft tissue swelling, disruption of bone cortex and periosteal elevation [3].

MRI can be used in conjunction with the plain radiograph to evaluate the possible presence of osteomyelitis and to identify pathologic anatomic findings as well as inflammation in the bone or soft tissue [3]. It should be noted that MRI is contraindicated in claustrophobic patients as well as those with implanted metallic devices such as pacemakers or aneurysm clips. If osteomyelitis is suspected, nuclear imaging modalities may be helpful. A three phase bone-scan introduces a radionuclide tracer which accumulates in areas of bone turnover. A gamma camera is then used

to track the uptake of this tracer immediately after injection (blood flow phase), 15 min after injection (blood pool phase) and about 3 h after injection (osseous phase) [30]. Osteomyelitis is marked by increased uptake during all three phases while cellulitis will show increased uptake during the first two phases only [31]. It should be noted that false negatives may be seen in early or chronic osteomyelitis with decreased perfusion [32].

The tagged white blood cell scan can also be useful in the patient with suspected osteomyelitis. A blood sample is taken from the patient and the white blood cells are tagged with one of several radiotracers before they are injected back into the patient several hours later. Imaging is done 24 h after re-injection and accumulation of the radiolabeled white blood cells is seen in the bone marrow at sites of inflammation or infection [11]. Unlike the three phase bone-scan, accumulation is not unique to bone.

Doppler ultrasound enables an evaluation of arterial blood flow. Using high frequency sound waves, the practitioner can quantify blood flow through the arteries in question. Duplex ultrasound, by combining pulsed Doppler spectral analysis and B-mode and color Doppler imaging, allows for a three-dimensional reconstruction of atherosclerotic plaque morphology [1]. Not only does this confirm the presence of vascular disease, but it also enables localization of the particular arterial segment that is affected [1].

MRA allows for the assessment of vasculature in those patients with severe allergy to IV contrast, contrast induced nephropathy or severe inflow disease and slow distal flow. It displays reconstructed images as arteriograms and is particularly helpful in the patient with foot pathology as it has excellent visualization of the small arteries of the foot [33]. MRA has been shown to be more sensitive than conventional angiography in identifying patent vessels at all levels in patients with severe vascular disease, with the greatest difference seen in relation to distal vasculature [34]. MRA can also be used to quantify the degree of arterial stenosis comparably to conventional angiography.

CTA (CT angiography) is considered to be the gold standard for imaging blood vessels [3].

In the case of the infected ischemic foot, it is used for an anatomic assessment prior to a planned intervention. Multiple planar views must be obtained in order to evaluate the severity of a stenotic lesion as atheromatous plaques are often asymmetric and eccentric [3]. The diabetic patient is particularly susceptible to contrast-induced nephropathy due to the effect of diabetes on kidney function [35]. The glomerular filtration rate should be calculated and used to estimate the risk of contrast-induced nephropathy. A patient with a GFR greater than 45 mL/min is at minimal risk for complications, while a GFR under 30 mL/min should receive intravenous hydration. A GFR between 30 and 45 mL/min merits oral hydration [36].

The arteriographic appearance of the vasculature can help to identify the level and severity of disease as well as provide insight into its etiology. Atherosclerosis produces segmental or diffuse plaques with varying degrees of stenosis [3]. The formation of collateral vessels is apparent in those with chronic disease while the absence of collateral vessels along with abrupt contrast cut-offs and/or filling defects

suggest arterial embolization [3]. Aneurysms might be inferred from an enlarged lumen, however, when partially thrombosed they may be difficult to visualize and so additional imaging with duplex ultrasonography is suggested. Arterial wall medial calcification can be demonstrated on scout films prior to the injection with IV contrast and the severity estimated. The advantage of contrast angiography over non-invasive methods of vascular assessment is in the potential for intervention at the time of the study.

38.6 Conclusion

Foot infection in the presence of ischemia is quite common in the diabetic patient. Providers should be aware of the comorbid conditions that leave patients more susceptible to foot infections, as well as those that predispose them to complications. Investigation of the infected ischemic foot should include a general inquiry into the history of the present illness as well as a basic physical exam. The presence of infection and ischemia, although often seen together, should be evaluated separately before making the two separate diagnoses of infection and ischemia. These two diagnoses can be reached using a combination of laboratory testing, ancillary testing and various imaging techniques. Precise documentation of the presentation and management is of the utmost importance, as many of these patients will present with recurrent episodes of ischemia and infection in the future.

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Chapter 39
Infected Ischaemic Foot: Surgical Management

Hisham Rashid and Michael E. Edmonds

39.1 Introduction

Although the critically ischaemic and the acutely ischaemic foot can become infected, it is the neuroischaemic foot that carries the main burden of infection. The spectrum can extend from a localised infection to severe spreading infection as described in Chap. 33 on the presentation of the infected diabetic foot. Infection and ischaemia are a potent combination. The Eurodiale study showed that the combination of both ischaemia and infection had a major impact on ulcer healing and major amputation and demonstrated the existence of a significant interaction between peripheral arterial disease and infection [1]. Peripheral arterial disease has been shown to double the risk of developing diabetic foot infection [2]. The risk of hospitalization and lower-extremity amputation is about 56 and 155 times greater, respectively, for diabetic people who had a foot infection than for those without [2]. Diabetic foot infections with underlying PAD have the greatest risk for amputation, increasing by up to 90% compared with those without PAD [3, 4]. Up to 58% of diabetic foot ulcers are already infected at initial presentation to a diabetic foot clinic and one-third of these present with both infection and PAD [3, 5]. The development of infection constitutes a foot care emergency which requires urgent referral to specialised foot care team [6]. The underlying principles are to diagnose infection, to culture the bacteria responsible, to treat aggressively with antibiotic therapy and to consider the need for debridement and surgery. When managing these very difficult and unstable feet, decision making should be guided by symptoms and signs of infections, results of properly taken wound swabs and tissue cultures and

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past and present knowledge of individual patients. Urgent intervention in these patients is essential to avoid serious complications, with the risk of widespread sepsis being very high, putting both the patient's limb and life at risk [7].

39.2 Diagnosis and Investigations

It is essential to diagnose infection early especially in immune-compromised patients with severe ischaemia who can only mount a minimal inflammatory response without the classical symptoms and signs of infection. Signs of systemic infection which include drowsiness, shivering, tachycardia, reduced body temperature (<35 °C) or raised body temperature (>37 °C) and hypotension are notoriously absent even in many severe infections of the diabetic foot. Among patients hospitalised for late infections, only 12–35% have significant fever and only 50% of episodes of severe cellulitis will provoke a fever or leucocytosis [8]. Despite the absence of systemic signs, clinical examination may reveal a pointing abscess and the extent of deep necrosis and infection affecting different layers of the foot may be considerable putting the foot at risk of requiring major amputation.

Laboratory investigations should help guide the clinician to an early diagnosis. A full blood analysis including a C-reactive protein is essential in all patients. A rise in serum C reactive protein may be an early indicator of infection. Acute renal impairment, secondary to sepsis, needs to be excluded by measuring serum electrolytes.

A plain radiograph of the foot with straight and oblique views and straight and lateral views of the ankle may also point to the presence of a foreign body or an abscess with gas producing organisms in diabetic patients. Also, osteomyelitis of the foot bones may be detected on the radiograph especially in the digital bones although in the recent onset infected foot, radiographic signs of osteomyelitis may not have yet developed, often taking two weeks to do so. In uncertain cases, an urgent magnetic resonance imaging (MRI) is helpful if deep seated infection is suspected in an inflamed but intact foot.

To diagnose possible ischaemia of the foot, a duplex scan, should highlight any significant disease of the arterial tree that will require revascularisation. In equivocal cases, computed tomography angiography (CTA) may be needed.

39.3 Management

It is crucial to treat infection with urgency either together with intravenous antibiotics only or together with emergency surgical drainage and debridement. The authors at King's College Hospital follow a strict algorithm in the management of these patients to guarantee a successful outcome (Fig. 39.1) [9]. In the event of severe infection and necrosis, intravenous antibiotics are administered immediately. If necrosis and or pus is present, debridement is carried out as an emergency and

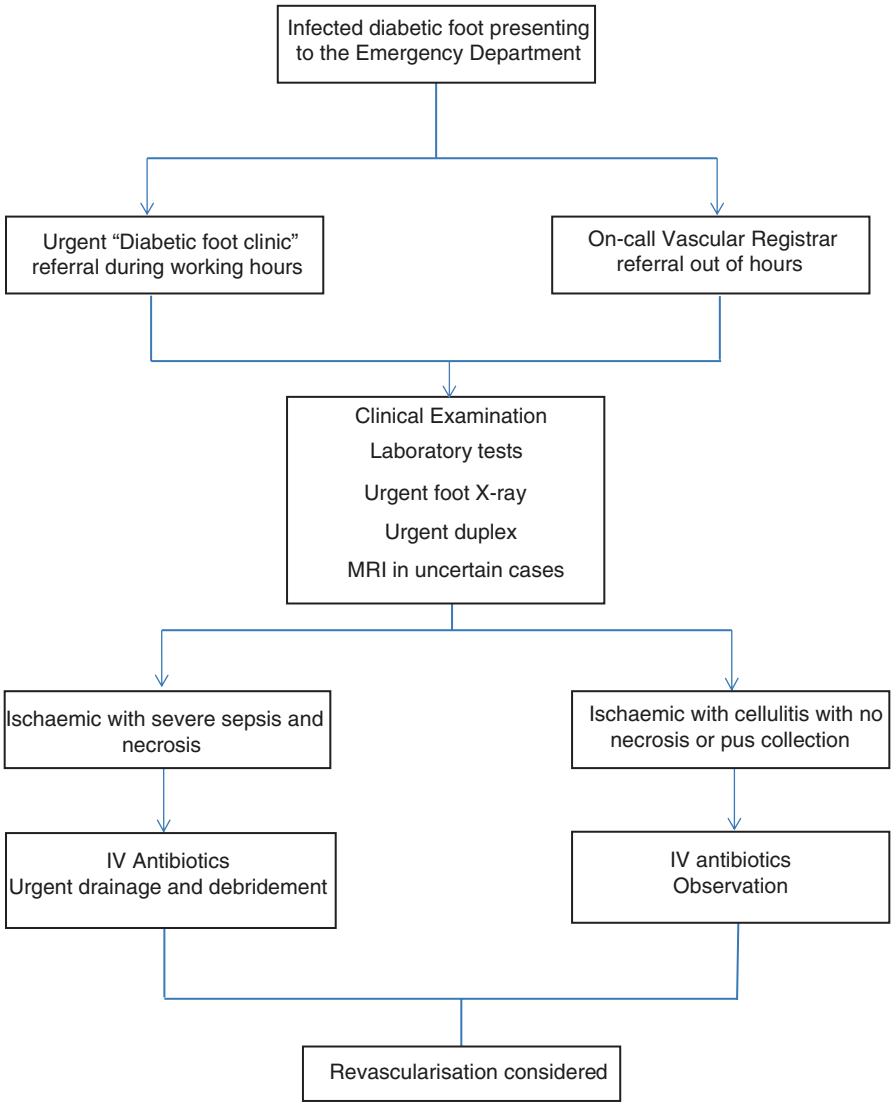

Fig. 39.1 Algorithm of the management of the infected ischaemic diabetic foot

revascularisation is carried out at the same time or soon after. It is important to note that there may be extensive infection of soft tissue that needs to be removed without the presence of a discrete abscess. White cell function is poor in diabetes and the leucocytes are unable to" wall off" infection into a specific collection of pus. In some cases, there may be an extensive cellulitis without soft tissue destruction and this should be treated with intravenous antibiotics and kept under close observation. Management is best carried out in a specialised foot centre in hospital.

39.3.1 Antibiotic Management

Therapy is commenced with wide spectrum therapy which is then focused according to the microbiology culture results. Clinical clues to guide antibiotic selection have been reviewed by Lipsky [10]. Initial antibiotic therapy for diabetic foot infections is empirical. It is important to avoid selecting either an unnecessarily broad or an unsuitably narrow regimen. Firstly, clinically severe infections need broad-spectrum therapy. Secondly, aerobic Gram-positive cocci, particularly Staphylococcus aureus (including methicillin-resistant S. aureus (MRSA) for patients at high-risk) should always be covered. Thirdly, therapy should also treat aerobic Gram-negative pathogens if the infection is acute on chronic or has failed to respond to recent antibiotic therapy. Fourthly, anti-anaerobic antibiotics should be given for necrotic infections in an ischaemic limb.

Thus, at initial presentation, it is important to consider a wide spectrum of antibiotics for three reasons:

- It is impossible to predict the number and type of organisms from the clinical presentation.
- There is no way of predicting who will progress to a rapidly ascending infection which becomes limb-threatening and even life-threatening.
- Diabetic patients are immunosuppressed. The neuropathy and ischaemia of the diabetic foot reduces the local resistance to invading bacteria.

39.3.2 Debridement

Early surgical intervention of the affected site is usually necessary as an integral part of infection management. This may include simple debridement of the soft tissues, or more extensive procedures such as wide incision, drainage or open amputation to eliminate extensive areas of infection. Indications for surgical intervention are infected sloughy tissue, localised fluctuance and expression of pus, crepitus with gas in the soft tissues on radiograph and purplish discoloration of the skin indicating subcutaneous necrosis. Infected tissue removed after debridement should be sent for culture as well as specimens from the debridement margin. Early commencement of intravenous antibiotics initially empirically, and then based on culture and sensitivity studies, is mandatory. Emergency drainage of pus and debridement is required to avoid systemic sepsis and death. Minor amputations may also be necessary in patients with severely infected and gangrenous toes. Unconventional minor amputation sufficient enough to drain sepsis and remove all necrotic tissues may be advisable in early stages in the hope to retain as much foot tissue as possible (Figs. 39.2 and 39.3). This will hopefully improve the postoperative functionality. Repeated debridement is commonly needed in severely infected cases especially if the inflammatory markers such as C reactive protein are not responding positively to treatment. In severe digital and forefoot sepsis, a

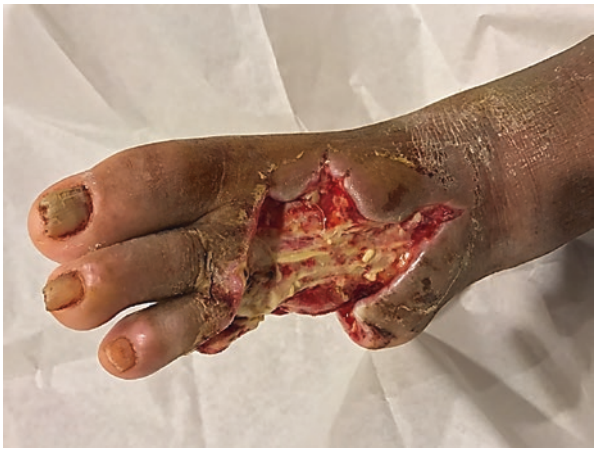

Fig. 39.2 Extensive debridement of the foot with amputation of the 4th and 5th toes

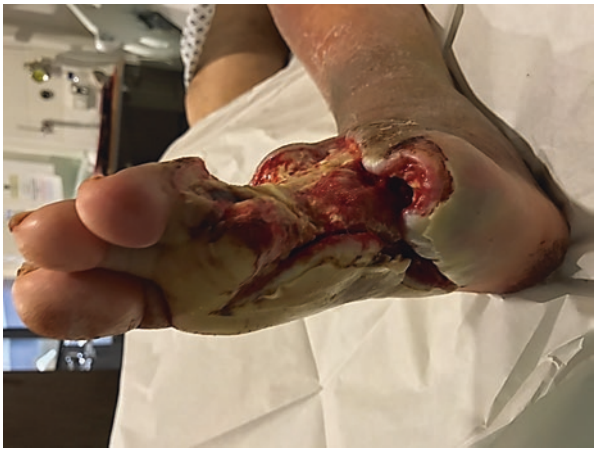

Fig. 39.3 Plantar surface demonstrating extensive deep debridement and amputation of 4th and 5th toes

trans-metatarsal amputation may be required. Primary closure should be avoided to allow continuous drainage and washouts and inspection of the deep tissues for the need of further debridement. Split-thickness skin grafts for large foot wounds accelerate wound healing (Fig. 39.4).

39.3.3 Revascularisation

Revascularisation is an important part of the management of the ischaemic foot that has become infected. If duplex ultrasound reveals lesions which are deemed suitable for angioplasty then patients proceed to digital subtraction angiography which permits clear visualization of vascular structures by subtracting superimposed bone and soft tissue densities and then on to angioplasty [11, 12].

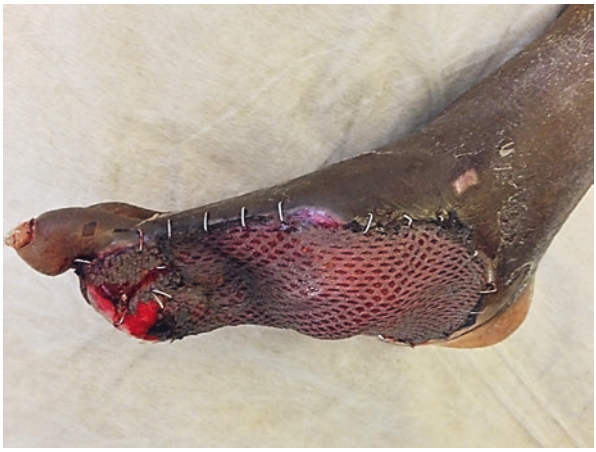

Fig. 39.4 Extensive skin graft of the medial aspect of the foot following successful debridement and full granulation

However, in some patients, angioplasty may not be technically feasible. Furthermore, if lesions are too widespread for angioplasty, then arterial bypass may be necessary to treat extensive tissue destruction which cannot be managed without the restoration of pulsatile blood flow to the foot. When patients present late, there is considerable tissue loss, often secondary to infection, accompanied by extensive occlusive arterial disease that is not amenable to angioplasty. In these circumstances, distal arterial bypass has been established as a valuable procedure in conjunction with surgical debridement, adjunctive reconstructive plastic surgery and antibiotic therapy [8]. Arterial surgery will be needed for disease of the common femoral artery and long occlusions of the superficial femoral artery, popliteal and tibial arteries. Distal bypasses are more successful if they are relatively short and are carried out from popliteal region to the ankle or foot. Thus, in cases of femoral and tibial disease, hybrid procedures, involving initially angioplasty above the knee and a distal bypass below the knee, are performed.

39.4 Conclusion

The management of the infected ischaemic foot is a clinical challenge especially in the diabetic patient. Severe infections need urgent admission to hospital for wide spectrum intravenous antibiotics, urgent surgical debridement and revascularisation.

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Chapter 40
Medical Management of the Infected Diabetic Foot

Jared Wasser, Michael E. Edmonds, and David Banach

40.1 Introduction

Foot infections in diabetic patients are complex challenges of increasing prevalence. Multispecialty medical and surgical intervention have become the standard of care in most cases and appropriate and timely antibiotic management are essential in treating these infections [1, 2]. Antibiotic selection and optimization can be challenging due to the varied presentations and often polymicrobial nature of these infections [3]. Further consideration must be given whether also to treat multidrug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* when choosing empiric therapy. Decisions regarding intravenous or oral routes for antibiotic administration will also influence initial therapeutic choices. Given these and other multifactorial considerations, it is advisable to include a specialist in infectious diseases or a clinical microbiologist on the treatment team, when available. This chapter will address the initiation of antibiotic therapy, including selection of antibiotic choice, antibiotic adjustment during treatment and an approach to determining the duration of treatment of the infected diabetic foot. This chapter discusses the medical management of infection in the neuropathic (including Charcot) foot and the ischaemic foot.

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40.2 Considerations When Choosing Empiric Antibiotic Therapy

40.2.1 Assessing the Severity of Infection

In clinical practice, infection is typically evidenced by signs of inflammation including local swelling or induration (tumor), erythema or redness (rubor), local tenderness or pain (dolor), and warmth of the involved tissue (calor).

The Infectious Diseases Society of America (IDSA) has developed a clinically useful classification scheme for grading the severity of infection in the diabetic foot [1]. The system developed by the IDSA has been validated and shown to accurately predict both the need for hospitalization and limb amputation, making it an excellent tool when deciding on management strategy [4]. The classification system is as follows:

- ***Uninfected***—No signs or symptoms of infection.
- ***Mild infection***—Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema is present, it must be >0.5 cm to ≤2 cm around the ulcer. Other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis) should be excluded.
- ***Moderate infection***—Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below).
- ***Severe infection***—Local infection (as described above) with the signs of a Systemic Inflammatory Response Syndrome (SIRS), as manifested by ≥2 of the following:
  - Temperature >38 °C or <36 °C
  - Heart rate > 90 beats/min
  - Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
  - White blood cell count >12,000 or <4000 cells/μL or ≥10% immature (band) forms

Due to the diminishing effects of diabetes on the inflammatory response through its actions on the vascular, neurological, and immune response, these typical signs of inflammation may be subtle or absent. Such atypical presentations require increased vigilance of treating physicians and surgeons to stage infected wounds and ulcers. In select patients, severe infections may manifest without systemic signs of infection. Thus, clinical judgement is important in determining severity within the context of an individual patient. Accurate assessment and classification of wounds is an important factor in selecting an initial, empiric antibiotic regimen for a patient.

Other (sometimes called secondary) features suggestive of infection include the presence of necrosis, friable or discolored granulation tissue, non-purulent secretions, foul odor, or the failure of a properly-treated wound to heal [5].

40.3 Factors Suggesting the Need for Hospitalization

While not all patients with diabetic foot infections require hospitalization, the International Working Group on the Diabetic Foot (IWGDF) has outlined some clinical and social factors that support the need for hospitalization [5].They are:

- Severe infection (described above)
- Metabolic or hemodynamic instability
- Intravenous therapy needed (and not available/appropriate as outpatient)
- Diagnostic tests needed that are not available as outpatient
- Critical foot ischemia present
- Surgical procedures (more than minor) required
- Failure of outpatient management
- Patient unable or unwilling to comply with outpatient-based treatment
- Need for more complex dressing changes than patient/caregivers can provide
- Need for careful, continuous observation

40.4 No Evidence of Infection

When no clinical signs of infection are evident in a patient with a diabetic foot, use of antibiotics is generally not warranted. Though there is some controversy around the concept that decreasing the "bioburden" of bacteria in a wound may help healing, most studies support withholding antibiotic therapy in wounds which are not infected [6–8].

The use of targeted antibiotic therapies, reserved for diabetic foot wounds that are clinically infected, is of paramount importance considering the excessive overtreatment of uninfected wounds. Treating only infected wounds may help to prevent later development of infections caused by drug-resistant organisms and maintain a wider arsenal of available antibiotics to treat when an infection arises [9]. There is also increased cost and the potential for medication-associated adverse effects when antibiotics are used unnecessarily.

40.5 Microbiology of the Diabetic Foot

The microbiology of the diabetic foot is unique. Infection can be caused by Gram-positive, Gram-negative and anaerobic bacteria, singly or in combination.

40.5.1 Gram-Positive Cocci, Including Methicillin-Resistant Staphylococcus Aureus (MRSA)

Group A streptococcus is a rare isolate from ulcers, but when present it can lead to severe systemic upset. Group B streptococcus is an important pathogen in the diabetic foot. MRSA is associated with the whole spectrum of clinical presentations of diabetic foot infections and commonly occurs in patients who have been hospitalized. There is a strain of MRSA that is found in the community, so-called community-acquired MRSA, which has been linked to outbreaks in groups of people in close contact in institutions such as prisons but can then be transferred to hospitals. These MRSA may not necessarily have the multi-resistance of the hospital-acquired MRSA but nevertheless can rapidly lead to severe infections. Approximately two-thirds possess the Panton–Valentine leucocidin toxin, which acts to form pores in the cell membrane of mononuclear cells and polymorphonuclear cells and can lead to severe tissue necrosis.

Due to the prevalent role that MRSA can play in diabetic foot infections (as high as 30%) appropriate coverage of this organism is an important factor when selecting antibiotic therapy [10–12]. The IDSA guidelines recommend empiric coverage of this organism in the following clinical scenarios:

- The patient has a history of previous MRSA infection or colonization within the previous 12 months
- The local prevalence of MRSA (i.e., percentage of all *S. aureus* clinical isolates in that locale that are methicillin-resistant) is high enough (50% for a mild and 30% for a moderate soft tissue infection) that there is a reasonable probability of MRSA infection
- The infection is sufficiently severe that failing to empirically cover MRSA while awaiting definitive cultures would pose an unacceptable risk of treatment failure

Examples of antibiotics with activity against MRSA include parenteral agents such as vancomycin, teicoplanin and daptomycin and oral agents including clindamycin, doxycycline, sodium fusidate, rifampicin, trimethoprim-sulfamethoxazole and linezolid.

40.5.2 Gram-Negative Bacilli-Pseudomonas Aeruginosa, and Multidrug-Resistant Organisms

Except in specific circumstances, or in cases of moderate or severe diabetic, foot infection, antibiotic coverage of Gram-positive cocci (i.e., staphylococcal and streptococcal species) may be sufficient. However, there are certain patient risk factors, apart from previous cultures isolating these organisms, that may increase the

likelihood of infection with Gram-negative organisms and particularly pseudomonas [1, 13]. These include:

- Previous treatment with antibiotics within the month prior to presentation
- High local prevalence of pseudomonas infections
- Warm climate
- Frequent exposure of the foot to water (e.g., soaking of feet)

As there is a poor immune response of the diabetic patient to infection, even Gram-negative organisms such as Citrobacter, Serratia and Pseudomonas, may cause severe tissue damage. When Gram-negative bacteria are isolated from a deep ulcer swab, they should not be regarded automatically as insignificant. Gram-negative bacteria have acquired various resistance patterns through the development of certain enzymes. These include extended spectrum beta lactamases known as ESBLs (extended-spectrum beta lactamases). By this means, they have developed resistance to extended-spectrum (third-generation) cephalosporins (e.g., ceftazidime, cefotaxime and ceftriaxone) but not to carbapenems (e.g., meropenem or imipenem). ESBL enzymes are most frequently produced by two bacteria: *Escherichia coli* and *Klebsiella pneumoniae*. Another group of lactamases are AmpC β-lactamases, (ampicillinases C) which are typically encoded on the chromosomes of many Gram-negative bacteria, notably Citrobacter, Serratia and Enterobacter species, where expression, is usually inducible.

Multi-drug resistant organisms (MDROs) including extended spectrum beta-lactamase (ESBL) producing Gram-negative bacilli, multi-drug resistant (MDR) *Pseudomonas aeruginosa*, and carbapenem-resistant enterobacteriaceae (CRE) have become of increasing concern in the treatment of diabetic foot infections. In a recent study of 50 patients with diabetic foot ulcers, 65.1% of bacterial isolates were Gram-negative bacilli, and of those 37.5% were ESBL producers and 31% were carbapenemase producers, respectively [14]. In another study of 188 patients with diabetic foot infection, MDROs were isolated in 23.9% of patients [15]. Risk factors for infections with MRDOs include prior antibiotic therapy, longer duration of antibiotics, frequency and duration of hospitalization, and osteomyelitis [16].However, it has been shown that infection with an MDRO does not necessarily increase time to healing for diabetic foot wounds [15].

40.5.3 Anaerobic Organisms

Anaerobic bacteria are frequently isolated from infected ischemic diabetic foot wounds [17]. Anti-anaerobic therapy is included in most empiric antibiotic regimens prior to debridement and drainage. Generally, in most mild and some moderate diabetic foot infections, they are not usually major pathogens and there is little evidence to support anti-anaerobic therapy in most adequately-debrided diabetic foot infections. However, in severe infections, infected wounds with extensive

necrotic tissue, gangrene, and/or a foul odor ("fetid foot"), particularly in the absence of surgical intervention, empiric treatment of anaerobes is advised [3, 18].

40.6 Empiric Antibiotic Therapy of the Infected Foot

The basic principle in treating moderate and severe infections is to initiate therapy with wide spectrum antibiotics and then focus to narrow spectrum antibiotics according to microbiological sensitivities. Other considerations in choosing initial therapy include the previous microbiologic data and culture results of the patient, and the prevalence of drug-resistant organisms in the community or institution. Dosage will depend on severity of the infection and the patient's co-morbidities including impaired renal function.

40.6.1 Mild Infections

In patients with a clinically mild infection, the foremost goal is adequate antibiotic coverage of aerobic Gram-positive cocci. Most importantly, empiric antibiotics should treat *Staphylococcus aureus*, which may or may not include MRSA in specific patients at high risk and depending on local prevalence [19]. Such risk factors include recent hospitalization, recent antibiotic administration, residence in a healthcare facility, and dialysis patients [19]. This can typically be achieved by antibiotics with narrow-spectrum activity. Table 40.1 includes a list of frequently used treatment options in the management of diabetic foot infections.

If there are no barriers to oral antibiotic therapy, such as gastrointestinal absorption impairment, agents with high bioavailability and an appropriate spectrum of activity are preferred in mild infections. Appropriate antibiotic choices include oral semisynthetic penicillins (dicloxacillin) and first-generation cephalosporins (cephalexin) with good activity against both staphylococcal and streptococcal species. If MRSA coverage is desired, oral trimethoprim/sulfamethoxazole or doxycycline are good options as they also cover methicillin-sensitive *Staphylococcus aureus* (MSSA). However, some coverage of streptococcal species is sacrificed with these drugs. Fluoroquinolones have excellent oral bioavailability and convenient, once-daily dosing; however, their staphylococcal coverage is often suboptimal and rates of resistance among *S. aureus* are high. Clindamycin is another oral treatment option with potentially good activity against community-acquired MRSA (CA-MRSA), but reports of increasing resistance amongst Gram-positive organisms may hinder its use as a first-line empiric agent for diabetic foot infections [20–22]. If used, inducible clindamycin resistance should also be excluded with the 'D' test [23].

Table 40.1 Antibiotics frequently used in the treatment of diabetic foot infections

Antibiotic	Spectrum of activity	Comments
Oral agents		
Cephalexin, Dicloxacillin (Flucloxacillin)	Gram-positive (streptococci, MSSA)	Dosing every 6 h
Clarithromycin	Gram-positive (streptococci, MSSA/MRSA)	
Clindamycin	Gram-positive (streptococci, MSSA/MRSA)	Resistance among MRSA increasing
Doxycycline	MSSA/MRSA, Some Gram-negative	Streptococcal activity may be limited
Trimethoprim-sulfamethoxazole	MSSA/MRSA, Some Gram-negative	Streptococcal activity may be limited
Trimethoprim (single agent)	MSSA/MRSA, Some Gram-negative	Similar to trimethoprim-sulfamethoxazole
Levofloxacin	Streptococci, Gram-negative	Suboptimal against MSSA/MRSA. High bioavailability, Gram-negative resistance may be high in some areas
Ciprofloxacin	Streptococci, Gram-negative	High bioavailability, Gram-negative resistance may be high in some areas
Amoxicillin-clavulanate	Streptococci, MSSA, Some Gram-negative, anaerobes	
Linezolid	Streptococci, MSSA, MRSA	Hematologic and neurotoxicity associated with use >2 weeks
Rifampin	MSSA, MRSA	Potentially hepatotoxic. Many important drug-drug interactions. Should always be used as part of combination therapy.
Sodium Fusidate	MSSA, MRSA	Potentially hepatotoxic. Should always be used as part of combination therapy. Not available in the United States
Metronidazole	Anaerobes	High oral bioavailability
Intravenous agents		
Oxacillin, Cefazolin	MSSA	First line parenteral therapy for MSSA. Frequent dosing.
Amoxicillin-clavulanate	Streptococci, MSSA, Some Gram-negative, anaerobes	
Ampicillin-sulbactam	Streptococci, MSSA, Some Gram-negative, anaerobes	Gram-negative coverage may be decreasing, no MRSA or pseudomonas coverage. Dosing every 6 h
Ceftriaxone	Streptococci, MSSA, Some Gram-negative	No MRSA or pseudomonas coverage, once daily dosing
Ceftazidime	Streptococci, MSSA, Broad Gram-negative including pseudomonas	No MRSA coverage, thrice daily dosing
Ticarcillin/Potassium Clavulanate	Gram-negatives, including pseudomonas, anaerobes	
Fosfomycin	Useful for MDR Gram negative bacteria	Intravenous formulation not available in the United States

(continued)

Table 40.1 (continued)

Antibiotic	Spectrum of activity	Comments
Ertapenem	Streptococci, MSSA, Some Gram-negative including ESBL-producing organisms, anaerobes	No MRSA or pseudomonas coverage, once daily dosing
Meropenem	Streptococci, MSSA, Some Gram-negative including ESBL-producing organisms, anaerobes	No MRSA coverage, thrice daily dosing
Metronidazole	Anaerobes	High oral bioavailability
Aminoglycosides	Gram–positive and Gram -negative including pseudomonas	Requires monitoring drug levels
Cefepime	Streptococci, MSSA, Broad Gram-negative including pseudomonas	No MRSA coverage
Piperacilllin-tazobactam	Streptococci, MSSA, Broad Gram-negative including pseudomonas, anaerobes	No MRSA coverage, Dosing every 6–8 h
Vancomycin	Streptococci, MSSA, MRSA	Requires monitoring drug levels
Teicoplanin	Streptococci, MSSA, MRSA	High doses (>15 mg/kg/day) may cause marked thrombocytopenia. Not licensed for use in the United States.
Tigecycline	Gram-positives, Gram negatives and some anaerobes.	Active against MRSA, VRE but Pseudomonas aeruginosa and many strains of Proteus spp. are resistant to tigecycline. Not recommended in UK unless no other antibiotic available
Colistin	Gram-negative including CPE producing organisms	Can cause nephrotoxicity and neurotoxicity
Daptomycin	Streptococci, MSSA, MRSA	Once daily dosing, Can cause elevated creatinine kinase levels

MSSA Methicillin-susceptible *Staphylococcus aureus*, MRSA Methicillin-resistant *Staphylococcus aureus*, VRE Vancomycin resistant enterococcus, ESBL Extended spectrum beta-lactamase, CPE Carbapenemase

40.6.2 Moderate and Severe Infections

For patients with moderate or severe infections that are limb or life threatening it is pertinent to prescribe empiric antibiotics with broad spectrum activity by the intravenous (IV) route. Parenteral antibiotics are utilized in these patients to achieve higher blood levels quickly. Specific empiric choices are listed in the Table 40.1. Typical broad-spectrum initial antibiotic choices should have activity against Gram-negative and Gram-positive (including MRSA) organisms, as well as anaerobes [1, 19, 24]. Choosing whether or not to treat pseudomonas should be based on whether or not the patient has specific risk factors, as outlined above. Pseudomonas infections have

become increasingly difficult to treat, and it is sometimes necessary to resort to antibiotics such as ticarcillin/clavulanic acid, colistin or fosfomycin. If *Stenotrophomonas maltophilia* is regarded as a significant organism in a diabetic foot infection, then co-trimoxazole is the optimum therapy, although it is associated with rare but serious side-effects, particularly in the elderly. Gram- negative organisms producing ESBLs should be treated with carbapenems whereas Gram-negative organisms with carbapenem resistance should be treated with colistin or an alternative agent with activity against carpabenemases. In these circumstances, consultation with an individual with expertise in clinical infectious diseases or microbiology is recommended**.**

40.7 Narrowing Antibiotic Therapy

Therapy should then be narrowed based on the results of microbiologic cultures and antibiotic susceptibility data and clinical response. A switch from parenteral to oral antibiotic regimens may be appropriate once the patient is clinically stable and able to tolerate oral therapy.

A key component of treating infected diabetic foot wounds is knowing when to narrow, or de-escalate, antibiotic therapy. As stated previously, the most effective and accurate way of doing this is to utilize culture identification of bacteria and antimicrobial susceptibility data to target antibiotics that will effectively treat specific pathogens involved in the affected wound. However, the clinical response of the patient to the empiric antibiotic regimen is of utmost importance. It is unwise to narrow a regimen in a patient failing the current therapy. If culture and sensitivity information is unavailable or non-diagnostic, therapy could potentially be narrowed, based on the initial empiric regimen and the patients' most-likely pathogens, based on their specific risk factors.

With the introduction of highly-bioavailable oral antibiotics, including fluoroquinolones and linezolid, oral therapy has become more acceptable and widely-used as appropriate therapy for infected diabetic foot ulcers [19].

40.8 Duration of Therapy

There is limited data on the appropriate length of therapy for diabetic foot infections. For mild skin and soft tissue infections 1–2 weeks of therapy is generally sufficient. Patients with more severe soft tissue infections usually require weeks of therapy [1, 18, 25]. Decisions regarding optimal duration of therapy are dependent on the patient's initial presentation severity, response to treatment, and the presence of any underlying osteomyelitis and whether infected bone and/or any prosthetic material has been adequately removed or debrided. Antibiotic therapy can typically be discontinued once signs and symptoms of infection have abated as antibiotic therapy is employed to treat infections and not heal wounds [9].

Patients with osteomyelitis are treated with prolonged courses of therapy, often intravenous initially and sometimes followed with oral therapy. Some patients who are poor candidates for surgical resection, or who have an implanted foreign body at the infection site, may require prolonged or intermittent suppressive antibiotic therapy [5]. In some circumstances, monitoring markers of inflammation such as the erythrocyte sedimentation rate and C-reactive protein may be useful adjunctive measures of response.

40.9 Side Effects of Antibiotic Therapy

40.9.1 Clostridioides Difficile

It is important to keep a very close surveillance for antibiotic-associated adverse effects, particularly vomiting and diarrhea. If this does occur, it is advisable to stop the antibiotics, at least for a short period, to evaluate for *Clostridioides difficile* colitis. Faeces should be sent for *Clostridioides difficile* testing but therapy should be started immediately with either oral vancomycin (intravenous vancomycin does not treat *Clostridioides difficile*) or oral metronidazole [26]. Alternatively, fidaxomicin 200 mg bid may be prescribed. Acidophilus lactobacillus tablets may also be given to help to restore the intestinal bacterial flora. Patients are advised to eat live yoghurt when taking antibiotics.

In severe cases of *Clostridioides difficile* infection, there may be abdominal pain associated with diarrhea and often a raised white blood cell count and fever. Patients may need admission to hospital and intravenous fluids. An abdominal CT scan may reveal loops of edematous large bowel. When patients who have foot infections. develop diarrhoea with a high white blood cell count and fever, it is a difficult to know whether the fever and raised white cell count are due to either worsening of the foot infection or the onset of *Clostridioides difficile* diarrhea. Close examination of the foot will determine whether infection here has worsened. If this is not the case, then the high white cell count and fever are likely to be due to colitis and the need for ongoing systemic antibiotics should be reassessed immediately.

40.10 Conclusion

Infection is the great destroyer of diabetic feet. Medical management of infection is crucially important to assess the severity of infection, ascertain the bacteria responsible for the infection and to treat aggressively with antibiotic therapy. It is imperative to have a working knowledge of the principal bacteria involved in these infections and their local antibiotic sensitivities including awareness of antibiotic-resistant organisms. Initial antibiotic therapy is empiric and is based on the clinical severity of infection and the suspected organisms involved.

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Epilogue

Although there have been many advances in the management of the diabetic foot, it nevertheless remains a major global public health problem. The three great pathologies which converge in the diabetic foot, neuropathy, ischaemia and infection, can lead to rapid progression to tissue necrosis. This progress towards necrosis is the fundamental feature of the natural history of the diabetic foot and can be rapid and devastating. This clinical presentation has come to be regarded as a "diabetic foot attack" similar to the heart and brain attacks of the coronary and cerebrovascular systems.

As the "diabetic foot attack" can quickly reach the point of no return with overwhelming necrosis, it is vital to diagnose it early and provide rapid and intensive treatment. Early diagnosis and intervention is crucial.

It is important to

- Heal the ulcer before infection occurs,
- Eradicate infection before necrosis develops
- Treat ischaemia before gangrene develops
- Diagnose the Charcot foot before deformity develops, or if deformity has taken place to prevent ulceration

When a diabetic foot is threatened, it is important to take back control of the clinical situation by achieving

- Wound control
- Mechanical control
- Microbiological control
- Vascular control
- Metabolic control
- Educational control.

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Such intervention can only be carried out by the expertise of an interdisciplinary care team working closely together in a dedicated diabetic foot clinic but also providing continuity of care for the patient when admitted to the hospital.

We hope that this book has given enough information to enable practitioners to understand the natural history of the diabetic foot, rapidly diagnose its problems and confidently undertake appropriate intervention in a timely manner.

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