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Clinical practice guidelines

Management of diabetic foot infections

Short text

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Question 1: Definition of diabetic foot infections

1a) What is the definition of diabetic foot infection and what are its clinical presentations?

Infection is defined by invasion of the tissues with proliferation of micro-organisms causing tissue damage with or without an associated inflammatory response by the host. Diabetic foot infections are generally secondary to a skin wound. **The diagnosis of diabetic foot infection is clinical. However, infection must be distinguished from bacterial colonization**, a physiological phenomenon occurring all over the skin and related to minimally virulent aerobic and anaerobic bacteria derived from the skin flora, endogenous flora or the environment. This phenomenon can be modified in diabetes mellitus, with a polymorphic appearance and growth of more virulent bacteria such as *Staphylococcus aureus* or *Streptococcus pyogenes*. The progression to infection occurs as a result of multiple factors related to the characteristics of the wound, the pathogenic bacteria and the host. The diagnosis of **infection** is based on the presence of at least two of the following signs: swelling, induration, erythema around the lesion, local tenderness or pain, local warmth or presence of pus. The severity of infection is assessed according to the International Consensus on the Diabetic Foot classification system (Table 1A).

Table 1A
International Consensus on the Diabetic Foot classification of foot wound infections

Grade 1	No symptoms, no signs of infection
Grade 2	Lesion only involving the skin (without involvment of deeper tissues nor systemic signs) with at least two of the following signs: • local warmth • erythema > 0.5–2 cm around the ulcer • local tenderness or pain • local swelling or induration • purulent discharge (thick, opaque to white or sanguineous secretion) Other causes of inflammation of the skin must be eliminated (for example: trauma, gout, acute Charcot foot, fracture, thrombosis, venous stasis)
Grade 3	• Erythema > 2 cm and one of the findings described above or • Infection involving structures deeper than skin and subcutaneous tissue, such as deep abscess, osteomyelitis, septic arthritis or fasciitis There must not be any systemic inflammatory response (see grade 4)
Grade 4	Any foot infection, in the presence of a systemic inflammatory response manifested by at least two of the following characteristics: - temperature > 38 °C or < 36 °C - pulse > 90 bpm - respiratory rate > 20 per min - $PaCO_2$ < 32 mmHg - leukocytes > 12,000 or < 4000 per mm^3 - 10% of immature (band) forms

Superficial infections involve tissue layers above the superficial fascia and present in the form of acute bacterial cellulitis. **Deep infections** involve the superficial fascia, muscles or bones and joints.

Cellulitis is a bacterial infection of the subdermis. The clinical features are characterized by local signs (erythema, initially around the lesions and then diffuse). Hyperthermia, ascending lymphangitis and regional lymphadenopathy are sometimes absent in diabetic patients.

Necrotizing cellulitis is characterized by tissue necrosis of the subdermis and then the dermis. **Necrotizing fasciitis** corresponds to involvement of the superficial fascia, presenting in the form of sloughing of the skin and a violaceous color of the integument without pus or abscess. Rapid deterioration of the general status, development of renal failure, sudden extension of the lesions, cutaneous sensory loss (difficult to demonstrate in patients with diabetic neuropathy) and the presence of skin detachment constitute warning signs of necrotizing fasciitis.

Wet gangrene is defined by blackish necrotic tissues. It is rapidly progressive with skin detachment and grayish pus with a nauseating odor, and can lead to rapid deterioration of the patient's general status with sepsis, metabolic disorders and renal failure.

Purulent collections can present in the form of **abscess** (collected form) or **phlegmon** (circumscribed by the tissues) in the soft tissues of the foot, or even the leg that may sometimes be difficult to demonstrate clinically and may require the use of imaging examinations.

Osteomyelitis and bone and joint infection will be described in a separate chapter (Chap. 5).

1b) What are the pathophysiological mechanisms of diabetic foot infections?

Diabetic patients are at greater risk than the general population to infections, particularly foot infections. Fifteen to 25% of diabetic patients develop a foot ulcer at some time during their life and 40–80% of these ulcers become infected. The pathophysiological mechanisms of diabetic foot infections are still a subject of controversy. The various hypotheses proposed include:

- a **deficiency of cell-mediated immune mechanisms** accentuated by hyperglycemia that can alter leukocyte functions,
- the harmful effects of **neuropathy** and **excessive pressure** on the wound,
- the **chronic nature** of the lesion,
- **hypoxia**, due to a poor local perfusion and accentuated by the host's hypermetabolic state and microbial cellular metabolism. Hypoxia promotes anaerobic subcutaneous infections and decreases the bactericidal activity of neutrophils,
- **arterial disease** decreasing the blood supply to the wound and consequently the influx of endogenous and exogenous factors (antibiotics) involved in the fight against infection,
- the particular **anatomy of the foot**, divided into several compartments, explaining the rapid spread of infection.

1c) What clinical classifications are available to guide the management of diabetic foot infections?

Many wound classifications have been proposed. The University of Texas classification (UT classification) is easy to use and should now be used as the **reference wound classification**. It comprises four grades according to depth and four stages according to the presence or absence of infection and/or arterial disease (Table 1B). A complementary classification of wound infections has been defined by the **International Consensus on the Diabetic Foot** (Table 1A). This classification comprises four grades, from grade 1 (no infection) to grade 4 (severe sepsis).

Table 1B
Classification of foot wounds in diabetic patients: University of Texas (UT) Wound classification combining grade and stage. This classification system is a double entry table taking into account the depth of the lesion (column) and the presence or absence of infection and/or ischemia (line). The amputation rate according to the wound category is shown in parentheses

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

Question 2: How to document acute diabetic foot infection?

2a) How to obtain reliable microbiological data?

2a1) What are the indications for bacteriological specimens?

Bacteriological specimens are only indicated in the case of clinically confirmed infection, starting at grade 2 of the International Consensus classification. Bacteriological specimens should not be obtained systematically from wounds with no clinical signs of infection.

2a2) What are the methods of microbiological isolation?

Protocols designed jointly by clinicians and microbiologists are essential to obtain clinically useful results. The objective is to obtain isolation and identification of the micro-organism(s) responsible for the infection from a specimen, while avoiding contamination by the commensal flora that colonizes the skin. **No consensus has been reached concerning the best technique for microbiological isolation**. Before taking any specimen, the wound must be prepared. Debridement with a sterile curette or scalpel is essential. The wound must then be cleaned with gauze soaked in sterile physiological saline. Antiseptics can be used, but they must be eliminated by sterile physiological saline before taking the specimen.

Fig. 1 summarizes the choice of specimens to be performed as a function of the type of wound.

Repeated specimens should be taken in the event of an unfavorable course or when the patient presents severe sepsis. Specimens must be sent to the microbiology laboratory **as rapidly as possible** (collaboration between clinicians, nurses and couriers), in **transport medium**. Specimens must be **inoculated** on conventional media and incubated at 37 °C. For specimens derived from deep tissues and aspirations, cultures must also be performed under anaerobic conditions. There is a poor correlation between the results of Gram stain and the results of culture of tissue biopsies.

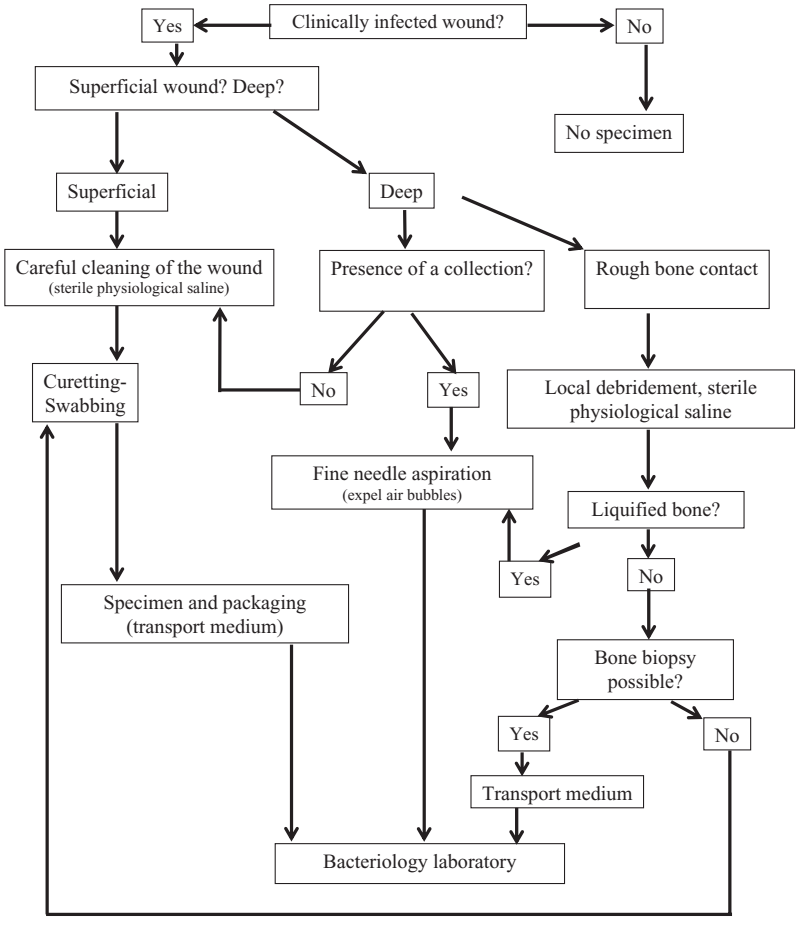


Fig. 1. Flow chart of the specimens to be taken as a function of the type of wounds identified in a diabetic subject.

2a3) Interpretation of the results and epidemiology

Interpretation of the results must take into account the conditions of collection of the specimen, the specimen transport time and transport conditions and the type of bacteria isolated. First-line treatment should disregard the least virulent or commensal bacteria (coagulase-negative staphylococci, Corynebacteria, *Pseudomonas aeruginosa*, enterococci). There is no 100% reliable microbiological method to distinguish between pathogenic and nonpathogenic micro-organisms at the present time. When there is a doubt, specimens must be repeated and these bacteria will be taken into consideration when they are isolated on several occasions or when the patient's septic state is worrisome.

Gram-positive aerobic bacteria are the most frequent micro-organisms; in this group, *S. aureus* is the micro-organism most frequently isolated. **Gram-negative aerobic bacteria**, essentially *Enterobacteriaceae*, are generally detected in chronic or previously treated infections. *P. aeruginosa* is frequently isolated after a long stay in hospital or when the wound is treated by moist dressings. **Strict anaerobic bacteria** are often associated with aerobic bacteria. The ecology of multiresistant bacteria must be taken into account, especially Methicillin-resistant *Staphylococcus aureus* (MRSA) which constitutes a very serious problem, although isolation of MRSA is not synonymous with increased virulence. Other bacteria must also be taken into account: *Enterobacteriaceae* resistant to third-generation cephalosporins, multiresistant *P. aeruginosa* and other environmental bacteria.

2b) What is the value of laboratory examinations?

No laboratory marker is sufficiently sensitive and specific to confirm the diagnosis of infection or colonization of a diabetic foot wound. Laboratory markers are often misleading, even in the case of severe lesions.

Question 3: Apart from microbiological factors, what other risk factors should be investigated?

3a) Mechanical factors

Diabetic neuropathy predisposes to the development of foot deformities and gait abnormalities with the appearance of pressure zones and reactive hyperkeratosis. Continued walking induces the appearance of a zone of inflammatory detachment underneath the zone of hyperkeratosis, leading to mal performance that penetrates into deeper planes and predisposes to the development of infection. The main mechanical factor worsening foot wounds is therefore **continued weightbearing**. Other mechanical factors have also been identified: poorly fitting shoes, nail diseases, acquired deformities (hallux valgus or quintus varus), œdema (predisposing to poor distal arterial perfusion) and prolonged bed-rest. These mechanical risk factors must be identified and eradicated.

3b) Peripheral vascular disease (PVD)

Evaluation of the underlying vascular state is essential in any diabetic patient with an infected wound. This evaluation is based on clinical examination and complementary investigations:

3b1) Clinical examination must look for signs of intermittent claudication, rest pain, that may often not be experienced by the patient due to diabetic neuropathy, with inspection of the foot, auscultation of arteries and palpation of pedal pulses.

3b2) Complementary investigations

a. Ankle-Brachial Index (ABI) must be systematically determined in all diabetic patients. It corresponds to the ratio between systolic blood pressure measured at the ankle and in the arm (brachial). The ABI may reveal PVD in a number of asymptomatic patients. Normal values are between 0.90 and 1.30. An ABI < 0.90 confirms the diagnosis of PVD. Interpretation of the ABI may be limited by medial sclerosis of ankle arteries which makes the arteries poorly compressible or incompressible, thereby falsely raising the systolic pressure. An ABI > 1.30 is indicative of incompressibility.

b. Arterial Doppler examination of the lower limbs is highly recommended in diabetic patients over the age of 40 years and/or who have suffered from diabetes for more than 20 years and/or in the presence of known coronary artery disease or atheroma of the supra-aortic vessels. **This examination must be systematically performed in the case of diabetic foot infection**. B-mode ultrasound identifies stenoses and occlusions, analyses the arterial wall and measures the external diameter of the artery at the site of the stenosis and at a presumably healthy site. Doppler studies provide hemodynamic analysis of flow at the stenosis and in the distal runoff.

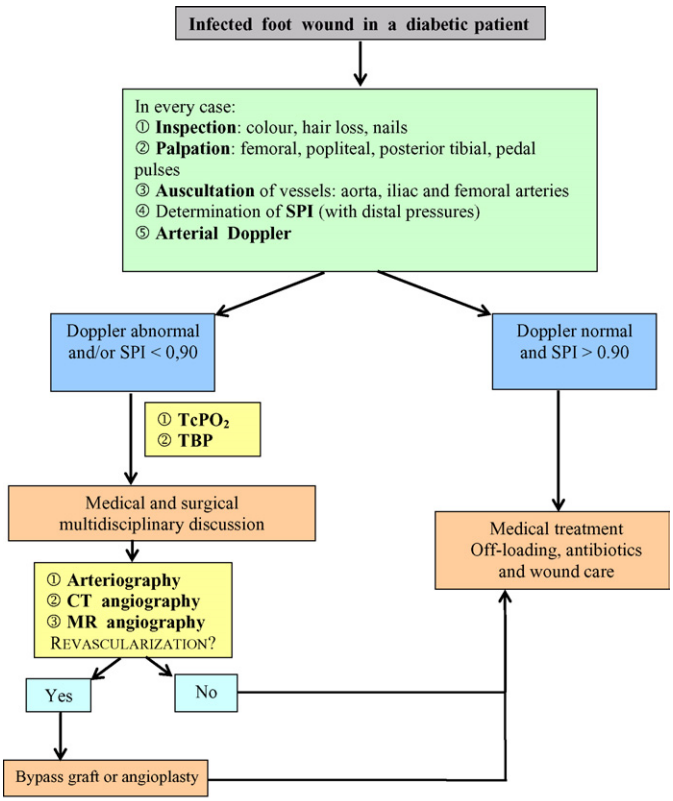
Arteriography remains the reference examination for the anatomical evaluation of PVD and to guide revascularization. **MR angiography** and **CT angiography** (performed without direct arterial injection and without injection of iodinated contrast agent for MR angiography) can be alternatives to arteriography of the lower limbs to evaluate the lesions, especially distal and calcified lesions.

c. Other examinations

Toe blood pressure (TBP), which can almost always be measured in diabetic patients, is indicated in the case of neuropathy associated with medial arterial sclerosis, when ABI is ≥ 1.30. PVD is defined by a 50 mmHg difference between ankle systolic pressure and TBP or by a toe/brachial systolic pressure index < 0.55. A TBP less than 30 mmHg corresponds to critical ischemia and a revascularization procedure must be envisaged.

Transcutaneous partial pressure of oxygen ($TcPO_2$) is an index of the severity of skin ischemia and the probability of spontaneous healing even in the presence of medial sclerosis. The normal value of $TcPO_2$ measured on the dorsum of the foot is about 50 mmHg in diabetic patients. For a $TcPO_2$ greater than 30 mmHg, healing is possible in more than 90% of cases. A value less than 20–30 mmHg indicates critical ischemia with a healing rate < 30%. It is falsely lowered in the case of edema of the dorsum of the foot or infection. As a value > 30 mmHg confirms the absence of severe ischemia in a case of diabetic foot infection, **this examination must be performed in the presence of arterial disease**.

Fig. 2 illustrates the practical approach.



ABI: Ankle-Brachial Index
$TcPO_2$: Transcutaneous partial pressure of oxygen
TBP: Toe Blood Pressure

Fig. 2. PVD and infected diabetic foot: diagnostic flow chart.

Question 4: What treatment modalities are available?

Fig. 3 illustrates the management of an infected wound in a diabetic patient.

4a) What is the value of a multidisciplinary approach?

Diabetic foot is a complex disease requiring global management of the patient and not only the foot. A **multidisciplinary approach** is essential and requires good coordination between all health care professionals involved.

4b) Which strategies should be implemented?

4b1) The role of blood glucose control

There are many arguments in support of **maintaining blood glucose as close to normal as possible**. Insulin therapy is usually required to ensure blood glucose control.

4b2) The importance of mechanical off-loading

Complete and permanent off-loading of the wound must be ensured as strictly as possible. Various modalities are available: bed rest, wheelchair (keeping the affected leg horizontal), removable or non removable casts. The patient's strict compliance with off-loading, tolerance and the condition of the off-loading device must be closely monitored.

4b3) Medical debridement

Mechanical debridement consists of excising necrotic soft tissues, devitalized and contaminated tissues and slough, leaving only healthy tissue in order to promote wound healing. The presence of arterial disease must be eliminated before performing any debridement procedure. In predominantly neuropathic ulcers, debridement must be continued until healthy tissue is reached, but in ischemic ulcers, debridement must be performed very cautiously and must be limited to a simple drainage. Ideally, debridement should be performed after or during revascularization. Debridement allows complete visualization of the wound, exposure of any extensions, better drainage of exudates and collection of deep bacteriological specimens and it also promotes healing. It must always be performed before application of any topical agents and must be repeated as often as necessary. Surgical debridement is discussed in Chapter 4d2.

4b4) Antiseptics and topical antibiotics

Antiseptics and topical antibiotics have no place in the topical treatment of infected foot wounds in diabetic patients.

4b5) Dressings

No consensus has been reached concerning the type of dressing to be used use on infected diabetic foot wounds. The principle of daily dressings to allow close surveillance of the infected wound is generally accepted. In the case of cellulitis, the edges of the inflammatory zone must be marked with a felt-tip pen to follow the course. Adhesive or occlusive dressings must not be used on infected wounds. The dressing must be adapted to the volume of exudate. Regardless of the type of dressing applied, detailed wound care protocols must be established and the course of healing must be objectively documented by regular measurement of the wound as well as photographs.

4b6) Control of edema

It has been shown that reduction of edema increases the healing rate of debrided diabetic foot infections.

4b7) Tetanus vaccine status must be systematically verified

4b8) Other treatments

Hyperbaric oxygen therapy and growth factors are not currently recommended as treatment for diabetic foot infections. Hyperbaric oxygen therapy can be considered in the case of severe arterial disease (critical ischemia) not suitable for revascularization.

4c) What antibiotics should be used in diabetic foot infections in the absence of osteoarticular involvement?

The objective of antibiotic therapy is not to sterilize wounds. Once **infection has been confirmed clinically**, bacteriological specimens are taken and empirical antibiotic therapy is immediately initiated due to the risk of a rapidly unfavorable course, especially in grade 3 and 4 wounds.

Empirical antibiotic therapy must cover the bacteria most frequently involved in these infections. Even in the absence of *S. aureus* on the specimens, antibiotic therapy must cover this micro-organism. Certain **features of the wound** that can guide empirical antibiotic therapy are presented in Tables 2 and 3. The choice of antibiotic must take into account the **cost of treatment**, the **mode of administration** and the risk associated with

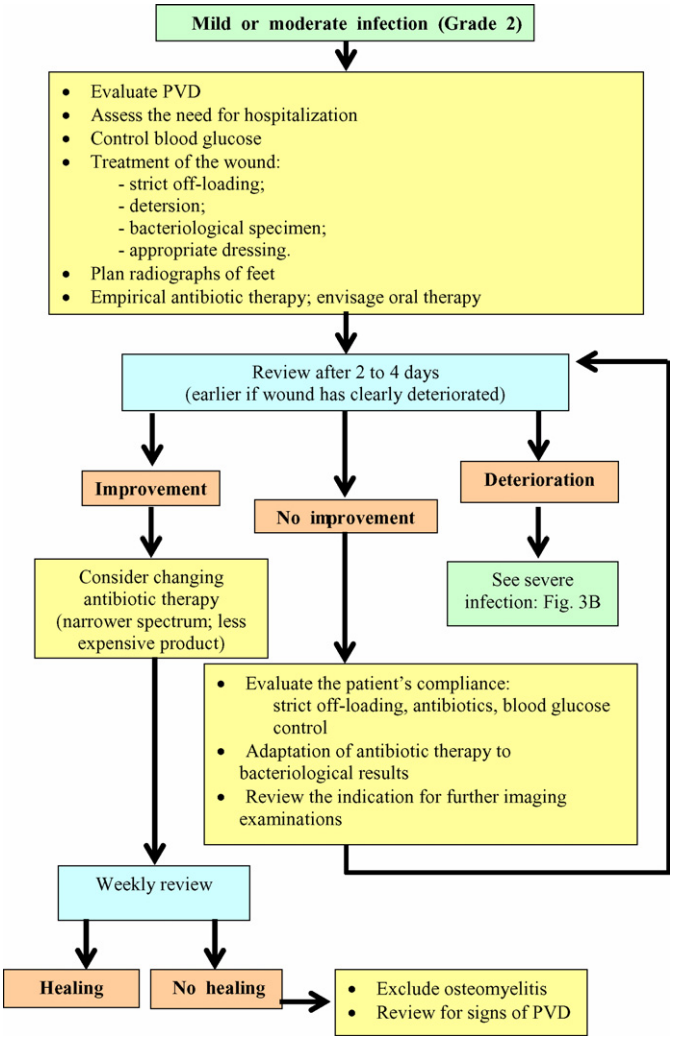


Fig. 3A. Approach to diabetic foot infections.

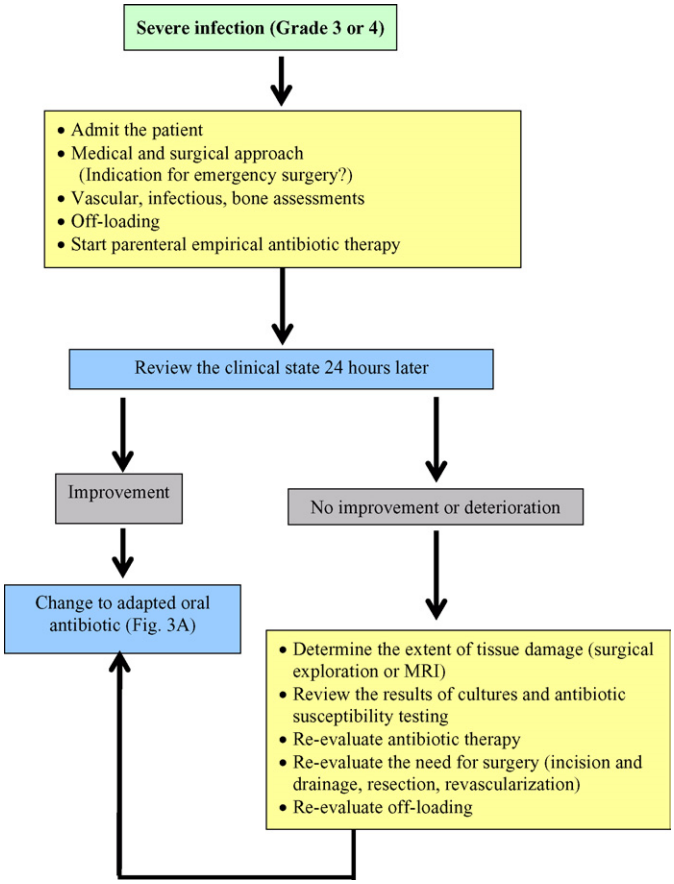


Fig. 3B. Approach to diabetic foot infections.

the presence of **multiresistant bacteria**. Table 4 presents proposals for first-line antibiotic treatment which take these parameters into account.

The state of the patient's infection must be reviewed after 48–72 hours. Two situations can be distinguished:

- favorable clinical course: the initial antibiotic therapy must be continued except when it uselessly comprised a broad spectrum to cover a possible MRSA and/or multiresistant Gram negative bacilli that were not isolated on the specimens (treatment simplification).
- unfavorable clinical course: the suitability of empirical antibiotic therapy in relation to the culture results must be verified and this treatment may need to be adapted to cover the pathogens isolated. When no resistant pathogen has been isolated, the presence of extension of the infection to deep tissues and/or tissue ischemia, poor compliance with antibiotic or any other cause of failure (especially non-compliance with off-loading) must be investigated.

The **parenteral route** should be used for severe infections, in the presence of ischemia, when the molecules used cannot be administered orally or when the patient's state is incompatible with oral therapy. The criteria for **hospitalization** are summarized in Table 5. In all other cases, outpatient oral therapy is recommended, provided regular medical follow-up can be ensured. Due to the frequently

Table 2
Clinico-bacteriological correlation between the various types of wounds and the bacteria involved and identified

Type of foot wound	Pathogens
Recent superficial wound without recent antibiotics	*S. aureus*, β-hemolytic *Streptococcus*
Chronic wound (≥ 1 month) or previously treated with antibiotics	*S. aureus*, β-hemolytic *Streptococcus*, *Enterobacteriaceae*
Wound treated with cephalosporins with unfavorable course	Enterococcus
Macerated lesion	*Pseudomonas* spp (in combination with other micro-organisms)
Persistent wound (ulcer ≥ 6 months), previous treatment with broad-spectrum antibiotics	Multiple pathogens: Gram-positive aerobic cocci (*S. aureus*, β-hemolytic *Streptococcus*, coagulase-negative *Staphylococcus*, *Enterococcus* spp), Corynebacteria, *Enterobacteriaceae*, *Pseudomonas* spp, Gram-negative non-fermenting bacilli ± fungi
Nauseating odor, necrosis, gangrene	Gram-positive aerobic cocci, *Enterobacteriaceae*, *Pseudomonas* spp, Gram-negative non-fermenting bacilli, strict anaerobes

Table 3
Systemic factors to be taken into account when prescribing antibiotics

Concomitant diseases	Implications
Renal failure	Take into account the nephrotoxic potential of certain antibiotics (aminoglycosides and glycopeptides) Possibly adapt the dosage and/or frequency of antibiotic administration Regularly monitor renal function (serum creatinine)
Heart failure	Take into account the salt content of certain antibiotics (fosfomycin) Regular clinical surveillance (œdema, acute pulmonary œdema, etc.)
Gastroparesis	Take into account the modification of the bioavailability of certain oral antibiotics (fosfomycin) Consider using parenteral antibiotic therapy
PVD	Tissue concentrations of the antibiotic are not always effective (even when serum levels are satisfactory) Increase the dosage?
Allergy	Patient's clinical interview, history Avoid antibiotics for which allergy has been demonstrated

Table 4
First-line antibiotics in diabetic foot infections (excluding osteomyelitis)

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

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

[a] AG: aminoglycosides (gentamicin or netilmicin).

[b] MSSA: methicillin-susceptible *Staphylococcus aureus*.

[c] MRSA: methicillin-resistant *Staphylococcus aureus*.

[d] GNB: Gram-negative bacilli.

Table 5
Factors suggesting the need for hospitalization

- Severe infection (grade 4)
- Poor patient compliance and limb-threatening infection
- Deep wound with suspected bone and joint involvement
- Rapidly unfavorable course of the wound
- Metabolic disorders
- Severe ischemia, gangrene
- Need for IV antibiotics than cannot be performed at home
- Need for a surgical procedure
- Patient follow-up at home is impossible
- Appropriate care at home is impossible

associated poor tissue perfusion, it seems legitimate to prescribe **maximum dosages of each molecule and to strictly observe dose intervals**. The optimal **duration** of antibiotic therapy has not been clearly established, but could be one to 2 weeks for simple forms and 2–4 weeks for moderate to severe forms of skin and soft tissue infections. When signs of infection have resolved, antibiotic therapy does not need to be continued until the wound has completely healed, but the other aspects of management must be continued.

4d) What surgical strategies are available?

4d1) Revascularization procedures

Revascularization procedures have two main objectives: to ensure salvage of a limb when viability is compromised by severe ischemia and to allow healing of ulcers.

In the case of severe (critical) ischemia associated with signs of infection, coldness of the foot, pallor, absent pulses, presence of necrosis and suggestive signs on vascular investigations (ankle blood pressure < 50 mmHg or $TcPO_2$ < 30 mmHg or TBP < 30 mmHg), revascularization must be systematically considered. The treatment of infection (off-loading, debridement, antibiotic therapy) must be started immediately and revascularization must be considered once the infection has been controlled. In the case of surgical exposure, the revascularization procedure should be performed as soon as possible to avoid extension of infection, absence of healing, or even life-threatening deterioration. Ideally, the revascularization should be performed at the same time as the debridement procedure.

In the case of more moderate ischemia, a less severe clinical situation and less unfavorable vascular investigations

(ankle blood pressure > 70 mmHg, $TcPO_2$ > 30 mmHg and TBP > 50 mmHg), revascularization can be deferred and proposed secondarily, especially in the case of delayed healing despite control of infection and well conducted medical treatment.

In every case, it is essential to evaluate the patient's arterial status to assess the need for a revascularization procedure, which could reduce healing time and reoperations.

The **criteria for revascularization** take into account: the patient's general state (operability), the potential for ulcer healing, the quality of the arterial distal runoff and the site of the lesions (arteriography or possibly MR angiography in patients with renal failure).

The **indications for revascularization** depend on the level of the lesions. Aorto-iliac lesions are treated by angioplasty or bypass graft. Femoropopliteal or tibial lesions should preferably be treated by angioplasty, which do not prevent the possibility of secondary bypass grafts. Multisegmental lesions, the most frequent situation, require a combination of angioplasty and bypass grafts.

Distal bypass grafts have transformed the prognosis of serious trophic disorders of the diabetic foot and are not performed sufficiently frequently. They must be performed only after infection has been controlled, preferably with venous material or allografts.

Lumbar sympathectomy is not indicated in the treatment of diabetic PVD with or without infected lesions.

4d2) Orthopaedic surgery

Conservative surgery can be considered in two circumstances:

- **Emergency**, in the case of limb-threatening or life-threatening infection, abscess complicated by a compartment syndrome or necrosis, or necrotizing cellulitis. Emergency surgery must be as conservative as possible. Amputations, even minor, must be exceptional.
- **Deferred**, in the absence of improvement in response to well conducted medical treatment. This procedure must be performed after vascular assessment and revascularization, if necessary, and must be as conservative as possible.

Amputation surgery sometimes still remains the only option in the case of severe, deep infection, especially in a context of ischemia. The choice of the **level of amputation** depends on the vascular status, while taking every effort to preserve heel weight-bearing with the prosthesis. No amputation must be performed without first performing complementary vascular investigations. **Major amputations (leg or thigh) must be exceptional** (for uncontrolled life-threatening infection or extensive gangrene or extensive, irreversible trophic disorders).

The **criteria for amputation** depend on the patient's arterial status:

- **in patients without PVD**, amputation should only be performed in the case of necrotic or extensive irreversible lesions;
- **in patients with PVD**, when a revascularization procedure is possible, amputation can be performed at the same time as revascularization or several days later. When revascularization is impossible, amputation is performed in the case of extensive and irreversible lesions.

Absence of healing of a chronic wound is not a systematic indication for amputation.

Question 5: What are the specificities of osteomyelitis of the diabetic foot?

5a) What is the definition of osteomyelitis of the diabetic foot?

Bone infection is frequent in diabetic patients, present in 30–80% of cases depending on the severity of the infection. It may consist of isolated osteomyelitis, especially of the toes and calcaneus, or more often bone and joint infection, while isolated septic arthritis is rare. Bone or joint infection generally occurs by contiguous spread from a skin wound, while a hematogenous origin of osteomyelitis or osteoarthritis of the foot is exceptional in diabetic patients.

5b) What are the signs suggestive of osteomyelitis of the foot in a diabetic?

Osteomyelitis must be suspected in the following cases: resistance to treatment, recurrent infection of an ulcer, especially when it is localized over a bony prominence, unfavorable or persistent course despite optimal management and a satisfactory arterial blood supply. Other clinical signs are also in favor of osteomyelitis:

- **rough bone contact** when probing with a sterile, blunt metal probe introduced through the ulcer, although the value of this procedure has recently been questioned;
- bone exposure ; the **edematous, erythematous "sausage**" appearance of a toe or abnormal mobility of a toe are also suggestive of bone and joint infection.

5c) How to establish the differential diagnosis with acute Charcot foot?

Charcot neuropathic osteoarthropathy evolves in two chronological stages, acute and chronic. The acute stage may raise the problem of the differential diagnosis with infection. **In the absence of an adjacent ulcer**, the diagnosis of Charcot foot is almost certain. **In the presence of an ulcer (active or healed)**, the differential diagnosis may be more difficult, or even impossible. Clinically, erythema is often more limited in cellulitis. Elevation of the limb (Brodsky manoeuvre) reduces œdema and local warmth in the case of Charcot foot, but has no effect in the case of infection. General symptoms and laboratory abnormalities reflecting infection are typically absent in Charcot foot. However, these signs may also be absent in diabetic foot infections. Nevertheless, the absence of neuropathy and the presence of severe PVD argue in favor of osteomyelitis or bone and joint infection rather than a diagnosis of Charcot foot. Charcot foot and osteomyelitis can also co-exist. **Standard radiography** is poorly contributive. Some authors consider **MRI** to be the examination of choice for the diagnosis of osteomyelitis, but MR images can be misleading. Labeled polymorphonuclear cells scintigraphy (coupled with Tc bone scintigraphy) can be useful, but may sometimes give false-positive results. The differential diagnosis can be based on Tc-nanocolloid bone marrow scintigraphy. In the last resort, bone biopsy may be necessary to establish the diagnosis.

In the presence of an ulcer, the management of Charcot foot and osteomyelitis is based on strict off-loading of the ulcer and management in a specialized center.

5d) What is the place of imaging in the diagnosis of osteomyelitis?

Plain radiographs should be performed as first-line investigation. Suggestive signs **over the wound** (periosteal reaction, osteopenia and osteolysis) only become obvious after destruction of 30–50% of the bone. Radiographs may therefore be normal and may need to be repeated 2–4 weeks later.

Other complementary investigations can be considered:

- **MRI** appears to have a better sensitivity and specificity, especially for lesions of the forefoot. The anatomical precision of this examination is particularly useful to guide a possible surgical procedure, but the distinction with Charcot foot still remains difficult;
- among the various **isotope studies**, Tc bone scintigraphy has a better sensitivity but a poor specificity. Labeled leucocyte scintigraphy and, more recently, scintigraphy using antigranulocyte antibodies, appear to have a better specificity for the diagnosis of osteomyelitis, but they can only be interpreted in comparison with Tc bone scintigraphy (coupled scintigraphy). Only coherent images confirm the diagnosis of osteomyelitis. A practical approach is proposed in Fig. 4.

No study is currently available to assess the possible contribution of imaging to diagnose cure of osteomyelitis.

5e) How to microbiologically document acute osteomyelitis of the diabetic foot?

Bone biopsy is the reference method for the bacteriological diagnosis of osteomyelitis (Fig. 1). It is indicated in the case of failure of first-line antibiotic therapy and must be performed after a 2 weeks treatment washout. The bone fragment can be obtained by surgery or percutaneous aspiration through healthy skin using a trocar, after very thorough disinfection, without obligatory local anesthesia due to the sensory neuropathy. The specimen must be immediately placed in a sterile container containing physiological saline to prevent drying.

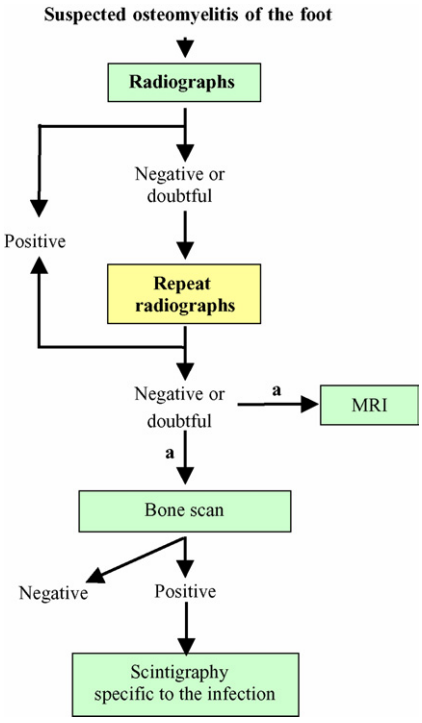


Fig. 4. Flow chart of complementary investigations in the case of suspected osteomyelitis of the diabetic foot (**a**: most authors consider MRI to be superior to scintigraphy for the diagnosis of osteomyelitis).

5f) What antibiotics should be used to treat bone and joint infection?

Treatment regimens recommend the use of combinations of molecules with high intraosseous diffusion (fluoroquinolones [for Gram negative bacilli infection], rifampicin or clindamycin [for Gram-positive cocci infection], fusidic acid). Table 6 proposes treatment regimens for acute osteomyelitis of the foot. Oral treatment reduces the length of hospital stay, costs and the risk of nosocomial infection.

The optimal duration of antibiotic therapy for osteomyelitis of the diabetic foot is difficult to determine due to the limited number of clinical trials. The following guidelines are proposed: when the infected bone has been completely excised leaving noninfected surrounding soft tissues, antibiotics should be continued for 48–72 hours; if all infected bone tissue has been resected, but soft tissue infection persists: treatment for 2–4 weeks (however, it is difficult to precisely determine the border between healthy and infected bone tissues prior to surgery); when the infected bone tissue has been only partly resected: antibiotic therapy should last 4–6 weeks; when no surgical resection has been performed: treatment should last at least 6 weeks.

Question 6: What are the modalities of prevention?

6a) Detection of diabetic patients with a high risk of foot problems

This consists of identifying risk factors (history of ulceration or amputation, sensory loss of the foot demonstrated by the monofilament test, PVD and foot deformities). These risk factors identify patients according to their level of risk, as defined in the International Consensus classification (Table 7) whose predictive value has been demonstrated by a prospective study.

6b) Prevention measures

6b1) Education

Patient education is essential right from grade 1 and must include the patient's family, comprising practical and adapted advice (awareness of sensory loss and its consequences, awareness of poor blood supply and its consequences, high-risk situations, self-examination of the feet, atraumatic footwear and hygiene and maintenance of the feet (nails, hyperkeratosis, fungal infections). **Nurse education** must emphasize the importance of regular examination of the feet of diabetic patients, scoring of the risk of foot problems, setting up of preventive strategies based on patient education and foot care.

6b2) Other measures

Podiatric care (removal of hyperkeratoses and nail care), good quality shoes, fashioning of orthopaedic shoes and adapted orthoses are essential, as these disorders are responsible for ulceration of the diabetic foot.

Table 6
Recommendations for the choice of antibiotic for acute osteomyelitis of the diabetic foot (documented)

Methicillin-susceptible *S. aureus*

Molecule	Dosage/24 h	Route of administration	Dose interval	Comment
Oxacillin or cloxacillin	100–150 mg/kg per day	IV	4 or 6 h	Until reception of specimens
± gentamicin	4 mg/kg per day	IV	24 h	4 mg/kg per day
OR				
Ofloxacin or pefloxacin[b]	600 mg per day 800 mg per day	IV/Oral IV/Oral	8 h 12 h	Oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	
OR				
Ofloxacin or pefloxacin[b]	600 mg per day 800 mg per day	IV/Oral IV/Oral	8 h 12 h	Oral route as soon as possible
+ fusidic acid	1500 mg per day	IV/Oral	8 h	
OR				
Rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	Oral route as soon as possible
+ fusidic acid	1500 mg per day	IV/Oral	8 h	
OR				
Clindamycin[a]	1800 mg per day	IV/Oral	8 h	Oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	
OR				
[Trimethoprim + sulfamethoxazole]	640/3200 mg	IV/Oral	12 h (equivalent to 2 tab/12 h of [Trimethoprim + sulfamethoxazole] (Bactrim Forte®)	Oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8–12 h	

[a] Only if susceptible to erythromycin.
[b] Caution in subjects > 60 years (1/2 dose).

Methicilin-resistant *S. aureus*

Molecule	Molecule	Route of administration	Dose interval	Comment
Vancomycin	1 g (loading dose) then 30 mg/kg	IV IV infusion	Loading dose (1 h) IV infusion or/12 h	Adjust according to serum assays[a]
± gentamicin	4 mg/kg per day	IV	24 h	For 48 h
OR + rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	IV for first 24–48 hours, then oral route as soon as possible
OR + fosfomycin	200 mg/kg per day	IV	8 h	Infusion over 1–2 h
OR				
Rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	IV for first 24–48 hours, then oral
+ fusidic acid	1500 mg per day	IV/Oral	8 h	route as soon as possible
OR				
[Trimethoprim + sulfamethoxazole]	640/3200 mg	IV/Oral	(equivalent to 2 tab/12 h of [Trimethoprim + sulfamethoxazole] (Bactrim Forte®)	IV for first 24–48 hours, then oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	
OR				
Teicoplanin	24 mg/kg per day 12 mg/kg per day	IV/Subcutaneous Subcutaneous	12 h loading dose 24 h	For 48 h, then every 24 h[a]
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	

[a] Adjust the dosages to obtain trough concentrations (discontinuous IV) or plateau concentrations (continuous IV) of 30 mg/l for vancomycin, or a trough concentration of 30–40 mg/l by HPLC for teicoplanin.

Table 6 (suite)
Recommendations for the choice of antibiotic for acute osteomyelitis of the diabetic foot (documented)

***Streptococcus* spp**

Molecule	Dosage/24 h	Route of administration	Dose interval	Comment
Amoxicillin	150–200 mg/kg per day	IV	4–6 h	Change to oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	IV for first 24–48 hours, then oral route at the physician's discretion
OR				
Clindamycin[b]	1800 mg per day	IV/Oral	8 h	Oral route as soon as possible
+ rifampicin	20–30 mg/kg per day	IV/Oral	8–12 h	
OR				
Vancomycin	1 g (loading dose) then 30 mg/kg	IV IV infusion	Loading dose (1 h) IV infusion or/12 h	Adjust to serum assays[a]
+ rifampicin	20–30 mg/kg per day	IV/Oral	8–12 h	
OR				
Teicoplanin	24 mg/kg per day then 12 mg/kg per day	IV/subcutaneous Subcutaneous	12 h loading dose 24 h	For 48 h, then every 24 h[a]
+ rifampicin	20–30 mg/kg per day	IV/Oral	8 or 12 h	

[a] Adjust the dosages to obtain trough concentrations (discontinuous IV) or plateau concentrations (continuous IV) of 30 mg/l for vancomycin, or a trough concentration of 30–40 mg/l by HPLC for teicoplanin.
[b] Only if susceptible to erythromycin.

Enterobacteriaceae

Molecule	Dosage/24 h	Route of administration	Dose interval	Comment
Cefotaxime	200 mg/kg per day	IV	4–6 h	
ofloxacin or ciprofloxacin	600 mg per day 800–1200 mg per day or 1000–1500 mg per day	IV/Oral IV or Oral	8 h 8 h or 12 h	Oral route as soon as possible
OR				
Ofloxacin or ciprofloxacin	600 mg per day 800–1200 mg per day or 1000–1500 mg per day	IV/Oral IV or Oral	8 h 8 h or 12 h	Oral route as soon as possible

Table 7
International Diabetic Foot Risk Classification

Grade 0	No sensory neuropathy or arterial disease
Grade 1	Presence of isolated sensory neuropathy
Grade 2	Combination of neuropathy AND arterial disease or foot deformities
Grade 3	History of ulceration or amputation