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Anti-infective management of infected skin ulcers

Stefano Di Bella[1], Roberto Luzzati[1], Filippo Mearelli[2], Giovanni Papa[1], Luca Spazzapan[3], Alessio Nunnari[2], Francesco D'Aleo[4], Carmelo Papola[4], Luigi Principe[4]

[1]Clinical Department of Medical, Surgical, and Health Sciences, Trieste University, Trieste, Italy;
[2]Internal Medicine Unit, Trieste University Hospital (ASUGI), Trieste, Italy;
[3]Plastic Surgery Unit, Trieste University Hospital (ASUGI), Trieste, Italy;
[4]Clinical Microbiology and Virology Unit, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

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SUMMARY

Infected skin ulcers represent a frequent and intricate clinical challenge, necessitating prompt and comprehensive multidisciplinary interventions to avert complications. Anti-infective therapy constitutes a cornerstone in the therapeutic paradigm. This manuscript delineates our approach to anti-infective management of infected ulcers, encompassing insights into clinical classifications, diagnostic features, exampless of early clinical decision-making in anti-infective treatment, comprehensive evaluation of infectious diseases encompassing host clinical considerations and potential interventions, determination of antibiotic therapy duration, methodologies for assessing clinical response, identification of potential causes for lack of clinical response, as well as strategies for outpatient parenteral antibiotic therapy and a diagnostic and therapeutic algorithm.

Keywords: Ulcers, infection, antibiotic therapy, microbiology.

INTRODUCTION

Infected skin ulcers are a common clinical problem with a significant impact on public health. Ulcers more commonly involve lower-extremities that are anatomically more prone to complications of vascular disorders, neuropathies and traumas. It is estimated that lower-extremity ulcers have a prevalence of 1-2% of the population in western countries [1, 2]. When facing ulcers, it is of fundamental importance to recognize if they are infected, especially in diabetic patients. Indeed, diabetic foot ulcers are more prone to infection, and more than half of them are recognized as clinically infected at the time of the patient's presentation to the clinician [3, 4]. Amputation is experienced in 20% of diabetic foot ulcers and is linked to a high risk of death in the subsequent years [5]. A prompt identification of infection and an adequate, patient-tailored, anti-infective therapy can make the difference, by avoiding the amputation. We provide an opinion paper based on a synthesis of both historical and contemporary literature evidence. Papers deemed worthy by the panel of authors were referenced to discuss the various paragraphs. Below we discuss the main issues of infected ulcers from an infectious diseases point of view.

Classifications

Several classifications for skin ulcers exist and almost always apply to diabetic foot ulcers.

An "orthodox classification" has been provided by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) (Table 1). This classification adopts 4 categories of lesions: uninfected, mild infection, moderate infection and severe infection [6].

Corresponding author
Stefano Di Bella
E-mail: stefano932@gmail.com

Table 1 - IDSA/IWGDF classification of skin ulcers.

Clinical classification of infection, with definitions	*IDSA/IWGDF classification*
Uninfected: no systemic or local symptoms or signs of infection	1 (uninfected)
Infected At least two of the following items are present: • Local swelling or induration • Erythema >0.5 cm around the wound • Local tenderness or pain • Local warmth • Purulent discharge Other causes of an inflammatory response of the skin should be excluded (*e.g.* trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis and venous stasis) - Infection involving only the skin or subcutaneous tissue (without involvement of deeper tissues and without systemic manifestations as described next) - Any erythema present extends <2 cm around the wound - No systemic signs or symptoms of infection	2 (mild infection)
- Infection involving structures deeper than skin and subcutaneous tissues (*e.g.* bone, joint, tendon or muscle) or erythema extending ≥2 cm* from the wound margin - No systemic signs or symptoms of infection	3 (moderate infection)
- Any foot infection with the systemic inflammatory response syndrome, as manifested by ≥2 of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mmHg • White blood cell count >12 000/mm^3 or <4000/mm^3, or >10% immature forms	4 (severe infection)

Another widely used classification, simple and well-performing in prognostic terms, is the Texas classification (Table 2) [7]. This classification consists of a combined matrix of 4 grades (related to the depth of the wound) and 4 stages (related to the presence or absence of infection or ischemia). The classification successfully predicts a correlation of the likelihood of complications in patients with higher stages and grades and a significantly higher amputation rate in wounds deeper than superficial ulcers [8].

Microbiology

The majority of acute infections of lower-extremity ulcers are caused by Gram-positive bacteria, especially staphylococci [9]. On the other hand, chronic infections of ulcers are often polymicrobic with Gram-positive, Gram-negative and anaerobic bacteria [10]. It is recommended to collect tissue samples for microbiology analysis (culture) before antibiotic therapy, especially in patients without systemic involvement. It is equally important to stress that for clinically uninfected ulcers, collecting a

Table 2 - University of Texas classification system for skin ulcers.

Stages	*Grades*			
	0	*1*	*2*	*3*
A	Healed pre or post ulcerative lesion completely epithelialized	Superficial wound not involving bone tendon or capsule	Wound penetrating tendon and capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and with ischemia	With infection and with ischemia	With infection and with ischemia	With infection and with ischemia

specimen for culture is not recommended [11-13]. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most commonly isolated etiological agents from chronic lower limb skin ulcers. *S. aureus* is often detected in the upper layers of the ulcers, while *P. aeruginosa* is found in the deeper layers [14]. In chronic ulcers, the elastase produced by *P. aeruginosa* degrades immunoglobulin G and complement system components, contributing to ulcer chronicity. It is also important to consider the role played by biofilms in chronic non-healing ulcers, which impair the effectiveness of antibiotic action, promote localized tissue hypoxia, reduce the availability of oxygen required for the normal healing process, and lead to significantly increased pathogen minimum inhibitory concentrations (MICs) that may contribute to therapeutic failure [15].

Particular infectious causes of ulcers

Skin ulcers can sometimes underlie diseases different from vasculopathy, neuropathy and trauma. Vasculitis is one of the major diseases to be considered in differential diagnosis. From a strictly infectious diseases point of view, there are relatively uncommon diseases (that will be here only mentioned) that need to be taken into account when facing ulcerated skin lesions: cutaneous anthrax, chromo(blasto)mycosis, diphtheria, *Francisella tularensis*, leishmaniasis, mycetoma, mycobacterial diseases (*e.g. Mycobacterium leprae*, *M. marinum*, *M. tuberculosis*, *M. ulcerans*), sporotrichosis and tertiary syphilis (gumma) [16, 17].

Diagnostics

Macroscopic observation and clinical examination of the ulcer, the surrounding area and the patient in its entirety are the first fundamental steps to judge an ulcer infected or uninfected and to assess the possibility of systemic progression. The main local signs of infection to consider are: local warmth, erythema, tenderness or pain, swelling and purulent discharge [10]. The secondary signs are: nonpurulent secretions, friable or discolored granulation tissues, undermining of wound edges and foul odor [11].

Many experts conceive the ulcer infection as a process that follows these steps: contamination -> colonization -> topical infection (critical colonization) -> local infection -> regional/spreading infection/cellulitis -> sepsis. With this in mind the Australian Wound Management Association (AWMA) provided clinical indicators of wound infection (Table 3), by specifying that "since bacterial impairment of wound healing is a continuum… worsening infection may or may not include some or all of the factors" [18].

Once the ulcer has been judged clinically infected, a prompt and accurate debridement of necrotic tissues and slough should be performed and tissue biopsies from the base of the ulcer should be collected. If diagnostic issues exist (*e.g.* vasculitic ulcers), it can be considered to send half of the bioptic material to the histopathology laboratory.

Table 3 - Clinical indicators of infection according to AWMA.

Level of bacterial impairment	*Clinical indicators of bacterial impairment to wound healing*
Topical infection/ critical colonization	– Dull wound tissue - absence of vibrant granulation tissue – Slough – Failure of wound to decrease in size or increase in wound size – Increased exudate – Hypergranulation/friable tissue – Demarcated and/or rolled and/ or raised wound margins
Local infection	– Wound breakdown/increase in wound size – Erythema - usually localized to peri-wound tissue – Increased pain or unexplained pain – Edema - usually localized to peri-wound tissue – Purulent or discolored, viscous exudate – Malodour – Bridging and/or pocketing within the tissue – Increased temperature of peri-wound tissue
Regional/ Spreading infection/ Cellulitis	– Spreading erythema - more than 2 cm from wound margin – Induration of regional tissues – Fever – Edema of regional tissues – Malaise and/or general feeling of unwellness
Sepsis	– High fever or hypothermia – Lymphangitis and regional lymphadenopathy – Delirium – Organ compromise or failure – Circulatory shock - hypotension, tachypnoea, tachycardia

Regarding the type of samples, an old debate exists between swab and tissue biopsies, derived from some evidence showing that correctly performed swabs could reach sensitivity and specificity of tissue samples. We (and many experts) suggest preferring tissue biopsies in order to limit the possibility of detecting bacteria colonizing the superficial portion of the ulcer. In fact, the quality of the sample obtained influences whether the isolate can be considered a true pathogen rather than a colonizer and tissues biopsies after thorough debridement are considered the most valuable samples [19, 20]. Some microbiology laboratories can determine the quantitative count of organisms per gram of tissue, but this is rarely necessary for clinical situations [21].

Examples of early clinical reasoning/approach

1) Disease extent and severity assessment

It is fundamental to figure out if the infection is only local or if systemic involvement signs exist, *e.g.*: fever (with or without chills), leukocytosis, expanding erythema and lymphangitis. A very high C-reactive protein should increase the suspicion of systemic involvement. Looking at the evolution possibility, it is important to exclude the progression toward a severe necrotizing infection, usually characterized by the presence of crepitus, bullae and extensive necrosis. Pain out of proportion to clinical signs should generate suspicion; LRINEC score could help in establishing pre-test probability, and an urgent computed tomography scan or magnetic resonance imaging should be performed to exclude a necrotizing infection (*e.g.* fasciitis) [22]. Necrotizing soft-tissue infections are life-threatening conditions and require an urgent consultation with a surgeon (*e.g.*, vascular, general, orthopedic).

2) Odour

Odour is another factor that can help clinicians, especially if a marked change is noticed from the patient and/or from their caregivers/health care professionals. A foul odour emergence is suggestive for infection (change in flora equilibrium with a pathogenic bacterial predominance over commensals/colonizers and high bacterial load) or for superinfection with anaerobes [23].

3) Excluding bone involvement

We suggest to maintain a high suspicion index in order to assess if infection of ulcers (especially those close to bone prominences such as ankles and feet) has progressed in an underlying osteomyelitis (Figure 1). A concomitant osteomyelitis would significantly change the therapeutic approach:

a) it would need a more aggressive debridement;
b) it would benefit from a deep sampling (bone biopsy);
c) it would require a longer antibiotic therapy (6 weeks if the bone is vital).

From an imaging point of view, when suspecting an underlying osteomyelitis, the first step is the plain X-ray but this is often followed by magnetic resonance imaging (for osteomyelitis in diabetic foot: sensitivity 90%, specificity 85%) [24, 25]. Histopathology examination of the bone can be useful to confirm the osteomyelitis, since the probe-to-bone not necessarily means that the bone is affected [26].

4) When to consider anaerobic coverage?

Anaerobes are difficult to cultivate in standard laboratories; therefore their absence of growth does not exclude their involvement. Their pathogenic role is still debated but some casistics have shown that the isolation of anaerobes was higher in those who subsequently underwent a lower extremity amputation [27]. The rate of anaerobic infection does appear to be highest in ischemic or necrotic ulcers, where the impaired blood supply and low redox potential may facilitate their proliferation [27]. An appearance of foul odor may suggest anaerobic superinfection.

Anti-infective treatment

1) When to treat

Only clinically infected ulcers should be treated with anti-infective agents, in fact data from the literature have not demonstrated advantages from prophylactic therapies or treatment of non-infected ulcers [28]. Usually, although it is recommended to postpone antibacterial therapy until tissue sampling, it is not recommended to wait for antimicrobial susceptibility testing, especially in diabetic patients. Therefore, the optimum would be to start antibiotics after bioptic tissues have been taken, pending bacterial identification and antibiotic susceptibility testing (Figure 1). An exception can be made in previously treated patients at risk for multidrug-resistant bacteria.

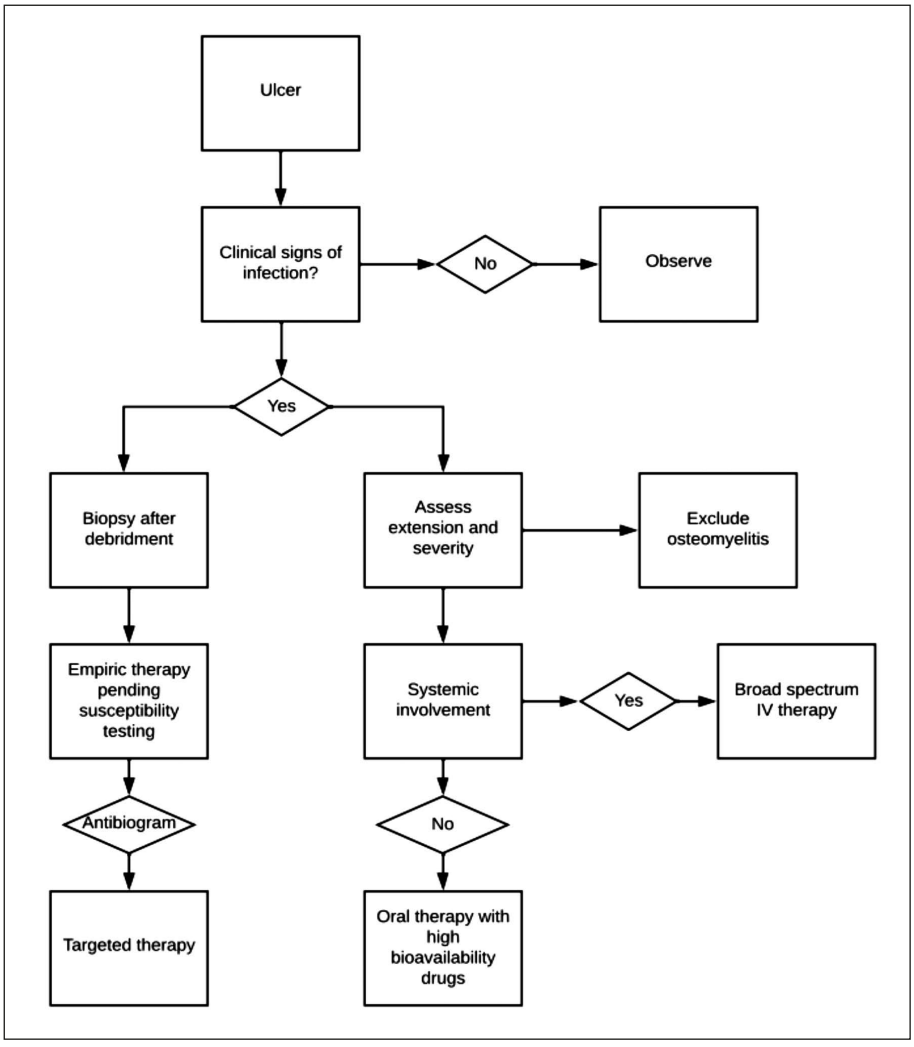

Figure 1
Reasoned diagnostic and therapeutic algorithm.

2) Topic antimicrobials: more shadows than lights

Regarding topical antibiotics, there are more shadows than lights. A commonly used compound, with adequate literature data is silver sulfadiazine, however the Canadian Agency for Drugs and Technologies in Health in 2017 stated "There is currently insufficient evidence to recommend the use of silver sulfadiazine for the treatment of infected or contaminated chronic wounds" [29]. Apart from a disappointing efficacy, there is also concern that topical antibiotics may further promote the emergence of bacterial resistance [30]. Some hope arises from bioengineered honey, which has shown activity against Gram-negative bacterial biofilms [31].

3) How to cover anaerobes?

Although the pathogenic role of anaerobes in ulcers is still a matter of debate, it has been demonstrated that anaerobes represented 49% of the total microbial composition in infected leg ulcers compared with 36% in noninfected leg ulcers [32]. Baron et al. suggest to always consider anaerobes in feet ulcers [19]. Anaerobes more commonly isolated from infected ulcers are *Bacteroides* spp. and *Peptostreptococcus* spp. [27]. Antibiotic resistances among anaerobes are increasing (especially among *Bacteroides* spp.), but a betalactam with a betalactamase inhibitor (*e.g.*, amoxicillin/clavulanate, piperacillin/tazobactam) remains a good option [33].

4) Systemic or not?
It is important to understand this crucial point: in the "systemic" patient it is preferred to direct the therapy toward hydrophilic drugs to maximize the activity on potential bacteremia, while in localized infections it is preferred the use of lipophilic drugs to achieve a greater tissue penetration. For example, in systemic patients we suggest using daptomycin instead of linezolid to cover methicillin-resistant *Staphylococcus aureus* (MRSA). On the contrary, in local infections we suggest using doxycycline instead of amoxicillin/clavulanate against methicillin-susceptible *S. aureus*. Age ≥65 years, involvement of non-lower extremities, liver cirrhosis, and systemic inflammatory response syndrome are recognized risk factors for bacteremia development in adults with cellulitis [34, 35].

5) Taking into account the minimum inhibitory concentration (MIC)
When antibiotic susceptibility testing becomes available, especially in monomicrobial infections, it is important to optimize the therapy taking into account the MIC of the different molecules by knowing the clinical breakpoint for a certain bacterium. This evaluation is helpful to increase the possibility of microbiological and clinical success, especially considering that very often the circulation is impaired, so it is much better to stay distant from the breakpoint.

6) Oral absorption (mild/moderate cases)
In mild/moderate infection, if a molecule with high oral bioavailability is used in a patient with good gastrointestinal function, it is acceptable to start orally. This would usually led to less complications (phlebitis) and would allow care for the patient in an outpatient setting. In Table 4 is reported a list of antibiotics with good oral bioavailability.

7) Know your local epidemiology
An updated knowledge of the local epidemiology is fundamental; for example, in our hospital 90% of staphylococci are susceptible to doxycycline and trimethoprim-sulfamethoxazole, making them good options for anti staphylococcal empirical therapy in mild-moderate infections. This should be re-evaluated every year with susceptibility data collected by the microbiology laboratory. In general, if a microorganism has a resistance >20% for an antibiotic in a certain epidemiology, avoid this drug in empirical therapy.

8) Local infections: rational antibiotic regimens
In mild to moderate infections in patients who have not recently received antibiotics, it is reasonable to start a therapy more focused to Gram-positive bacteria, often with MRSA coverage, since the majority of these patients have risk factors for MRSA [12]. We suggest the following regimens: doxycycline + clindamycin; doxycycline + cefazolin; linezolid. We use doxycycline (usually active against MRSA) in combination because it is poorly active against *Streptococcus pyogenes*. In patients without MRSA risk factors, amoxicillin/clavulanate is a reasonable empirical choice for not already "antibiotic experienced" patients.

9) Systemic empiric antibiotic regimens
In patients with severe infections depending on the degree of systemic involvement intravenous therapy should be preferred and therapy should cover Gram-positive, Gram-negative (including *Pseudomonas*) and anaerobes, *e.g.*, daptomycin +

Table 4 - Antibiotics with good oral bioavailability commonly used for infected ulcers [36, 37].

Antibiotic	*Oral absorption*	*Pro*	*Cons*
Ciprofloxacin	70%	Active on susceptible *Pseudomonas*	Poor anti anaerobic activity
Clindamycin	90%	Selective on Gram+	Can predispose to CD infection
Doxycycline	90%	Good anti-staphylo activity	Poor anti-strepto activity
Levofloxacin	99%	Good tissue penetration	Poor anti-anaerobic activity
Linezolid	100%	Active against MRSA	Myelotoxicity if long therapy
Moxifloxacin	89%	Active against susceptible anaerobes	Rarely tested, R increasing
TMP-SMX	80%	Active against staphylococci (including MRSA)	Potential allergic reactions

CD: *Clostridioides difficile*; MRSA: methicillin-resistant *Staphylococcus aureus*; R: resistances; TMP-SMX: trimethoprim-sulfamethoxazole.

piperacillin/tazobactam (± fosfomycin) or daptomycin + meropenem.

10) Antipseudomonal agents

Pseudomonas is a difficult-to-treat pathogen. Empirical coverage for *Pseudomonas* should be considered in patients who are colonized, particularly those with lower extremity ulcers or diabetic foot ulcers, as well as patients residing in regions with warm and humid climates [38]. The only orally active agent is ciprofloxacin but resistances are quite high. Commonly used antibiotics with antipseudomonal activity are: amikacin, cefepime, ceftolozane/tazobactam, meropenem and piperacillin/tazobactam. Cefepime, ceftolozane/tazobactam and piperacillin/tazobactam would allow continuous infusion [39]. Fosfomycin can be often used as partner drug, especially alongside cephalosporins [40, 41].

11) Multidrug-resistant (MDR) bacteria

Multidrug resistant bacteria require case-by-case therapies. Combination regimens are often used and fosfomycin is often considered because of its synergistic potential. Linezolid is usually a good choice for Gram-positives while for Gram-negatives the last resources and their relative microbiological targets are shown in table 5, keeping in mind that MDR bacterial infections deserve a case-by-case evaluation, often driven by susceptibility testing.

12) Long acting antibiotics

Recently, long-acting antibiotics have been approved for clinical use. Dalbavancin and oritavancin are sometimes considered for infected ulcers ± osteomyelitis in special situations (*e.g.*, poor compliance). Both drugs have activity against Gram-positives (including MRSA), are approved for skin and soft tissue infections and have solid data also in patients with osteomyelitis [42, 43]. Therapeutic drug monitoring for both dalbavancin and oritavancin is being increasingly used in cases that need multidose administrations, although the interpretation of oritavancin serum levels is still an issue [44].

A reasoned diagnostic and therapeutic algorithm for the management of infected skin ulcers is provided in Figure 1.

Holistic infectious diseases evaluation: host clinical issues and potential countermeasures

When choosing an antimicrobial therapy, basic principles of pharmacokinetic/pharmacodynamic (PK/PD) should be kept in mind and adapted to the patient (liver and/or renal impairment, hypoalbuminemia, allergies, etc.). We describe several important factors that may influence the choice and that deserve to be evaluated below:

- advanced liver disease -> *e.g.* ascites -> altered volume of distribution, prefer cefotaxime to ceftriaxone, prefer meropenem to ertapenem,
- arterial vasculopathy -> difficulty of antibiotics to reach the target site -> prefer lipophilic drugs with good diffusion in soft tissues, *e.g.* quinolones, tetracyclines, linezolid,
- bone involvement -> prefer lipophilic drugs such as regimens including quinolones, consider rifampicin or fosfomycin as partner drugs,
- diabetes -> damaged microcirculation -> expect a slower response, prefer lipophilic drugs with good diffusion in soft tissues, *e.g.*, quinolones, tetracyclines, linezolid),
- hypoalbuminemia -> especially negatively influence PK/PD of antibiotics with high protein-bound drugs, *e.g.* ertapenem, ceftriaxone (prefer meropenem and cefotaxime, respectively) [45],
- obesity -> PK/PD issues that can require dose adjustment, *e.g.* linezolid standard dosing may be inadequate, use actual body weight to calculate clindamycin dose,

Table 5 - New anti multi-drug resistant antibiotics and their microbiological targets.

	KPC	*OXA-48*	*MBL*	*PA XDR*	*AB XDR*
Cefiderocol					
Ceftazidime/avibactam					
Imipenem-relebactam					
Meropenem/vaborbactam					

AB XDR: *Acinetobacter baumannii* extremely-drug-resistant; KPC: *Klebsiella pneumoniae* carbapenemase; MBL: metallo-betalactamase; PA XDR: *Pseudomonas aeruginosa* extremely-drug-resistant.

– previous *Clostridioides difficile* infection -> prefer drugs with low colitis induction potential *e.g.* dalbavancin, doxycycline, linezolid, piperacillin/tazobactam,
– renal failure -> adjust posologies of hydrophilic drugs as needed, prefer lipophilic drugs *e.g.* minocycline.

Antibiotic therapy duration
For mild to moderate skin and soft tissue infections, 1-2 weeks of therapy is usually effective, for severe infections (systemic involvement) the length is usually protracted to 2 weeks (in selected cases of slow response in patients with peripheral artery disease 4 weeks). Antibiotics should not be continued through complete healing of the ulcer. If there is concomitant osteomyelitis therapy usually lasts 6 weeks (if the bone is judged viable) [46].

How to assess clinical response?
The majority of diabetic foot ulcers take a minimum of 20 weeks to heal [47, 48]. The ulcer area needs to be measured regularly. Apart from ulcer reduction, other signs that suggest amelioration are: pain decrease, malodour reduction, decrease of surrounding erythema and decrease of local temperature.
Any increase ≥20% between two measurements should be considered as an increase in wound size. If over a 4-week period of appropriate treatment (not only anti-infective), the ulcer size does not decrease by at least 20%, delayed healing should be noted [49].

Blood tests are also useful to confirm a trend, *e.g.* white cell count, C-reactive protein, erythrocyte sedimentation rate.

Possible causes of lack of clinical response
A non-exhaustive list of potential causes of clinical failure is herein reported:
– Antibiotic therapy directed toward a colonizer (real pathogen not identified).
– Underlying vascular failure too strong (limb ischemia).
– Necrotic tissue (unidentified) not removed.
– Bacterial resistances not detected or new resistances developed.
– Multiple bacterial phenotypes (*e.g.* multiple *Pseudomonas* populations).
– Reinfections with new bacteria.
– Poor therapy adherence (especially in outpatients).

Outpatient parenteral antibiotic therapy (OPAT)
For patients who are not severely sick, but would benefit from intravenous therapy (*e.g.* impaired gastrointestinal absorption, few options for resistances) some antibiotics are suitable for outpatient parenteral antibiotic therapy (OPAT) (Table 6). Some of them can be administered once daily and the others can be administered in 24-h continuous infusion with elastomeric pumps (in this case the patients would usually need a medium-long term venous access such as Midline or PICC) [50].

Table 6 - Antibiotics suitable for OPAT [39].

Antibiotic	*Diluent*	*Dilute to reach a concentration lower than*
Cefazolin	D5W, NS	25 mg/mL
Cefepime	NS	12.5 mg/mL
Ceftaroline	D5W, NS	6 mg/mL
Ceftolozane/tazobactam	D5W, NS	12.5 mg/mL ceftolozane 6.25 mg/mL tazobactam
Ceftriaxone	Can be administered every 24 h	
Clindamycin	D5W, NS	1 mg/mL
Ertapenem	Can be administered every 24 h	
Penicillin G	D5W, NS, RA	100.000 UI/ml
Piperacillin/tazobactam	D5W, NS	50 mg/mL piperacillin 6.25 mg/mL tazobactam
Vancomycin	D5W, NS	5 mg/mL

D5W: dextrose 5% in water; NS: normal saline.

CONCLUSION

Our work, while acknowledging its limitation as an opinion paper according to authors' perspective, highlights the fact that the management of infected cutaneous ulcers presents a nuanced challenge, necessitating a multidisciplinary approach for optimal outcomes. A comprehensive clinical assessment forms the cornerstone, entailing a meticulous examination of key indicators to discern the infectious nature of an ulcer. Subsequent steps involve deep tissue sampling for microbial culture, facilitating a tailored therapeutic strategy that not only addresses isolated pathogens but also considers pertinent variables such as potential contaminations, the presence of fastidious microorganisms, and the formation of biofilms. Equally paramount is the diligent exclusion of underlying osseous involvement in equivocal cases, thus enabling the determination of the optimal duration for antibiotic therapy.

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