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Optimising Antimicrobial Therapy in Diabetic Foot Infections

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Contents

Abstract . . . 195
1. Pathophysiology . . . 196
2. Microbiology . . . 197
3. Defining and Diagnosing Infection . . . 198
   3.1 Infection versus Colonisation . . . 198
   3.2 Osteomyelitis . . . 199
4. Principles of Treatment . . . 199
   4.1 Treatment of Uninfected Ulcers . . . 200
   4.2 Treatment of Infection . . . 201
      4.2.1 Topical Therapy . . . 201
      4.2.2 Oral Therapy . . . 201
      4.2.3 Parenteral Therapy . . . 202
      4.2.4 Instillation/Implantation Therapy . . . 203
5. Evidence-Based Approach for Managing Diabetic Foot Infection . . . 203
   5.1 Definitive Antibacterial Therapy . . . 205
   5.2 Duration of Therapy . . . 206
   5.3 Surgical Intervention . . . 208
   5.4 Management of Osteomyelitis . . . 208
   5.5 Adjunctive Therapy . . . 209
6. Conclusion . . . 210

Abstract

Foot infections are common and the most serious lower extremity complication contributing to amputations, particularly in patients with diabetes mellitus. Infection is most often a consequence of foot ulcerations, which typically follows trauma to a neuropathic foot. Foot infections may be classified as mild, moderate and severe; this largely determines the approach to therapy. Gram-positive bacteria are the sole causative pathogens for most mild and moderate infections. These infections can usually be treated with culture-based narrow-spectrum antibacterials along with appropriate surgical debridement in an outpatient setting. In contrast, severe infections are often polymicrobial, requiring hospitalisation and treatment with broad-spectrum antibacterials along with appropriate medical and surgical interventions. The initial empirical antibacterial regimen may be tailored based on the results of culture and sensitivity tests from properly obtained

specimens. Several antibacterial regimens have demonstrated effectiveness in randomised controlled trials, but no single regimen has shown superiority. Managing diabetic foot osteomyelitis is particularly controversial and requires reliable cultures to select an appropriate antibacterial regimen. Surgical resection of the infected and necrotic bone favours a good outcome in chronic osteomyelitis. The recommended duration of antibacterial therapy ranges from 1 to 4 weeks for soft tissue infection, to >6 weeks for unresected osteomyelitis. The incidence of meticillin-resistant *Staphylococcus aureus* infection is increasing in both the healthcare setting and the community. This should be considered when selecting an antibacterial, especially if the patient does not improve with initial antibacterial therapy. Certain other organisms, such as *Pseudomonas aeruginosa* and *Enterococcus* spp., while potentially pathogenic, are often colonisers that do not require targeted therapy.

Foot infections in diabetic patients cause substantial morbidity and occasionally even mortality. Infected or ischaemic ulcers are the major cause of diabetes mellitus-related hospitalisation in the US, accounting for 25% of all such admissions.[1-4] Infection most often occurs after foot trauma or ulceration, and this sequence is the most common cause of non-traumatic lower extremity amputation.[5,6] Optimal management of diabetic foot infections by a comprehensive, coordinated multidisciplinary team of experts can reduce infection-related morbidity and the need for hospitalisation. Such a team approach can decrease the overall incidence of limb amputation, help convert potentially major amputations to minor ones, and reduce overall cost of healthcare. Appropriate antimicrobial therapy must be combined with optimal wound care and necessary surgical interventions for a favourable outcome in diabetic foot infections.[7]

Treatment of diabetic foot infections is too often based on anecdotal experience rather than available data. On behalf of the Infectious Disease Society of America (IDSA), an international team of experts have recently developed comprehensive guidelines for the diagnosis and treatment of diabetic foot infections.[8] We have adapted several sections of these guidelines for this review.

We present an approach to treating diabetic foot infections that is most geared to North American practitioners. We recognise that there are different therapeutic agents and approaches available in other developed countries, and that resources and treatments are constrained in most developing countries. The studies of treatment of diabetic foot infection are difficult to interpret because they have used varying outcome measurements. Most recent antibacterial studies have used the proper measurements, resolution of signs and symptoms of infection, as the primary outcome of interest.

1. Pathophysiology

Any infra-malleolar infection in a patient with diabetes is considered a diabetic foot infection. This includes paronychia, cellulitis, necrotising fasciitis, infectious gangrene, septic tendonitis, septic arthritis and osteomyelitis. The most common lesion that leads to infection is a foot ulcer, in which bacteria can proliferate and ultimately destroy tissue and provoke a host response. The major predisposing factor for foot ulceration is peripheral neuropathy, with accompanying disturbances of sensory, motor and autonomic function. A secondary factor that predisposes to infection, or leads to more severe infections, is peripheral vascular disease. Repetitive minor trauma or excessive pressure on a deformed foot that lacks protective sensation leads to a break in the skin envelope barrier, especially in an ischaemic limb.[9-11] This allows microbes that colonise the skin to gain access to the subcutaneous tissues. Here, large numbers of relatively non-virulent organisms or small numbers of virulent pathogens can cause an invasive infection, especially in a

patient with deficient local or systemic immunity. Some pathogens secrete a glycocalyx that forms biofilm, together with multi-layered cell clusters. The bacterial colonies within the biofilm are resistant to immuno-effectors and have reduced susceptibility to antibacterials *in vivo*. Diabetes-related metabolic and immunological disturbances lead to altered specific and nonspecific cellular immune responses.[12-14]

Infection is rarely a cause, but rather most often a consequence, of ulceration. Curing an infection is a separate (albeit related) issue which may contribute but is not defined by healing of an ulcer.

2. Microbiology

Gram-positive cocci are the predominant organisms that colonise the skin and infect diabetic foot wounds. Staphylococci, particularly *Staphylococcus aureus* but also coagulase-negative species, and to a lesser degree β-haemolytic streptococci (groups A, B, and sometimes C or G) are the most commonly isolated diabetic foot pathogens. These are often the only pathogens in acute infections in patients who have not recently received antibacterials.[15-22] Polymicrobial infections are more frequent in patients with chronic ulcers or who have been previously treated.[23-27] They often include Gram-negative organisms, while obligate anaerobes are typically seen in severe infections, especially in patients with an ischaemic limb.[2,4,28] Various clinical syndromes that are associated with specific pathogens are shown in table I.[8]

Infection with miseillin-resistant *S. aureus* (MRSA) is a growing problem in diabetic foot infections. In one study, 12% of *S. aureus*, 46% of *S. epidermidis* and 45% of *S. haemolyticus* isolates were resistant to meticillin.[28] Two studies conducted at the same institution in the UK demonstrated an increase in the prevalence of MRSA between 1998 and 2001.[29,30] In both studies the predominant organism isolated from diabetic foot ulcers was *S. aureus*; the prevalence was 28.8% in the 1998 study and 48.3% in the 2001 study. MRSA strains were isolated from 30.2% of patients in 2001, almost double the 15.2% reported 3 years earlier.[29,30] In a study of 84 diabetic patients from Athens, Greece, *S. aureus* was the most common pathogen among the Gram-positive bacteria isolated from infected and uninfected foot ulcers, and almost 50% of *S. aureus* isolates were MRSA.[31] The prevalence of MRSA was significantly higher in patients with infected than uninfected foot ulcers. Of note was that MRSA isolation was not associated with factors (e.g. previous hospitalisation, use of antibacterials,

Table I. Pathogens associated with various clinical foot-infection syndromes[8]

Foot-infection syndrome	Pathology
Cellulitis without an open skin wound	β-Haemolytic streptococci[a] and *Staphylococcus aureus*
Infected ulcer and antibacterial naive[b]	*S. aureus* and β-haemolytic streptococci[a]
Infected ulcer that is chronic or was previously treated with antibacterial therapy[c]	*S. aureus*, β-haemolytic streptococci and Enterobacteriaceae
Ulcer that is macerated because of soaking[c]	*Pseudomonas aeruginosa* (often in combination with other organisms)
Long duration nonhealing wounds with prolonged, broad-spectrum antibacterial therapy[cd]	Aerobic Gram-positive cocci (*S. aureus*, coagulase-negative staphylococci and enterococci), diphtheroids, Enterobacteriaceae, *Pseudomonas* spp., nonfermentative Gram-negative rods and, possibly, fungi
'Fetid foot': extensive necrosis or gangrene, malodorous[c]	Mixed aerobic Gram-positive cocci, including enterococci, Enterobacteriaceae, nonfermentative Gram-negative rods and obligate anaerobes

a Groups A, B, C and G.

b Often monomicrobial.

c Usually polymicrobial.

d Antibacterial-resistant species (e.g. meticillin-resistant *S. aureus*, vancomycin-resistant enterococci or extended-spectrum β-lactamase-producing Gram-negative rods) are common.

etc.) known to predispose to MRSA. This could be due to a high prevalence of MRSA in the community in Athens. Several studies suggest that outcomes of diabetic foot infections are worse in patients infected with MRSA. In the study by Tentolouris and colleagues,[30] MRSA infection of foot ulcers was associated with delayed healing compared with ulcers infected with meticillin-sensitive *S. aureus* (mean [range] of 35.4 [19–64] and 17.8 [8–24] weeks, respectively; $p = 0.03$). In addition, the MRSA persisted for up to 4 months after initial surveillance culture. However, this was not substantiated by another study.[32] At this point, the jury is still out on the clinical importance of MRSA isolates from diabetic foot infections.

Many other microorganisms may be isolated from diabetic foot infections, especially in patients who have recently been treated with antibacterials. Two species deserve special mention because they are commonly isolated and might require specially selected antibacterial coverage: *Enterococcus* spp. and *Pseudomonas aeruginosa*. While these organisms are often part of the flora from foot infections, they are usually part of a mixed infection or more commonly represent colonisers than true pathogens.[33] Thus, it is not usually necessary to specifically target antibacterial therapy against these bacteria. However, it is important to remember that even relatively avirulent organisms, e.g. coagulase-negative staphylococci and diphtheroids, may be true pathogens in diabetic foot infections. When these organisms are isolated repeatedly or from aseptically obtained deep tissue specimens, in high colony counts in the absence of other pathogens, or when the patient is substantially immunocompromised, it is reasonable to consider targeting antibacterial therapy at them. When isolated in the presence of other, more virulent pathogens or from contaminated specimens they can usually be ignored.

3. Defining and Diagnosing Infection

All open wounds are colonised with microorganisms. Thus, infection is not diagnosed microbiologically but clinically, based on the presence of purulent secretions (pus) or at least two of the cardinal manifestations of inflammation (redness, warmth, swelling or induration, pain or tenderness). We believe that only clinically infected ulcers require appropriately obtained cultures and properly selected antibacterial therapy.[34,35] The percentage of ulcers that are clinically infected will vary with the setting in which patients are seen; it will be higher where access to care is limited and patients present with long-standing ulcerations. A recent prospective study amongst patients with limited access to healthcare in Texas, USA, showed that 56% of diabetic foot ulcers showed clinical signs of infection at presentation.[36]

Current recommendations for the methods of collecting and processing wound specimens for culture are as follows.

1. Obtain cultures only if there is clinical evidence of infection.
2. Debride and cleanse the wound before taking a specimen for a culture.
3. Obtain tissue specimens from ulcers by curettage (using a dermal curette or scalpel).
4. Aspirate purulent secretions or possibly cellulitic skin.
5. Biopsy deep tissue or bone infections.
6. Avoid sending wound swabs for culture.
7. Obtain blood cultures if patient is systemically ill.
8. Label and send specimens promptly in sterile containers or transport media for aerobic and anaerobic cultures.

3.1 Infection versus Colonisation

It may be difficult to know whether organisms isolated from a wound represent colonisers or pathogens, especially if cultures yield several species. Generally, isolates from a clinically uninfected wound would be considered colonisers, but some infected wounds (e.g. in a patient with limb ischaemia or peripheral neuropathy) may lack classic findings of infection.[37] Criteria that suggest culture results represent infection rather than colonisation include:

- bacterial growth of over 10^5 organisms per gram of tissue;

- growth of an organism (especially a known pathogen) in pure culture;
- repeated isolation of the same organism;
- growth of the organism from the deep tissue in the setting of inflammation and purulent drainage; and
- a Gram-stained smear of the wound showing neutrophils and organisms morphologically compatible with those grown on culture.

3.2 Osteomyelitis

Contiguous spread of infection from the soft tissues can involve the underlying bone. The incidence of bone involvement in patients with a diabetic foot infection is generally reported to be about 20%[36] but can be up to two-thirds in patients with limb-threatening infections.[38] Because diabetic patients with neuro-osteoarthropathy can have non-infectious bone lesions (e.g. Charcot foot), these must be differentiated from infection.[39] Unfortunately, there is no consensus on the best approach to diagnosing foot bone osteomyelitis in diabetic patients. Suggestive clinical findings include an ulcer that overlies a bone, that is long-standing and deep, that does not heal over 6 weeks despite appropriate antibacterials, wound care and off-loading, and a highly elevated erythrocyte sedimentation rate or C-reactive protein level.[40-42] The ability to palpate bone by gently exploring the wound with a blunt sterile metal probe had a positive predictive value of 89% in one study of patients with limb-threatening infection, in which the pre-test probability of osteomyelitis was 66%.[43] A more recent study, in which the incidence of osteomyelitis was 20%, found that the positive predictive value of a positive probe to bone (PTB) test was only 53%.[44]

Similarly, Lavery et al.[45] evaluated the utility of the PTB test in the diagnosis of osteomyelitis in a cohort of 1666 diabetic patients. Over a mean of 27.2 months of follow-up, 247 patients developed a foot wound and 151 patients developed 199 foot infections. Osteomyelitis was found in 30 patients, 12% of all patients with a wound and in 20% of patients with foot infections. When all wounds were considered, the PTB test had a positive predictive value of only 57%; however, the negative predictive value was 98%. In other words, PTB tests in patients with a low prevalence of osteomyelitis appear to have a low positive predictive value but a negative test may exclude the diagnosis.

Plain radiographs may be normal in the early stages of osteomyelitis but subsequent films done a few weeks later may show periosteal elevation and bone destruction. Any focus of bony destruction beneath an ulcer should be considered to potentially represent osteomyelitis unless proven otherwise. Other available non-invasive imaging studies include nuclear medicine scans (e.g. bone and leukocyte), which are more sensitive than plain radiographs, but relatively nonspecific. Magnetic resonance imaging (MRI), where available and affordable, is the best of the imaging techniques for bone, as well as soft tissue, infections. Obtaining a specimen of bone for histology and culture is the standard for diagnosing bone infection, and also allows the clinician to make the most informed choice of antibacterial therapy. It is easy to obtain necrotic or infected bone samples during operative debridement. When surgery is not planned, specimens can usually be obtained by percutaneous bone aspirate or biopsy, going through intact and uninfected skin. Many surgeons are reluctant to perform this procedure for fear of complications but it has proven to be quite safe.[46,47] Interventional radiologists perform percutaneous bone biopsy in some institutions.[48] Bone cultures may be negative because of sampling error or previous antibacterial therapy. In addition, the differences in the features of osteomyelitis and Charcot's arthropathy are not clearly defined.

4. Principles of Treatment

Treatment of a patient with diabetic foot infection can be provided by any interested and experienced clinician, but is best rendered by a multidisciplinary team of healthcare specialists.[49-51] The approach comprises evaluating the need for hospitalisation, comprehensive supportive medical care, appropriate antibacterial therapy, a vascular evaluation, any necessary surgical debridement, off-

loading any wounds caused by pressure, formulating a wound-care plan and considering any necessary adjunctive therapy. In addition, one must consider the patient's psychological state and social situation, as caring for a diabetic foot wound at home requires a highly functional patient or adequate home support. Because the severity of the wound helps determine the proper approach to treatment, the IDSA devised a simple clinical severity classification scheme, as outlined in table II. This helps in assessing the severity of infection.[52-57]

4.1 Treatment of Uninfected Ulcers

Infection is generally defined as a state where organisms introduced into a wound are proliferating, causing host damage, and triggering a host immunological and inflammatory response. Because antibacterial use is associated with potential adverse effects, financial cost and increased antibacterial resistance, it should be restricted to situations of proven efficacy.[59-63] Using antibacterials to treat clinically uninfected diabetic foot ulcers is a somewhat contested topic. Some maintain that these ulcers are prone to infection, which can be difficult to diagnose in a patient with foot ischaemia or neuropathy, and infection can lead to serious consequences.[64]

There is increasing discussion of the concept of 'wound bioburden' or 'critical colonisation', meaning the presence of sufficient organisms (usually defined as $>10^5$ per gram of tissue) to impair wound healing.[65] The progress of bacterial growth in a wound from colonisation to infection depends not only on the numbers of bacteria but also on the host immune response and the presence of ischaemia. There is also evidence that bacteria within a chronic wound live within biofilm communities, and these may be protected from host defences.[66,67] Unfortunately, very few clinicians send tissue specimens for culture and very few clinical microbiology laboratories do quantitative wound cultures. Furthermore, there is no convincing published evidence that treating critically colonised wounds with antibacterials hastens healing. Studies treating clinically uninfected ulcers with antibacterials have suggested no benefit. In one study, 10 of 20 patients in a placebo group versus 6 of 19 in the antibacterial treatment group showed healing of ulcers. Mean reduction in the ulcer radius was 0.41 mm/day (95% CI 0.21, 0.61) in the placebo group versus 0.27 mm/day (95% CI 0.15, 0.39) in the antibacterial group (neither difference is statistically significant). In conclusion, there was no benefit from antibacterial treatment as a supplement to standard therapy in uncomplicated neuropathic foot ulcers. However, a type II statistical error could not be excluded in this small study.[68]

In another study of 64 patients with a diabetic foot ulcer, patients who received oral antibacterials were significantly less likely to develop clinical

Table II. Clinical classification of a diabetic foot infection[8]

Clinical manifestations of infection[a]	Infection severity	PEDIS grade[b]
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of two or more manifestations of inflammation (purulence or erythema, pain, tenderness, warmth or induration), but any cellulitis/erythema extends ≤2cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable, but who has one or more of the following characteristics: cellulitis extending >2cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycaemia or azotaemia)	Severe	4

a Foot ischaemia may increase the severity of any infection and the presence of critical ischaemia often makes the infection severe.

b International Consensus on the Diabetic Foot.[58]

PEDIS = perfusion, extent/size, depth/tissue loss, infection and sensation.

evidence of an ulcer infection, require hospitalisation and heal their ulcer than those who did not (these data, cited in a review, have not been independently published).[66] Treating all diabetic foot ulcers with antibacterials would lead to a dramatic increase in the number of treatment courses. More data from larger, well designed trials are needed to further assess this issue. Until then, we would only treat ulcers with less classical signs of infection (e.g. friable base, poor granulation tissue, foul odour) if they were failing to heal despite otherwise appropriate care. Occasionally, patients are treated to eradicate colonisation with an epidemiologically significant organism, e.g. MRSA.

4.2 Treatment of Infection

4.2.1 Topical Therapy

Treating an infected open wound has the potential advantage of using topical antimicrobial therapy. This allows the use of relatively low doses of the agent while obtaining high levels at the site of infection. Furthermore, some agents that cannot be administered systemically can be used topically. However, there are at least two major concerns about topical antimicrobial therapy. First, most agents will not disseminate very far from where they are applied, so it is important to use this route of therapy only for mildly infected (i.e. relatively superficial and with limited cellulitis) open wounds. Secondly, because some topical agents (especially antiseptics) can be deleterious to wound healing, by damaging epithelial cells, they should be avoided. Some have suggested that dressings containing the antiseptics cadexomer iodine[69] or silver[70] are effective in preventing or treating mild infections. The safety and efficacy of these treatments for wound infections compared with other therapies can only be established by controlled trials.

We have identified nine studies that compared outcomes of treatment with various topical preparations for diabetic foot ulcers (table III). There was no evidence of a statistically significant difference in clinical outcome associated with any particular topical agent compared with another.[71] Apelqvist and colleagues[69] reported a nonsignificantly lower cost associated with using cadexomer iodine dressings than with standard care.[69] Vandeputte and Grayson[72] reported more ulcer healing with a glycerol (glycerin) hydrogel than chlorhexidine, but it is unclear whether their clinical assessment was blinded. However, Markevich and colleagues[73] noted better ulcer healing with larval therapy than with hydrogel dressings.[73] Lipsky and colleagues,[74] in a randomised, double-blind controlled trial, showed that topical pexiganan cream (an antimicrobial peptide) was as effective in treating mildly infected diabetic foot ulcers as oral ofloxacin. Other studies showed aggressive debridement with epidermal grafting using autologous tissue engineering grafts to be useful, especially for dorsal ulcers.[75,76] Coutts and Sibbald,[70] in an observational noncomparative study of ulcers, demonstrated improved ulcer healing, decreased bacterial burden and resolution of surface slough with the use of a silver-containing hydrofibre dressing.

4.2.2 Oral Therapy

Oral antibacterial agents can be used when there is a drug that has the appropriate antibacterial spectrum, and the gastrointestinal absorption and bioavailabilty of the drug is high enough to achieve adequate serum (and, thereby, wound) levels. Oral antibacterials for treating aerobic Gram-positive cocci (e.g. penicillins, cephalosporins and macrolides) have been available for decades, although the gastrointestinal absorption of most is suboptimal. Two oral anti-anaerobic agents, metronidazole and clindamycin, have good bioavailability. Highly bioavailable oral fluoroquinolones have become available in the past two decades. These agents have excellent activity against aerobic Gram-negative bacteria and some of the newer ones have broader-spectra that include most Gram-positives (other than MRSA) and anaerobes. Of course, oral agents are only appropriate for a patient who does not have nausea or vomiting, swallowing difficulties or gastrointestinal absorption problems. For many mild to moderate infections therapy can be started with an oral antibacterial or switched to oral therapy after an initial course of parenteral treatment. Selected oral antibacterials have been shown

Table III. Topical therapy for diabetic foot ulcers (DFU)

Study (year)	Study design (infection status)	No. of patients	Study drugs	Outcome	Results [% of patients]
Apelqvist et al.[69] (1995)	RCT (uninfected)	35	Cadexomer iodine vs streptokinase or dry	Need for surgical intervention	18 vs 28 (NS)
			saline gauze	Healing of ulcer	29 vs 11 (NS)
Vandeputte and	RCT (uninfected)	29	Hydrogel dressing vs	Amputation	7 vs 36 (NS)
Grayson[72] (1997)			gauze and	Ulcer healing	93 vs 36 (S)
			chlorhexidine	Incidence of infection	7 vs 50 (S)
				Systemic/local antibacterials required	7 vs 100 (S)
Lipsky et al.[74] (1997)	RDBCT; infected	415	Pexiganan cream vs ofloxacin	Amputations Clinical cure Eradication of infection Adverse effects	2.4 vs 1.6 (NS) 26 vs 28 (NS) 40 vs 44 (NS) 11 vs 9 (NS)
Marchina and Renzi[77] (1997)	RCT (uninfected)	NA	Antiseptic spray (content not described) vs 2% eosin and 3% chloroxylenol spray	Healing at 15 days	50 vs 82 (NA)
Rhaiem et al.[78] (1998)	RCT; uninfected	56	Systemic antibacterials vs sugar dressings	Healing rate	40 vs 50 (NS)
			Systemic antibacterials vs standard dressings	Healing rate	46 vs 40 (NS)
Markevich et al.[73] (2000)	RCT (uninfected)	70	Larval therapy vs hydrogel dressing	Ulcer healing	7.1 vs 2.9 (NS)
Caravaggi et al.[75]	Multicentre, RCT	79	Autologous tissue-	Overall ulcer healing	65.3 vs 49.6 (NS)
(2003)	(uninfected)		engineered graft vs	Plantar ulcer healing	55 vs 50 (NS)
			non-adherent paraffin gauze	Dorsal ulcer healing	67 vs 31 (S)
Yamaguchi et al.[76] (2004)	RCT (uninfected)	38	Aggressive bone debridement plus epidermal grafting vs standard treatment	Osteomyelitis Amputation	Significant decrease in both osteomyelitis and amputation ($p = 0.0001$)
Coutts and	Observational,	30	Silver-containing	Decreased ulcer size	70
Sibbald[70] (2005)	noncomparative (uninfected? [unclear	(4 with DFU)	hydrofibre dressing	Decrease purulence and surface slough	75
	from article])			Resolution of peri-wound maceration	85

NA = not available; **NS** = not significant; **RCT** = randomised, controlled trial; **RDBCT** = randomised, double-blind, controlled trial; **S** = significant.

to be beneficial in treating mild to moderate diabetic foot infections, as summarised in table IV.[68,79-82]

4.2.3 Parenteral Therapy

Patients for whom oral therapy is not appropriate, who require an agent that is not available orally, or who have a severe infection, require parenteral therapy, at least initially. Most parenteral therapy is given intravenously, but some agents, e.g. ceftriaxone, can be injected intramuscularly, at least for a few doses. Intravenous therapy is usually given in an inpatient setting but has also been successfully provided as part of an outpatient intravenous antibacterial programme. Table V provides a detailed analysis of selected clinical trials of treatment of diabetic foot infections that used parenteral antibacterial therapy. Because of variations in study design, types and severity of infection, we can not reliably compare the outcomes from these clinical trials. Most studies found equivalent efficacy and safety for the tested agents, and no single drug regimen has shown

superiority over the others.[33,38,83-92] Of note is one study of 52 patients with a limb-threatening diabetic foot infection that was resistant to conventional antibacterials in which the addition of intravenous fosfomycin offered an effective treatment choice increasing the likelihood of limb preservation.[92]

4.2.4 Instillation/Implantation Therapy

Some studies have investigated alternative ways of delivering antimicrobials. In patients with poor arterial flow to the infected site, some have used techniques such as infusing antibacterials into the femoral artery or into lower leg veins. There have been too few studies of these techniques to recommend them, and revascularisation of an ischaemic limb seems a better approach. Similarly, some have used methods to implant antimicrobials into a wound, such as with an antibacterial-impregnated collagen sponge, cement or beads.[93] These depot devices can be implanted (either temporarily or left in place) to deliver high concentrations of antibiotics in local tissues without causing systemic toxicities. Methylmethacrylate beads have been used for many years[93] but are limited in that they can be combined only with agents (e.g. aminoglycosides) that can tolerate the high temperatures the process generates, and they must eventually be removed. However, calcium sulfate beads can be combined with most antibacterials and dissolve in the wound.[94]

5. Evidence-Based Approach for Managing Diabetic Foot Infection

IDSA guidelines committee made an effort to delineate the level of evidence in their guidelines. The evidence for most of their recommendations is restricted to an expert opinion rather than randomised controlled trials.[8] The guidelines suggest that optimal management of these complex infections entail carefully assessing the severity of the infection, the medical co-morbidities of the patient (including the medications they may be receiving) and any history of intolerance or allergies to antimicrobials.[95-97] Most initial treatment regimens are empirical. The selection of antibacterials used should be based on a consideration of the spectrum of microorganisms covered, route of administration required, available culture results, any recent antimicrobial therapy, epidemiological information of note and local antibacterial resistance patterns.[8]

Mild to moderate infections are caused predominantly by Gram-positive organisms, especially *S. aureus* and to lesser extent β-haemolytic streptococci. In many clinical settings, patients with these infections can be treated on an outpatient basis with a narrow-spectrum oral antibacterial, such as a semisynthetic penicillin (e.g. dicloxacillin) or first-generation cephalosporin (e.g. cephalexin). Where MRSA is highly prevalent, one must consider if the

Table IV. Oral antibacterial therapy of diabetic foot infections

Study (year)	Study design	No. of pts	Study drugs	Outcome	Results [% of patients][a]
Peterson et al.[79] (1989)	RCT	46	Ciprofloxacin 750mg vs ciprofloxacin 1000mg	Foot amputation Adverse effects	17 vs 25 (NS) 0 vs 2 pts (NS)
Lipsky et al.[80] (1990)	RDBCT	29	Clindamycin vs cephalexin	Clinical cure Healing of ulcer Eradication of bacteria Adverse effects	78 vs 72 (NS) 37 vs 31 (NS) 77 vs 69 (NS) 1 vs 2 pts (NS)
Chantelau et al.[68] (1996)	RDBCT	44	Amoxicillin/clavulanic acid vs placebo	Healing of ulcer Absence of microbes in deep wound culture at the completion of study	27 vs 45 (NS) 32 vs 27 (NS)
Gerards et al.[81] (2000)	Observational, noncomparative	191	Amoxicillin/clavulanic acid	Healing of ulcer Adverse effects	76 4.7
Senneville et al.[82] (2001)	Observational, noncomparative	17	Rifampicin/ofloxacin	Clinical cure at 6 months Remission at 22 months	88.2 76.5

a Unless otherwise indicated.

NS = not significant; **pts** = patients; **RCT** = randomised, controlled trial; **RDBCT** = randomised, double-blind, controlled trial.

Table V. Parenteral antibacterial therapy of diabetic foot infections

Study (year)	Study design	No. of patients	Study drugs	Outcome	Results [% of patients][a]
Grayson et al.[38] (1994)	RDBCT	48	Ampicillin/sulbactam vs imipenem/cilastatin	Amputation	69 vs 59 (NS)
				Clinical cure at the end of treatment	58 vs 60 (NS)
				Clinical cure at follow-up	56 vs 69 (NS)
Bouter et al.[83] (1996)	Randomised, open, comparative	22	Imipenem/cilastatin vs piperacillin + clindamycin	Clinical cure	18 vs 25 (NS)
				Bacterial eradication	41 vs 61 (NS)
Erstad et al.[84] (1997)	RDBCT	18	Ampicillin/sulbactam vs cefoxitin	Amputation	44 vs 44 (NS)
				Clinical cure	6 vs 39 (S)
Graham et al.[85] (2002)	RCT	399	High-dose levofloxacin vs ticarcillin/clavulanic acid	Clinical cure	84.1 vs 80.3 (NS)
				Microbiological cure	83.7 vs 71.4 (NS)
Marvaso et al.[86] (2002)	Prospective, noncomparative	38	Piperacillin/tazobactam	Clinical cure	74 complete resolution
				Microbiological cure	10 improvement
Lipsky et al.[87] (2004)	RCT	241	Linezolid vs ampicillin/sulbactam or amoxicillin/clavulanic acid	Clinical cure	69 vs 63 (NS)
				Mean duration of therapy	17.2 vs 16.5 days (NS)
Clay et al.[88] (2004)	RCT	70	Metronidazole + ceftriaxone vs ticarcillin/clavulanic acid	T <38.0°C WBC <10 mm^3 Wound healing Euglycaemia	86 vs 82 (NS)
				Cost savings	Metronidazole + ceftriaxone savings of $US61.06 per admission (2004 values)
Lobmann et al.[89] (2004)	Multicentre, RCT	90	Ceftriaxone vs chinolones	Clinical cure or improvement	66 vs 64.4 (NS)
Lipsky et al.[33] (2005)	Multicentre, RDBCT	445	Ertapenem vs piperacillin/tazobactam	Clinical cure or improvement	94 vs 92 (NS)
Lipsky and Stoutenburgh[90] (2005)	RCT	103	Daptomycin vs vancomycin or semi-synthetic penicillin	Clinical cure Microbiological response	66 vs 70 (NS) (NS)
Harkless et al.[91] (2005)	RCT	314	Piperacillin/tazobactam vs ampicillin/sulbactam	Clinical cure or improvement	81 vs 83 (NS)
Stengel et al.[92] (2005)	Multicentre, compassionate	52	IV fosfomycin + β-lactam	Limb preservation	92.3

a Unless otherwise indicated.

IV = intravenous; **NS** = not significant; **RCT** = randomised, controlled trial; **RDBCT** = randomised, double-blind, controlled trial; **S** = significant; **T** = temperature; **WBC** = white blood cell count.

organism is likely to be healthcare acquired (and, therefore, resistant to most antibacterials other than vancomycin, quinupristin/dalfopristin, linezolid, daptomycin or tigecycline) or community-acquired (and more likely sensitive to additional antibacterials, e.g. clindamycin, doxycycline, co-trimoxazole [trimethoprim/sulfamethoxazole]). If enterococci noted on culture are thought to be true pathogens, one may need to treat with an aminopenicillin, e.g. amoxicillin. Similarly, if *P. aeruginosa* is deemed a pathogen, the selected regimen may need to include a fluoroquinolone (e.g. ciprofloxacin), a β-lactam/β-lactamase inhibitor combination (e.g. piperacillin/tazobactam), an advanced-generation cephalosporin (e.g. cefoperazone, ceftazidime or cefepime) or a class II carbapenem (e.g. imipenem/cilastatin or meropenem).[8]

For patients who have been previously treated with an antibacterial, or those with more severe or chronic infections, polymicrobial infections are more likely and we recommend selecting initial therapy that is broad spectrum. The chosen regimen should have activity against Gram-positive organisms, as well as most of the more common Gram-negative organisms (Enterobacteriaceae and, occasionally, *P. aeruginosa*) and obligate anaerobes (e.g. peptococci, peptostreptococci and, occasionally, *Bacteroides* spp.). Infections in an ischaemic limb or complicated by extensive necrosis or gangrene more often have anaerobic pathogens. Specimens for culture and sensitivity testing should be taken from almost all wounds, and the results should be used for narrowing the spectrum or tailoring therapy to the most appropriate agents. Severe infections are often immediately limb-threatening and usually warrant hospitalisation for supportive, diagnostic, medical and surgical care. In addition to antimicrobial therapy, these patients need optimised glycaemic control and attention to any other metabolic derangements. Suggested empirical antibacterial regimens based upon clinical severity of infection are summarised in table VI.[8]

5.1 Definitive Antibacterial Therapy

An issue of concern is whether or not all organisms isolated from a polymicrobial wound culture must be covered by the selected antibacterial regimen. One can often ignore relatively low virulence organisms, e.g. diphtheroids or coagulase-negative staphylococci, and *P. aeruginosa* and enterococci when they are found in a polymicrobial infection.[33] A somewhat more controversial pathogen is MRSA. In two prospective studies, Lipsky and colleagues[33,87] have found that the addition of vancomycin to the antibacterial regimen for patients with

Table VI. Suggested empirical antibacterial regimens[a], based on clinical severity, for diabetic foot infections[8]

Agent(s) and route	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral based on clinical situation and agent(s) selected	Intravenous (at least initially)
Dicloxacillin	Yes		
Clindamycin	Yes		
Cephalexin	Yes		
Co-trimoxazole (trimethoprim/sulfamethoxazole)	Yes	Yes	
Amoxicillin/clavulanic acid	Yes	Yes	
Levofloxacin	Yes	Yes	
Cefoxitin		Yes	
Ceftriaxone		Yes	
Ampicillin/sulbactam		Yes	
Linezolid[b] (with or without aztreonam)		Yes	
Daptomycin[b] (with or without aztreonam)		Yes	
Ertapenem		Yes	
Cefuroxime with or without metronidazole		Yes	
Ticarcillin/clavulanic acid		Yes	
Piperacillin/tazobactam		Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin		Yes	Yes
Imipenem/cilastatin			Yes
Vancomycin[b] and ceftazidime (with or without metronidazole)			Yes

a Note: definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have US FDA approval for complicated skin and skin-structure infections, and only linezolid is currently specifically approved for diabetic foot infections.

b For patients in whom meticillin-resistant *Staphylococcus aureus* infection is proven or likely.

MRSA in wound cultures (along with other pathogens) did not alter the clinical or microbiological outcome. Other studies[91,98] of skin and soft tissue infections have shown similar results. While we do not advocate failing to treat a potentially virulent pathogen like MRSA, we think that in some polymicrobial infections empirical targeted therapy for this organism may not be needed. The clinician should then reassess the need for anti-MRSA therapy if this organism is isolated on culture.

The goal of antibacterial therapy is to select a regimen with high efficacy and as narrow a spectrum as possible against the causative organism(s), based on the culture and sensitivity results of an appropriate specimen. These requirements should be reviewed along with any potential adverse drug effects and interactions between various antibacterial regimens and other concomitant medications. The clinician should choose an agent, route of administration and duration of therapy based upon susceptibility results, half-life of the drug chosen and its cost effectiveness, as outlined in table VII.[8] Patients who are likely to adhere to treatment and have good home support should be considered for outpatient parenteral antimicrobial therapy (OPAT).[99-101] This usually requires a drug with prolonged half-life, e.g. ceftriaxone or ertapenem, so that it may be administered once a day. Certain newer agents with excellent bioavailability (e.g. fluoroquinolone or linezolid) may be administered by the oral route for long-term therapy, especially in the setting of osteomyelitis. Pressure off-loading and other aspects of wound care must be reviewed and closely monitored while the patient is managed in an outpatient setting.[102-106]

5.2 Duration of Therapy

The duration of antibacterial therapy required for various types of diabetic foot infections has not been well studied. On the basis of the length of treatment used in the available clinical trials and their own clinical experience, the IDSA Diabetic Foot Infection Guidelines Committee recommended that a 1- to 2-week course of an antibacterial is usually sufficient for mild to moderate infections, while more complex or severe infections may require up to 3 or 4 weeks of therapy. For osteomyelitis, the duration of therapy largely depends on the degree of bone resection; when the infected bone is not surgically resected, therapy should be given for at least 4–6 weeks.[40] Table VII outlines the duration of therapy according to specific setting.[8]

Table VIII lists antibacterials frequently used to treat diabetic foot infections. The oral dosage and cost (in US dollars, 2006 values) of the medications are included.

Table VII. Suggested route, setting and duration of antibacterial therapy, by clinical syndrome[8]

Site, by severity or extent of infection	Route of administration	Setting for therapy	Duration of therapy
Soft tissue only			
Mild	Topical or oral	Outpatient	1–2wk; may extend up to 4wk if slow to resolve
Moderate	Oral (or initial parenteral)	Outpatient/inpatient	2–4wk
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2–4wk
Bone or joint			
No residual infected (e.g. post-amputation)	Parenteral or oral	Inpatient, then outpatient	2–5d
Residual infected soft tissue (but not bone)	Parenteral or oral	Inpatient, then outpatient	2–4wk
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	Inpatient, then outpatient	4–6wk
No surgery, or residual dead bone postoperatively	Initial parenteral, then consider oral switch	Inpatient, then outpatient	>3mo

Table VIII. Average wholesale price for antibacterials for diabetic foot infections[107]

Drug	Dose	Frequency	Cost per day ($US; 2006 values)
Oral			
Dicloxacillin capsules	250mg	q6h	2.64
	500mg	q6h	4.80
Clindamycin capsules	150mg	q6h	11.20
	300mg	q6h	22.80
	450mg	q6h	33.60
Cephalexin capsules	250mg	q6h	2.80
	500mg	q6h	6.00
Co-trimoxazole (trimethoprim/sulfamethoxazole)	DS tablet	qid	7.40
	DS tablet	bid	3.70
Amoxicillin/clavulanic acid	500mg	tid	15.00
	875mg	bid	12.00
Levofloxacin tablets	250mg	Daily	9.22
	500mg	Daily	10.56
	750mg	Daily	16.90
Linezolid tablets	600mg	q12h	126.30
Cefuroxime tablets	250mg	bid	10.80
	500mg	bid	19.60
Metronidazole tablets	250mg	qid	9.76
	500mg	qid	17.12
Ciprofloxacin tablets	500mg	bid	11.60
	750mg	bid	12.16
Parenteral			
Co-trimoxazole injection	15 mg/kg/day		41.60
Ampicillin/sulbactam	1.5g	q6h	32.54
Clindamycin injection	600mg	q8h	33.60
	600mg	q6h	44.80
	900mg	q8h	40.80
	3g	q6h	61.44
Levofloxacin injection	250mg	Daily	20.00
	500mg	Daily	40.00
	750mg	Daily	60.00
Cefoxitin	1g	q6h	61.20
	2g	q6h	108.80
Ceftriaxone	1g	q24h	39.00
	2g	q24h	69.00
Linezolid injection	600mg	q12h	170.90
Aztreonam	1g	q8h	66.00
	2g	q8h	126.00
Daptomycin	500mg vial	q24h	168.00
Ertapenem	1g	q24h	59.98
Cefuroxime injection	750mg	q8h	21.00
	1.5g	q8h	42.00

Continued next page

Table VIII. Contd

Drug	Dose	Frequency	Cost per day ($US; 2006 values)
Metronidazole injection	500mg	q6h	61.36
	1000mg	q24h	30.68
Ticarcillin/clavulanic acid	3.1g	q4h	96.00
	3.1g	q6h	64.00
Piperacillin/tazobactam	3.375g	q6h	67.96
	4.5g	q8h	64.56
Ciprofloxacin injection	400mg	q12h	60.00
Imipenem/cilastatin	500mg	q6h	133.28
Vancomycin	1000mg	q24h	34.60
	1000mg	q12h	69.20
Cefepime	1g	q12h	36.00
	2g	q12h	72.00
Ceftazidime	1g	q8h	43.80
	2g	q8h	85.50

bid = twice daily; **DS** = double strength; **qid** = four times per day; **q*x*h** = every *x* hours; **tid** = three times daily.

5.3 Surgical Intervention

Most diabetic foot infections require some surgical intervention. Because of the anatomic complexities of the foot, several compartments must be evaluated. Thus, an interested and appropriately trained surgeon should assess most patients with more than a mild infection. Perhaps the most common surgical procedure performed is wound debridement, which removes callus and necrotic tissue, and can reduce the bacterial burden and promote wound healing. Some patients require incision and drainage of abscesses or deep soft tissue infections. Any foreign body in the wound should be removed, if possible. An ischaemic limb may require revascularisation, and this can be done and may be necessary prior to definitive antibacterial therapy or surgical resection of the infected tissue or bone. After the initial assessment, wounds should usually be reassessed within 48–72 hours. Early surgical intervention has been shown to improve outcomes in hospitalised patients.[108,109]

5.4 Management of Osteomyelitis

The presence of osteomyelitis underlying an ulcer impairs wound healing and acts as a focus for relapse of soft tissue infection. The need for surgical resection of necrotic and infected bone is the subject of some controversy. Henke and colleagues[110] suggest that osteomyelitis of the foot and toe in adults is a surgical disease and that the conservative management worsens lower extremity salvage. In a single-institution analysis of 237 consecutive patients, aggressive surgical debridement/digit amputation and selected use of arterial bypass improved ulcer healing and limb salvage, while antibacterial therapy alone was associated with decreased wound healing and limb salvage.[110] We believe that bone infection requires surgical resection when feasible and prolonged antibacterial therapy when not. When the affected bone has been completely resected, the wound may be treated as a soft tissue infection. If residual infected bone is left, the patient will probably require 4–6 weeks of antibacterial therapy. Many use antibacterial-impregnated beads (see section 4.2.4), notwithstanding the fact that there are few well designed trials of their effectiveness. Typically, gentamicin, tobramycin or vancomycin is used in the beads. When non-absorbable bone cement beads are used, they are usually removed after 2–4 weeks. The absorbable calcium sulfate pellets do not have to be removed, although the wound can leak some of the calcium sulfate for several weeks as it is being absorbed.[93,94]

Systemic antibacterials are generally given by the parenteral route, at least in the initial weeks. Howev-

er, with the newer agents that have an excellent bioavailability, this may not be necessary. Parenteral therapy may be delivered in the outpatient setting (OPAT),[99-101] when feasible. Most patients seem to benefit from combined limited resection and antibacterial therapy. Some authorities believe that, although limited resection of the infected bone may cure the osteomyelitis, it may result in altered biomechanics and additional cycles of ulceration. Patients with chronic osteomyelitis who do not have troublesome symptoms or limb-threatening involvement may opt for conservative medical treatment. At least 11 retrospective studies have shown that antibacterial therapy alone, usually consisting of at least 3 months of mostly oral (usually fluoroquinolone) therapy can induce remission in about two-thirds of patients.[111] However, it is unclear from these studies how patients were selected and how 'cure' of infection was documented. In some patients in whom infection cannot be cured, keeping disease in remission with intermittent short-course or long-term suppressive oral antibacterials may be appropriate. Other reasons for nonsurgical treatment and long-term suppression include:

- radical surgery aimed at curing infection would cause unacceptable loss of lower limb function;
- severe, non-reconstructable vascular disease may result in loss of a limb if surgical resection is undertaken;
- infection is confined to the fore foot with minimal soft tissue loss; or
- the risk of surgical treatment outweighs the risk of inadequately treated infection.

There are few antibacterial trials[110,112] and no randomised controlled surgical trials to help assist the clinician in determining the best form of treatment for most patients with osteomyelitis. Achievable bone concentrations of various antibacterials is a much discussed issue, but it is not clear that it can be accurately determined or that it correlates with clinical outcome.

5.5 Adjunctive Therapy

In addition to antibacterials and surgery, several types of adjuvant treatments have been advocated for diabetic foot infections. These include antimicrobial wound dressings[13,113-115] and maggot (larval) debridement therapy.[116-120] Adjunctive measures aimed at improving wound healing include vacuum drainage system,[121-124] recombinant growth factors[125-131] and skin substitutes.[132-134] The role of these measures has not yet been adequately defined.

Two forms of therapy have been advocated for several years and have been the subject of recent meta-analyses. Recombinant human granulocyte colony-stimulating factors (G-CSF) has been shown to enhance neutrophil function *in vitro* in patients with diabetic foot infections.[135] G-CSF preparations have now been investigated in five randomised controlled trials involving patients with diabetic foot infections, as shown in table IX.[136-140] Evidence from a meta-analysis of these trials found that using G-CSF (in addition to antibacterial therapy) does not appear to accelerate the resolution of infection but is associated with a decreased rate of lower limb amputation and other surgical procedures.[141]

Hyperbaric oxygen (HBO) therapy is another commonly advocated adjunctive treatment. Many retrospective studies and case reports suggest that this high technology and expensive treatment can help salvage severely infected limbs, but only recently have there been some randomised controlled trials.[142-146] Preliminary evidence from a meta-analysis of four studies suggests that HBO significantly reduces major amputations. The number of patients enrolled was small; however, there were other problems with the trials.[147] Additional randomised controlled trials are necessary to validate the beneficial effects of this expensive treatment that is available only in limited areas.[148,149] Certainly, only properly administered systemic (as opposed to local) HBO therapy is likely to have any benefit.

None of the adjuvant therapies can substitute for well selected antimicrobial therapy and appropriate surgical interventions.

Table IX. Randomised, controlled trials of granulocyte colony-stimulating factor (G-CSF) injections as adjuvant therapy of diabetic foot infections[141]

Study (year)	No. of patients	Study drugs	Outcome	Results [% of patients]
Gough et al.[136] (1997)	20	G-CSF vs placebo	Amputation[a] Ulcer healing	0 vs 10 (NS) 20 vs 0 (NS)
de Lalla et al.[137] (2001)	20	G-CSF vs standard care	Amputation[a] Cure or stable ulcer at 6 months	15 vs 45 (NS) 81 vs 75 (NS)
Yonem et al.[138] (2001)	15	G-CSF vs standard care	Amputation[a]	13 vs 20 (NS)
Kastenbauer et al.[139] (2003)	20	G-CSF vs placebo	Ulcer healing	0 vs 10 (NS)
Viswanathan et al.[140] (2003)	20	G-CSF vs placebo	Resolution of infection Amputation[a] Hospitalisation[b]	90 vs 30 (NS) 0 vs 30 (NS) 7.4 vs 8.8 (p = 0.02)

a Of affected lower extremity.

b For lower extremity infection.

NS = not significant.

6. Conclusion

Infection is a serious complication of diabetic foot infections and is now the most common cause of lower limb amputation in the developed world. Foot infections can be classified clinically as mild, moderate or severe, and this classification largely determines the proper approach to therapy. Some mildly infected ulcers can be treated with topical antibacterials, and most mild to moderate infections can be treated with oral agents, usually in an outpatient setting. Severe infections usually require broad-spectrum intravenous therapy, at least initially, although newer agents with good bioavailability may change this practice.

Aerobic Gram-positive cocci are the most important pathogens in diabetic foot infections, and are often the sole agents in mild to moderate infections. The incidence of MRSA is on the rise, in the community and the healthcare setting, and the outcome of patients with infections due to resistant bacteria is generally not favourable. This needs to be taken into account when choosing antibacterial regimens. Usually, treatment is started with an empirical regimen, and then modified based on the results of culture and sensitivity tests from properly obtained specimens, as well as the patient's response to empirical therapy and surgical intervention.

Many agents have now been found to be effective in treating diabetic foot infections in randomised controlled trials, but no single regimen has been shown to be best. Various adjunctive therapies have been used in recent years and these may play a beneficial role in some patients. However, currently none can substitute for well selected antibacterial therapy and appropriate surgical intervention rendered by a multidisciplinary team of healthcare specialists.

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