

## Oral versus intravenous antibiotics for moderate infections



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Infections are common in diabetic foot wounds and, for the majority, the way infection should be treated is straightforward. However, there are some considerations that need to be taken into account, such as the presence of peripheral vascular disease, that may make judging the severity of an infection more difficult. In addition, the challenges in diagnosing osteomyelitis can make it difficult to choose the best antimicrobial agent. Finally, the most widely used guidelines do not consider admissions avoidance, a situation that clinicians in busy foot clinics meet on a regular basis. This article discusses each of these issues and what impact they have on managing these patients.

Clinicians working in a specialist diabetic foot clinic will be aware that infections are common in foot ulcers. Previous work has shown that 58% of patients presenting to a foot clinic have evidence of infection; the proportion is greater than 80% in patients that require hospitalisation for treatment of a foot ulcer (Prompers et al, 2007). Having an infection significantly increases the risk of subsequent lower extremity amputation (Lavery et al, 2006). It is, therefore, reasonable to suggest that adequately treating infection in an outpatient at an early stage may help prevent progression of the infection and also any deterioration.

To help clinicians diagnose and treat such infections, there are well-received guidelines (Lipsky et al, 2012), as well as systematic reviews (National Institute for Health and Care Excellence (NICE), 2011; Peters et al, 2012). There are also many classifications to help determine the severity of infection that may be used as guides to determine the intensity of intervention needed (Wagner, 1981; Lavery et al, 1996; Lipsky et al, 2012). These classifications have been validated to show they provide a degree of prognostic accuracy (Wukich et al, 2013; Pickwell et al, 2015).

However, there are concerns about these classification systems that may make them difficult to use in a busy diabetic foot clinic. For example, the validation of the Infectious Diseases Society of America (IDSA) classification of infection by Wukich et al (2013) was only designed for those patients who had already been admitted with severe infections, and did not consider its use in the mild or moderate infections seen in outpatients. Other potential issues will also be considered in this article.

### Definition of infection and the risk of misjudging severity

The diagnosis of infection — considering clinical, biochemical and microbiological parameters — is not straightforward. The IDSA states that infection should be defined clinically by the presence of two or more features of ‘inflammation or purulence’ (Lipsky et al, 2012). The classical features of inflammation are erythema, warmth, pain, tenderness and induration. In most cases, the presence of infection is obvious. But what of those individuals who have severe peripheral vascular disease or hyperglycaemia? Erythema, warmth and induration require sufficient blood supply, something that may not be present in those with severe peripheral arterial disease (Hill et al, 1999). In addition, a person with longstanding diabetes may also develop peripheral neuropathy, making the foot insensate.

Finally, there is the concept of ‘glucose toxicity’. In optimal conditions, neutrophils produce a number of effects that are necessary to fight bacterial infection. These include cellular adherence, chemotaxis (attracting the right kind of ‘bacteria-killing’ cells to the site of infection), phagocytosis, and the production of a variety of factors that directly kill the bacteria, such as respiratory bursts (Davidson et al, 1984; MacRury et al, 1989; Alexiewicz et al, 1995; McManus et al, 2001). Neutrophil function is compromised when confronted with high glucose concentrations (Mowat and Baum, 1971; Bagdade et al, 1974; Joshi et al, 1999), although function appears to recover when glucose concentrations improve (Bagdade et al, 1978). Other blood tests, such as C-reactive protein, or erythrocyte

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sedimentation rate, may be used, but are very non-specific.

Therefore, in someone with severe peripheral vascular disease, peripheral neuropathy and hyperglycaemia (a description that fits a large number of clinic patients), it may not be difficult to miss, or misjudge the potential severity of, an infection.

### Potential risks of hospital admission

A hospital stay means a patient is more likely to receive intravenous antibiotics, swift attendance of the specialist foot team, good nursing care, and relatively swift access to radiology modalities. But being an inpatient with diabetes is also associated with harm. Data from the National Diabetes Inpatient Audit (NaDIA) show that such harm is relatively frequent (Health and Social Care Information Centre, 2014). Harm may be specific to diabetes, e.g. acquired heel ulcers, hypo- or hyperglycaemia, and missed drug doses, and other concerns related to hospitalisation in general, such as a risk of deep vein thrombosis and hospital-acquired infection. In addition, there is a direct and indirect impact on the patient and society, for example, from loss of income.

### Problems in assessing bone involvement

Osteomyelitis is a common complication of diabetic foot ulcers, with reports suggesting

there is bone involvement in 15% of mild foot infections, and in over 50% of more serious infections (Lipsky et al, 2006; Lavery et al, 2009; Richard et al, 2011). Osteomyelitis is often a precursor to lower extremity amputation (Carmona et al, 2005; Lavery et al, 2006). Therefore, an accurate diagnosis of osteomyelitis underlying diabetic foot ulcers is essential to optimise outcomes. As mentioned above, the classic features of infection may be absent in the diabetic foot. Unless there is a classic 'sausage toe' (Rajbhandari et al, 2000), the radiographic appearances of osteomyelitis often lag days, or even weeks, behind the clinical presentation.

Attempts to histologically characterise the early development of osteomyelitis have involved surgical bone biopsies (Esmonde-White et al, 2013). While this method produces accurate compositional analysis results, it is too invasive for most specialist foot units. Furthermore, there are conflicting data on the use of bone biopsy and the subsequent microbiological analysis of the sample of bone removed. One group of authors reported that in a series of patients with diabetes undergoing surgery for foot infections, 29.1% of those with positive cultures of bone specimens had no histopathological findings consistent with a diagnosis of osteomyelitis. However, they also reported that 25% of patients with positive histology had negative cultures (Weiner et al, 2013).

Controversy therefore remains over the best way to diagnose osteomyelitis (Berendt et al, 2008). There is currently no single test that can confirm or rule out acute osteomyelitis. A combination of a careful history and examination, accompanied by a high index of suspicion, followed by the key laboratory and radiological investigations are key in making the diagnosis (Lipsky, 2008; Fleischer et al, 2009; Teh et al, 2009; Dinh et al, 2013).

However, the issue becomes more complicated, because, in addition to a lack of consensus on definition, there has also been no consensus on how to diagnose osteomyelitis. The 'probe-to-bone' test is widely used because it suggests that, if a sterile probe can touch the bone through a wound, microbes must also be able to get into the bone. First described by Grayson et al (1995), the use of this test to diagnose osteomyelitis continues to be a subject of debate. This is because, in the initial paper, the diagnosis of osteomyelitis was made by a pathologist looking at histological changes in the bone samples, rather than

**Table 1. The classifications of severity of infection of the Infectious Disease Society of America (IDSA) and International Working Group of the Diabetic Foot (IWGDF).**

Clinical description	IDSA	IWGDF
No symptoms or signs of infection	Uninfected	1
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be >0.5 cm to ≤2 cm around the ulcer	Mild	2
Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g. abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)	Moderate	3
Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following: <ul style="list-style-type: none"> <li>• Temperature &gt;38°C or &lt;36°C</li> <li>• Heart rate &gt;90 beats/min</li> <li>• Respiratory rate &gt;20 breaths/min or PaCO<sub>2</sub> &lt;32 mmHg</li> <li>• White blood cell count &gt;12,000 or &lt;4,000 cells/μl or ≥10% immature (band) forms</li> </ul>	Severe	4

SIRS: Systemic inflammatory response syndrome  
Source: Lipsky, 2012.

undertaking a microbiological diagnosis. These findings are often disputed, with low levels of intra- and inter-observer variability being reported, leading to a lack of concordance between histopathologists (Shone et al, 2004; García Morales et al, 2011; Meyr et al, 2011; Cecilia-Matilla et al, 2013).

Even bone biopsy may be misleading. Research demonstrates that up to 25% of people who have a bone biopsy showing no initial microbiological growth go onto develop osteomyelitis within 2 years (Senneville et al, 2012). Bony biopsy is an invasive procedure, carried out by a radiologist or an orthopaedic surgeon (Senneville et al, 2008), which adds to the cost of care and the risk of complications.

In a study by respected authors in the field (Lavery et al, 2007), the diagnosis of osteomyelitis was made by a microbiologist. However, microbiological testing of bone samples may yield either false-positive results, because of contamination by bacteria from skin flora, or false-negative results because of prior antibiotic therapy, low levels of pathogenic organisms, problems arising during the sampling-to-culture process or when the biopsy misses the osteomyelitic area (Zuluaga et al, 2006).

Research to assess the usefulness of new technologies is under way using genomic studies to analyse the 'microbiome' (the genetic analysis of the organisms), either at the time of infection or how the microbiological burden changes over time. It is hoped that, in time, these technologies will become cheaply available to enable clinicians to individualise treatments.

## Admissions avoidance

The IDSA and the International Working Group for the Diabetic Foot (IWGDF) use different classifications to define the severity of infection [Table 1]. The IDSA also provides detailed suggestions for antibiotic choices at each stage of severity (Lipsky et al, 2012). However, there is one issue that the comprehensive IDSA practice guideline (Lipsky et al, 2012) does not consider: admissions avoidance. The guideline relies mainly on the provision of either oral antibiotics for those with 'mild' or 'moderate' infections (PEDIS grade 2 or 3), or intravenous antibiotics for those with severe infections (PEDIS grade 4).

In most circumstances, those requiring intravenous antibiotics would require hospital admission due to an inability to

administer intravenous antibiotics to an outpatient. Many patients fall in between the 'moderate' and 'severe' categories: those for whom oral antibiotics would be too little and those for whom intravenous antibiotics would be too much. There has been previous research to show that people in this 'severe-borderline admission' category can be treated with alternative methods of antibiotic administration in primary care, e.g. once-daily intramuscular antibiotics given by a community nurse (Gooday et al, 2013). These data showed that the need for admission was halved in patients who, prior to the development of this protocol, would have been admitted to hospital for intravenous therapy. In addition, the length of hospital stay was significantly reduced in the remaining patients who still required admission. Together, this led to a significant cost saving (Gooday et al, 2013).

The team from King's College Hospital in London, UK, have recommended the continued use of intravenous antibiotics administered through a peripherally inserted central cannula (PICC) line in outpatients (Bates et al, 2013). These data (presented in abstract form only) suggest that the use of a PICC line can also prevent hospital admission in 30% of cases with over half of the ulcers, but this approach also has limitations (Alejandro et al, 2013). A systematic review and meta-analysis of PICC line use in a general population of more than 29,000 patients concluded that deep vein thrombosis was more common when central venous lines were used (Chopra et al, 2013). There were several limitations in the studies from King's College Hospital, which mean that more prospective research is needed using larger samples from a diabetic foot clinic. However, there is an argument to be made for the consideration of alternatives to the current position advocated by the IDSA and IWGDF.

The decision about how to treat an infected wound also depends on the demands of the local healthcare system. For those who work in a system that gets paid for treating people — where the more aggressive the treatment, the more the institution or individual gets paid — admitting people with foot ulcers makes sense. This approach does not take into account inconvenience to the patient or the economic impact on society. However, for those who work in a healthcare environment where society in general gets penalised (usually through taxation) for providing more expensive treatments, the incentive to keep people out of hospital is greater than the drive to admit.

But that is a political argument that many may disagree with.

### Ask what the patient wants

It is important to ask whether the patient wants to be admitted. The days of paternalistic medicine are long gone, and over the last few years the 'patient choice' agenda, together with an emphasis on 'patient-centred care', has turned the focus to getting patients better as quickly as possible while reducing the risk of further morbidity (e.g. amputation), using a management plan that has been discussed and agreed with the patient (Committee on Quality of Health Care in America, 2001). This means providing care that is respectful of, and responsive to, an individual patient's preferences, needs and values; and ensuring that a patient's values guide all clinical decisions.

### Conclusions

The diagnosis of a foot infection in someone with diabetes and assessing wound severity can both be more complicated than they may at first appear. It is likely that most of those running foot clinics have at some time misjudged a wound and its treatment. This in itself may not always be a bad thing, as long as clinicians learn from their mistakes.

There are many factors that influence the clinical decisions that need to be made before choosing the right treatment for a moderate foot infection for someone with diabetes. Current guidelines, while excellent in their depth, are often too didactic. They represent the 'science'. They do not consider the breadth of factors that busy clinicians in the foot clinic have to discuss, in particular those factors most important to the patient. In addition, the wider implications for the taxpayer and the impact on society in general which arise from a hospital admission are overlooked, such as the potential for loss of income for the patient, loss of productivity for society and the large costs of admission. The decision to admit depends on a great variety of factors: on the clinician, the organisation, the available resources, and the patient. Weighing all of these is what may be considered the 'art' of medicine.

As with much else in diabetic foot care, much more research needs to be undertaken to clarify the questions raised here.



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