Diabetic foot infections: Learnings and ambitions

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Professor Lipsky will be speaking on antibiotics at *The Diabetic Foot Journal* conference (London, 8 October 2007). To book your place please go to:

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Twenty years ago I presented the results of my first investigation into diabetic foot infections, which was published 3 years later (Lipsky et al, 1990). The study was stimulated by seeing many people with diabetes with a foot infection and discovering that there was almost no literature on the topic to guide our treatment. While there were a few studies of the bacteriology of diabetic foot infections, only two previously published randomised trials of antibiotic therapy specifically included individuals with these infections. Most authorities recommended that people with a diabetic foot infection be hospitalised and treated with broad-spectrum parenteral antibiotic therapy. Our study made several novel observations: first, most infections were caused by aerobic Gram-positive cocci, but a substantial minority were polymicrobial, including Gram-negative and obligately anaerobic pathogens; Second, curettage and aspiration specimens yielded more isolates (especially anaerobes) than swabs; Third, people with what we would now call mild-to-moderate infections could be safely and effectively treated as outpatients with either of two oral antibiotic regimens, given for only 2 weeks.

What have we learned about diabetic foot infections since then? Hundreds of papers on the topic have been published in the past two decades; while we have learned much, we are left with many unanswered questions.

Epidemiology

In the past year, two prospective studies have finally addressed the issue of how frequently people with diabetes develop foot infections (4.5% per year) and how often diabetic foot ulcers are clinically infected (55%; Lavery et al, 2006; Prompers et al, 2007). The most important risk factors for a foot infection are incurring a foot wound and having peripheral vascular disease. It is important to learn more about which individuals are at risk for foot infections and what factors (especially modifiable ones) increase risk.

Microbiology

Numerous studies have documented that the microbiology of diabetic foot infections in countries around the world is similar to what we reported (Citron et al, 2007), with the major exception of the rising incidence of infections caused by methicillin-resistant *Staphylococcus aureus* (Dang et al, 2003; Tentolouris et al, 2006) and a higher frequency of *Pseudomonas* and Enterobacteriaceae infections in hot climates (Abdulrazak et al, 2005; Shankar et al, 2005; Yoga et al, 2006). Antibiotic resistance has also increased for some other diabetic foot isolates, such as: extended-spectrum ß-lactamase resistance among Gram-negative pathogens (Carvalho et al 2004; Gadepalli et al, 2006; Kandemir et al, 2007). In addition, reports have now documented the increased prevalence of fungal foot infections in people with diabetes (Chanussot and Arenas, 2007; Eckhard et al, 2007). Several investigations have demonstrated that deep tissue specimens provide more accurate microbiological results than superficial swabs, especially for bone infections (Pellizzer et al, 2001; Kessler et al, 2006; Nelson et al, 2006; Senneville et al, 2006). The main remaining microbiological questions are how to distinguish pathogens from colonisers on cultures and whether or not new technologies can help to accelerated the identification of etiologic agents and, perhaps, their virulence factors or antibiotic susceptibilities (Lipsky, 2007a).

Classification

Many studies have proposed classification schemes for diabetic foot complications. Virtually all consider the size and depth of the wound and most also include the presence or absence of limb ischaemia or wound infection. Only two classifications, however, are specifically designed to assess the severity of a diabetic foot infection. These, developed by the International Working Group on the Diabetic Foot (IWGDF; Lipsky, 2004) and the Infectious Diseases Society of America (IDSA; Lipsky et al, 2004a) rate infections from absent (no purulence or inflammation) to mild (limited in area and superficial in depth), moderate (deeper or more extensive) or severe (accompanied by systemic signs or symptoms of infection or substantial

metabolic perturbations). The IDSA classification has been validated to predict clinical outcome (Lavery et al, 2007a; Lipsky et al, 2007a). I would welcome studies demonstrating whether or not these classifications can guide clinicians on such important matters as when to hospitalise an individual, perform surgery, or initiate broad-spectrum parenteral therapy.

Treatment

In the past two decades many antibiotic regimens have been studied in people with a diabetic foot infection, including some large randomised controlled trials. Virtually all have shown that one regimen is not inferior to another, but in so doing the studies have demonstrated the efficacy of a number of agents, three of which are now FDA approved specifically for diabetic foot infection (linezolid, ertapenem, and piperacillin/tazobactam; Lipsky et al, 2004b; Lipsky et al, 2005). These studies have also confirmed that, in properly selected people, oral antibiotic therapy is safe and effective and that most mild-to-moderate infections require no more than 1–2 weeks of antibiotic therapy, while more extensive or severe infections may benefit from a week or two longer. Treatment is usually empiric to start. There are clinical clues that can help in selecting an appropriate regimen (Lipsky, 2007b). Definitive therapy should be based on the clinical response to empiric therapy and presumably on the results of culture and sensitivity testing, but this has yet to be proven. It would also be helpful to properly investigate whether or not clinically uninfected diabetic foot wounds benefit from antimicrobial therapy.

Osteomyelitis

Diagnosing and treating bone infection remains the most contentious aspect of dealing with a diabetic foot infection. Many studies have explored the diagnostic value of various imaging tests, virtually all concluding that MRI is the most accurate (Ertugrul et al, 2006; Tan and Teh, 2006; Kapoor et al, 2007). Recently, two studies have better defined the role of the 'probe to bone' test for diagnosing osteomyelitis (Shone et al, 2006; Lavery et al, 2007b). Clearly, all diagnostic studies are most useful in those with an intermediate (as opposed to high or low) pre-test probability of osteomyelitis. A recent progress report by the IWGDF proposed a diagnostic scheme for diabetic foot osteomyelitis, but this will require validation (2007). The same report provided a summary of the results of a systematic review of studies of treatment of diabetic foot osteomyelitis, from which the committee could draw few useful conclusions. A key issue, which is as yet unsettled, is the role of surgical resection in this condition. Most agree that if infected bone is not removed antibiotic therapy must be prolonged.

In conclusion, two decades have brought many papers and some useful data to inform our care for diabetic foot infections. But it is surprising how little has changed and how much more we need to learn to provide our patients with optimal outcomes. There are many opportunities for interested investigators to 'probe for answers' to some of these important clinical questions. ■

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