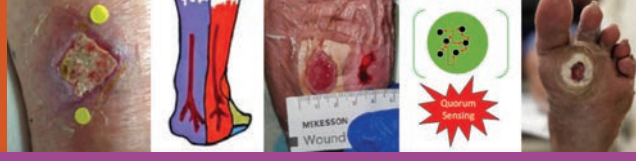

Finding the Right Path

Consider these factors for antimicrobial therapy in diabetic foot infections.

BY JOHN M. GIURINI DPM, DRISHTI DHAWAN, DPM, AND MICHELLE KUNG, DPM

Introduction

As the seventh leading cause of death in the United States, diabetes continues to be of growing concern. It is predicted that the number of individuals affected by diabetes will increase by 50% between 2011 and 2030.[1] While diabetes poses a major public health problem, its burden is further complicated by its associated pathologies, namely peripheral neuropathy and peripheral arterial disease. These co-morbidities will lead to foot ulcerations in 19-34% of diabetic patients. Foot infections will develop in 50-60% of these patients and 20% of these will develop osteomyelitis (OM).[2] This leads to an overall poor prognosis as 20% of diabetic foot infections (DFI) result in amputation and 17% result in mortality within one year.[2]

Despite continued efforts in combating the disease, there is no one universally accepted protocol for the management of DFIs. While the 2012 Infectious Disease Society of America's (IDSA) guidelines for the treatment of diabetic foot infections recommend oral antibiotics for mild to moderate soft tissue infections and parenteral antibiotics for moderate to severe soft tissue/bone or joint infections, recent studies have found no difference in treatment failure rates between these two therapeutic routes. Furthermore, while there is consensus that proximal bone margins provide great value in determining residual infection and guiding antibiotic treatment, there remains no standardized method to procure a clean margin.

This article will discuss those factors to consider in choosing between oral versus extended IV antibiotics for the treatment of DFIs. Furthermore, we will present the current IDSA guidelines and our current specimen collection and antibiotic protocols. Lastly, we will propose some topics of discussion regarding the management of DFIs.

Diagnosis of Osteomyelitis

The diagnostic accuracy of OM is crucial for proper management. Diagnosis is based on a combination of clinical, radiographic, and laboratory findings. Clinically, patients may present with local and/or systemic signs of infection. Clinical symptoms of chronic OM, however, are nonspecific. These include chronic pain, malaise, exposed bone, and non-healing wounds with persistent sinus tracts/drainage. The probe-to-bone (PTB) test was described by Grayson, et al. in 1995 as having an 89% positive predictive value (PPV) for diagnosing OM.[3] In 2006, Lavery, et al. reported the PTB test to have a PPV of 57% and a negative predictive value of 98%, suggesting that negative test results can aid in the exclusion of OM.[4] This test is now routinely used by clinicians for the assessment of OM.

OM is typically not detected on plain radiography in the first two weeks of the disease course because at least 50% of the bone must be resorbed to be visualized on plain films. After this point, localized osteopenia and cortical irregularities may begin to present.[5] MRI provides better clinical information in the early stages of OM and is especially useful in determining the localization (soft tissue vs. bone) and extent of infection. MRI has been reported to have a sensitivity of 78-90% and a specificity of 60-90% for detecting OM.[6]

In instances where MRI is contraindicated, nuclear imaging can provide comparable results. PET imaging provides the highest sensitivity and specificity (96% and 91%, respectively) for diagnosing OM; however, it is not readily available and is not considered a cost-effective modality.[6]

Despite continued efforts in combating the disease, there is no one universally accepted protocol for the management of DFIs.

Elevated inflammatory markers such as WBC, ESR, and CRP, may be utilized but are non-specific for diagnosing OM. Blood cultures may be obtained when OM is suspected; however, they are positive only in cases of hematogenous spread. The gold standard for diagnosis of OM diagnosis remains a bone biopsy for histopathologic assessment. This can be achieved percutaneously or open. Percutaneous needle biopsy has been demonstrated to have a sensitivity and specificity of 87% and 93%, re-

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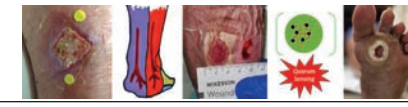

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spectively, for the diagnosis of OM.[7]

It also offers the advantage of avoiding contact with deep wounds, therefore reducing the risk of specimen contamination. Nonetheless, the open surgical approach is still favored because it ensures adequate acquisition of a specimen. The specimen should be sent for both aerobic and anaerobic bacterial culture with the addition of fungal and mycobacterial cultures when clinically indicated.[7] In clinically stable patients, empiric IV antimicrobial treatment should be delayed until the bone biopsy is performed. It should be noted that although it is the gold standard for diagnosis of OM, bone biopsy procedures are not standardized and may be performed utilizing a variety of instruments such as rongeurs, trephine, Jamshidi needle, drill bit, osteotome, curette, etc.

In a study by Meyr, et al., the inter-observer agreement between different diagnostic tests for OM (i.e. PTB, plain films, MRI, bone biopsy with histopathologic and microbiologic analysis) was assessed and compared.[8] The authors found inter-observer agreement to be low overall among the five modalities. The highest level of agreement in the diagnosis of OM was noted between plain films and MRI, while a poor level of agreement was noted between PTB and bone biopsy results.[8]

These results support the combined use of clinical, radiographic, and histopathologic modalities in the diagnosis of OM as the tests by themselves may have high levels of intrinsic unreliability.

Proximal Bone Margins

Proximal bone margins have been regarded by many sources to have strong prognostic value. Kowalski, et al. found that proximal margins positive for residual OM correlate with higher rates of treatment failure in a group of 111 patients.[9] In another retrospective review of 66 cases by Johnson, et al., patients with positive proximal bone margins required further surgical intervention and exhibited higher mortality rates.[10] Simpson, et al. performed a prospective study comparing the recurrence of OM in patients who did not undergo resection of the proximal margin versus those who had a clearance margin of > 5 mm and < 5 mm.[11] They found that patients with a clearance margin of > 5 mm had lower rates of OM recurrence while patients with no clearance margins had the highest rates of recurrence (0% and 100%, respectively).[11]

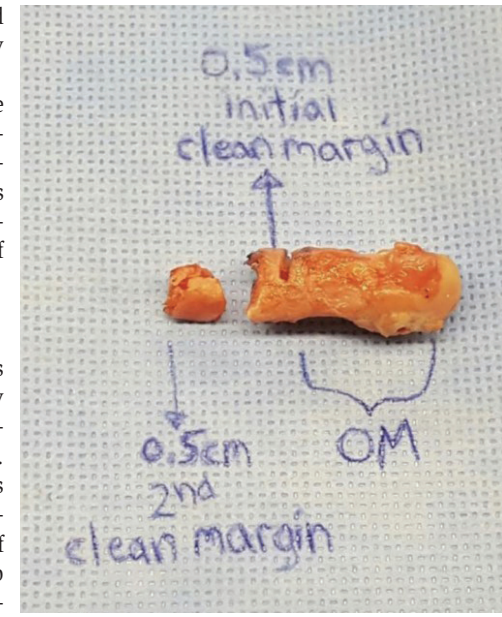

Figure 1: Recommended method of obtaining clean margins as proposed by Bernstein et al. (Reprinted with permission from Bernstein B, Stouder M, Bronfenbrenner E, Chen S, Anderson D. Correlating pre-operative MRI measurements of metatarsal osteomyelitis with surgical clean margins reveals the need for a one-centimeter resection margin. *J Foot Ankle Res.* 2017.10.(40)

The authors maintain that removing all infected bone and soft tissue was the most critical factor in resolving infection. Lastly, in a 12-month retrospective study by Weng, et al., authors found that negative proximal

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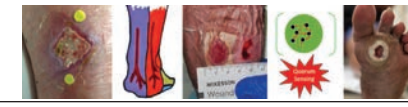
Oral Antibiotics and Their Coverage and Bioavailability (%)

Staphylococcus	*Enterococcus*	*Streptococcus*	*Enterobacteriaceae*	*Pseudomonas*
MRSA	Linezolid (100%)	**GAS/GBS**	Ciprofloxacin (70%)	Ciprofloxacin (70%)
Linezolid (100%)	Ampicillin (50%)	Penicillin VK (50%)	Levofloxacin (99%)	Levofloxacin (99%)
TMP/SMX (90%-100%)	Nitrofurantoin (80%)	Amoxicillin (85%)	Moxifloxacin (90%)	Delafloxacin (60%)
Clindamycin (90%)	Amox/Clav (85%)	Cephalexin (90%)	Amox/Clav (85%)	
Doxycycline (95%)		Levofloxacin (99%)	Amoxicillin (85%)	
		Clindamycin (90%)	Cefixime (40%-50%)	
MSSA		Linezolida (100%)	Cefuroxime (70%)	
Cephalexin (90%)			Cephalexin (90%)	
Dicloxacillin (50%-75%)		**S Pneumoniae**	TMP/SMX (90%-100%)	
		Amoxicillin (85%)		
		Doxycycline (95%)		
		Azithromycin (30%-50%)		
		Levofloxacin (99%)		

Figure 2: Coverage and bio-availability of different oral antibiotics (Reprinted with permission from Floris L. The Role of Oral Antibiotics in Bacterial Bloodstream Infections. *US Pharm.* 2021. 46(4):17-20)



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bone margins were associated with reduced re-operation rates, shorter antibiotic duration, lower hospital admission rates, and lower mortality rates.[12]

In spite of the above evidence, there remains a lack of standardization on how to obtain the proximal margins. Bernstein et al. performed a prospective study where they obtained 21 metatarsals positive for OM by MRI[13] and measured the distance of OM based on imaging. A partial osteotomy was performed at this marked location followed by an osteotomy 0.5cm more proximal. This was labeled the "first proximal margin". A second osteotomy was created 0.5cm more proximal and was labeled the "second proximal margin" (Figure 1).

They found that the rate of positive proximal margin between 0.5cm versus 1.0cm was 50% and 9% respectively. It is their recommendation that the proximal margin be 1.0cm from the measurement of OM on the MRI. However, this may need to be modified in instances where the proximal margin may violate a new joint space, disrupt important tendinous attachments, result in an overly short metatarsal, or compromise a more distal amputation.

FIGURE 3

Antibiotic Guidelines for Managing Diabetic Soft Tissue and Osseous Infections

Site of Infection, by Severity or Extent	Route of Administration	Setting	Duration of Therapy
Soft-tissue only			
Mild	Topical or oral	Outpatient	1-2 wk; may extend up to 4 wk if slow to resolve
Moderate	Oral (or initial parenteral)	Outpatient/ inpatient	1-3 wk
Severe	Initial parenteral, switch to oral when possible	Inpatient, then outpatient	2-4 wk
Bone or joint			
No residual infected tissue (eg, postamputation)	Parenteral or oral	. . .	2-5 d
Residual infected soft tissue (but not bone)	Parenteral or oral	. . .	1-3 wk
Residual infected (but viable) bone	Initial parenteral, then consider oral switch	. . .	4-6 wk
No surgery, or residual dead bone postoperatively	Initial parenteral, then consider oral switch	. . .	≥3 mo

Figure 3: Antibiotic guidelines for managing diabetic soft tissue and osseous infections (Reprinted with permission from Lipsky BA, Berendt AR, Cornea PB, Pile JC, Peters EJG, Armstrong DG…Senneville E. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* 2012. 54(12):e132-173.)

In spite of the above evidence, there remains a lack of standardization on how to obtain the proximal margins.

Oral vs. IV Antibiotics

Empiric antibiotic therapy is often initiated in patients with moderate to severe soft tissue and bone/joint infections based on the results of initial wound cultures. These are most accurate when deep tissue cultures are obtained versus superficial swab cultures. The final choice of antibiotics should be based on the results of deep tissue specimens or bone biopsy. Once source control of the infection has been attained, there is a debate in the literature on the next best course of treatment. Conversion to oral antibiotics carries the advantages of reduced costs, absence of catheter-associated complications such as infection and thrombosis, ease of administration, and early discharge from the hospital.[14]

On the other hand, oral antibiotics may not be appropriate when there is known resistance to oral agents or where there is poor enteral absorption.[12] Additionally, achieving adequate serum levels may be difficult in patients with known peripheral vascular disease or gastrointestinal issues (e.g., astroparesis).

Intravenous antibiotics address many of these concerns. They improve patient compliance and offer immediate drug delivery. They are also not affected by gastric absorption and result in higher serum levels. Therefore, the decision to transition from IV to oral antibiotics should take into consideration the severity of the infection, microorganisms involved, bioavailability of the oral agent, and patient adherence/compliance. Figure 2 summarizes antibiotic coverage and bio-availability in the oral form.

Current IDSA Guidelines

The 2012 IDSA guidelines advocate for timely conversion from IV

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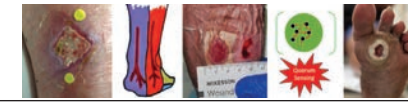

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to oral antibiotics once patients are hemodynamically stable and their infection is controlled. Patients with mild to moderate skin and soft tissue infections (SSTIs) can be switched to oral antibiotic therapy for 1-2 weeks or 1-3 weeks respectively.[15] For more severe SSTIs, it is recommended that IV antibiotics be instituted initially with consideration of switching to the oral route when the patient is systemically stable and when culture results are available. The recommended duration of antibiotic therapy for severe SSTIs should be 1-4 weeks in total.[15]

IDSA guidelines also recommend obtaining intra-operative bone specimens at the resected margin for definitive diagnosis of residual OM and for antibiotic therapy guidance. It is recommended that bone margins negative for OM be treated for a short duration of oral or IV antibiotics for 2-5 days.[15] Patients with positive bone margins require at least 4 weeks of antibiotic treatment and possibly longer (> 3 months) if the bone is considered to be non-viable.[15] Osseous infections that have not been surgically resected are recommended for > 3 months of oral or IV antibiotics.[15] Figure 3 summarizes the current IDSA antibiotic regimen guidelines for SSTIs and osseous infections.

Antibiotic Protocol at Home Institution

Antibiotic guidelines at our home institution are similar to those proposed by IDSA. Patients with mild superficial infections are typically managed in the outpatient setting with oral antibiotics. Diabetic patients with OM can be treated conservatively with 12 weeks of antibiotics or surgically with radical resection. If proximal margins return negative for residual infection, a short 2-5 day duration of antibiotic therapy is adequate. If there is a persistent infection or necrotic bone, prolonged antibiotic therapy of > 4 weeks is recommended (Figure 4). Bone and tissue specimens should be sent to microbiology and pathology to evaluate for residual infection and to direct antibiotic course (Figure 5).

Factors to Consider

It is a widespread belief that IV antibiotics are inherently superior and more effective than their oral

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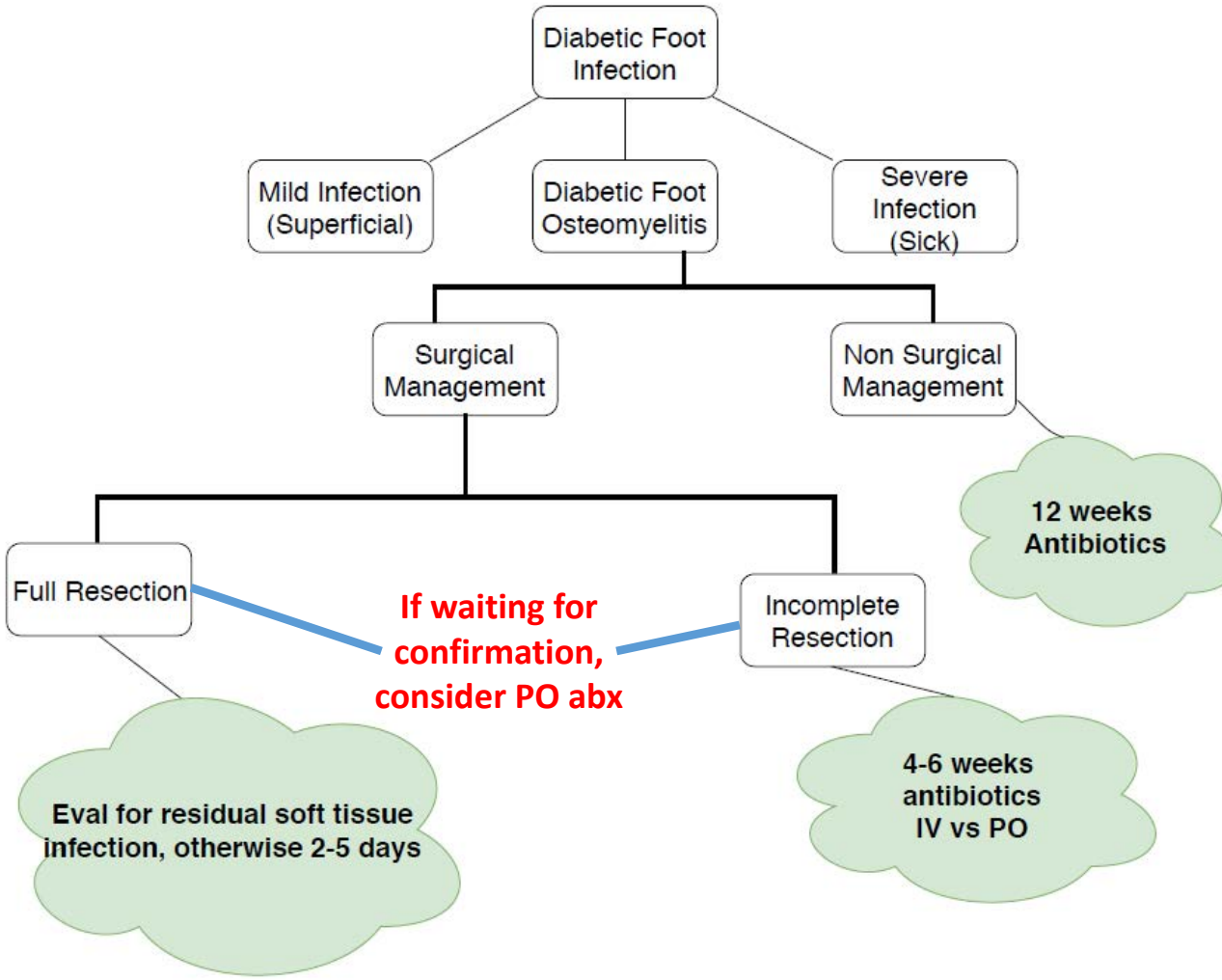

Figure 4: Author's current algorithm for antibiotic therapy of osteomyelitis

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counterparts. However, recent studies such as that by Li, et al. provide strong evidence against this notion. Their renowned Oral Versus Intravenous Antibiotics for Bone and Joint Infections (OVIVA) trial was the first prospective study that assessed the non-inferiority of oral vs. IV antibiotic therapy. The trial consisted of 1054 patients who developed an infection after undergoing orthopedic surgery.[12] Patients were randomly assigned to one of two treatment groups: either oral antibiotics for 6 weeks or IV antibiotics for 6 weeks.

Their results found that oral antibiotic therapy was non-inferior to IV antibiotic therapy with a reported treatment failure rate of 13.2% and 14.6%, respectively.[12] Results also demonstrated no significant difference between serious adverse events between the two treatment groups, although catheter complications were more common in the IV group.[12] It should be noted, however, that the study only focused on orthopedic surgical infections and therefore may not adequately reflect outcomes for non-surgical infections. Furthermore, antibiotic selection varied between patients and relied solely on the expertise of infectious disease specialists. Lastly, rifampin was frequently utilized as a therapeutic agent in the study. However, it is not commonly used in OM.

Despite these limitations, the OVIVA trial still provides valuable insight as it rebuked the long-held belief that IV antibiotics were superior to oral antibiotics.

In another study conducted by Gill, et al., a retrospective analysis was performed to determine differences in treatment failure rates between oral and IV antibiotics for the management of residual OM following amputation in the diabetic population. The study included a total of 65 patients, all of whom had bone margins that were positive for OM after amputation and had received at least 4 weeks of antibiotic therapy after surgery. After one year of follow-up, it was found that there was no statistical difference in treatment failure rates in patients receiving oral vs. IV antibiotics (47% and 53%, respectively).[6]

The results also indicated that wounds with a more severe IDSA classification at initial presentation were more likely to be in the treatment failure group.[16] No other patient demographics, including age, sex, BMI, PVD, HbA1c, tobacco use, or homelessness, were found to have a significant correlation to treatment outcomes. These findings further suggest that there should be less apprehension in utilizing oral antibiotic therapy for the management of residual OM as both routes of therapy have been shown to be equally effective.

Other Considerations

Pathological assessment of bone specimens is possible only after the decalcification process (which requires 2-7 days) is complete. Considering this, one important question becomes: Is it more beneficial to send patients home with antibiotics during this waiting time vs. having them stay in the hospital? Prolonged length of stay may

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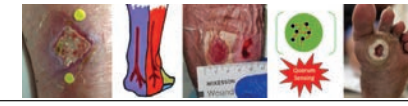

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not only be unnecessary, but it may also increase patient susceptibility to other hospital-associated illnesses. In this instance, it may be reasonable to refer to intraoperative findings. Healthy bone presents with a strong cortex and bleeding surface, while infected bone presents with a soft cortex, gray discoloration, necrosis, and non-viable tissue.

With adequate resection and viable bone, highly bio-available oral agents, such as fluoroquinolones, trimethoprim/sulfamethoxazole, linezolid, metronidazole, and doxycycline, may be utilized to great effect. Even in instances of positive bone margin, oral antibiotic therapy may still be effective in managing residual OM.

Another notable concern regarding the route of antibiotic therapy for DFIs is the presence and severity of peripheral artery disease (PAD). In the presence of PAD, the overall quality and extent of perfusion are compromised, which results in insufficient antibiotic delivery to the area of infection. In such instances, IV antibiotics may be preferred over oral antibiotics to maximize systemic concentrations. However, as mentioned before, certain oral antibiotics have been found to achieve the same level of bio-availability as their IV counterparts (Figure 1).

Pathological assessment of bone specimens is possible only after the decalcification process is complete which requires 2-7 days.

This raises the question of whether these two routes of administration demonstrate similar systemic concentrations despite the presence of PAD. This is a reasonable concern given that the overall prevalence of PAD in diabetic patients over 40 years old has been estimated to be 20%.[17]

Conclusion

The global health burden of diabetes is significant and increasing worldwide. The diabetic patient population poses a greater risk for multisystem complications, including DFIs. When poorly managed, DFIs elevate the odds of limb loss and mortality. Optimal management requires the appropriate selection of antibiotics. The appropriate route of antibiotic administration for DFIs remains a subject of ongoing discussion within the literature. While IV antibiotics remain the current gold standard, transition to oral antibiotics is encouraged when source control is achieved and patients demonstrate clinical stability.

Oral antibiotics have been demonstrated to be as practical and efficacious as IV antibiotics in the

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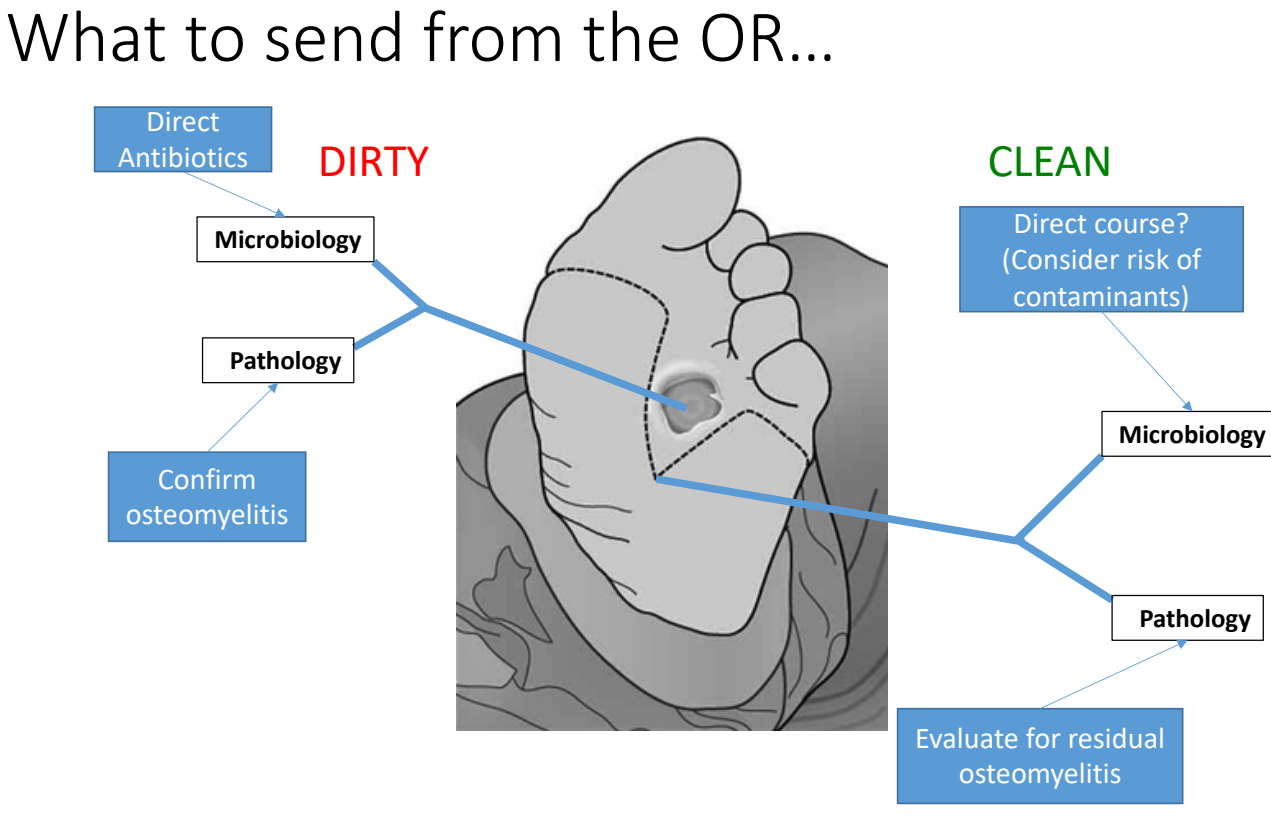
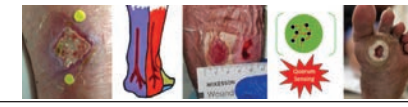


Figure 5: Recommended method of obtaining dirty and clean margins for microbiological and pathological analysis



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treatment of DFIs in several clinical studies. The choice of antibiotic delivery should involve a multidisciplinary approach and take into consideration the cost-effectiveness of oral vs. IV antibiotics as well as patient risk factors.

Current IDSA guidelines advocate for the use of intra-operative specimens of both infected and proximal clean bone margins for guidance of antibiotic therapy. Research emphasizes the predictive value of obtaining proximal margin pathology as patients with negative proximal bone margins display lower rates of re-operation and mortality. Bone margin histopathology warrants consideration in the context of stewardship interventions aimed at optimizing antimicrobial delivery and mitigating risks. Additional research is indicated to propose a standardized approach to proximal margin resection, considering both patient anatomy and post-operative functionality.

Current IDSA guidelines advocate for the use of intra-operative specimens of both infected and proximal clean bone margins for guidance of antibiotic therapy.

The authors of this paper adhere to IDSA guidelines for antimicrobial delivery in patients with SSTis and OM, with the guidance of proximal bone margins for tailored therapy. The question remains, however, on the utility of in-hospital admission post-operatively. If surgeons suspect a high clinical probability of infection source control post-operatively, it may be reasonable to discharge patients with broad-spectrum oral antibiotics until histopathology reports are finalized.

Future studies are needed to assess the association between proximal margin resection, antimicrobial delivery, and length of hospital stay with the prognosis of patients with DFI. Efforts to optimize the treatment course of DFI are imperative to reducing the healthcare burden of diabetes and improving patient quality of life. **PM**

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