Polymicrobial Wound Infections: To Treat or Not to Treat Every Detected Microbe?

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Abstract

With advanced molecular detection techniques, more microbes are being detected in wounds than may have been identified by traditional culture. This raises the question, does every positive result need to be treated? Are some positive bacteria or fungi only colonizing but not infecting the wound? Will treating all detected organisms speed healing and improve outcomes? Here we explore the current research on polymicrobial infections, including biofilms and fungal co-infection, and provide some guidance on when and how to treat.

Introduction

The diversity and number of microorganisms detected in wounds is greater when analyzed using molecular methods compared to traditional microbial culture (Frank DN, 2009). Often multiple potentially infective microbes are isolated from a wound specimen by PCR or other advanced molecular detection (AMD) technique. This may be confusing to the clinician who may be used to a smaller range of organisms detected in wounds. Some of the most common organisms usually recovered from acute and chronic wounds include S. aureus, streptococcal sp, and pseudomonas. New research on chronic infections is finding more anaerobes, gram negatives and fungal species than previously identified through culture alone. The question is, are they all involved in the infection and should treatment cover all identified organisms?

Wound colonization vs infection: Does the wound need treatment at all?

The surface of a wound is not sterile and quickly becomes colonized with numerous commensal, environmental, and potentially pathogenic microorganisms. All skin and wounds become colonized, but not all wounds become infected or require antimicrobial treatment. This is a clinical distinction; a positive microbiological laboratory result of any kind does not answer the question of whether a wound is infected.

Wound colonization

The skin is covered by indigenous microbes such as staphylococci, corynebacteria, propionibacteria and yeasts. Any break in the skin, such as dermatitis, ulcers, traumatic or surgical wounds, also becomes colonized. Colonization is defined as the presence of replicating microorganisms adherent to the wound in the absence of injury to the host (D.T. Williams, 2004). The abundance and diversity of microbes will depend on the type of wound, the wound depth, the location on the body, the level of tissue perfusion and the host immune response. Wound colonization or the detection of microorganisms in a wound does not alone necessitate antimicrobial treatment.

Wound infection

If virulence factors expressed by the microbes in a wound overcome the host immune system, infection occurs. The subsequent microbial invasion and dissemination into viable tissue creates local and systemic inflammatory responses. Characteristic local responses which indicate infection are a purulent discharge or painful spreading erythema which indicate cellulitis around a wound. Systemic responses may include fever, changes in white blood cell count, increased CRP and other inflammatory markers.

Chronic wounds and biofilms

Determining infection from colonization is of particular difficulty in diabetic foot ulcers (DFU). DFUs are complicated by impaired host immune response and poor blood flow due to micro-vascular disease. Normal indicators of infection may not be evident due to the muted host response. When diabetic foot infection (DFI) is present, it occurs in multi-layered microbial communities surrounded by a self-produced protective extracellular biofilm (James GA, 2008). Biofilms contribute to chronicity and delayed healing of most, if not all, chronic wounds (James GA, 2008). By creating a community of multiple bacterial and fungal species, microbes can reap benefits such as passive resistance, metabolic cooperation and DNA sharing (J. Jneid, 2017). Biofilm communities may be resistant to single antimicrobial agents.

Detection and Treatment of Anaerobes and Fungi in Chronic Wounds

Anaerobes are found when detection methods favor their recovery, and are more commonly involved in both acute and chronic wound infections than previously thought (P. G. Bowler, 2001). In a study with optimized anaerobic conditions, a wide range of anaerobes was cultured from DFIs (M. Claros, 2013). Dowd et al introduced the concept of the functionally equivalent pathogroup (FEP), in which multiple organisms inhabit a wound, structurally oriented in layers with anaerobes in the deeper, hypoxic parts of wound (Dowd SE W. R., 2008).
Using molecular methods (16s ribosomal RNA sequencing), Choi et al demonstrated that obligate anaerobes not only co-exist with more commonly identified pathogenic species, they could also predominate the microbiota of chronic wounds (Choi Y, 2018). Hussain et al also found anaerobes commonly in chronic wounds using next generation sequencing (Hussain, 2016).

Amoxicillin-clavulanate is a good empiric antibiotic treatment choice for uncomplicated skin infection in which anaerobes are suspected (Eron LJ, 2003). Off-label use of topical metronidazole was reported to result in a reduction or eradication of wound odor, decrease in wound drainage, improvement in wound appearance, decrease in surrounding cellulitis, halting of tissue necrosis, and decrease in pain (Paul JC, 2008).

Detection and Treatment of Fungal Co-infection in Chronic Wounds

Fungal communities in chronic wounds are predictive of healing time and associated with poor outcomes (Kalan L, 2016). The most prevalent fungal biofilm-forming human pathogen is Candida albicans (Melphine M. Harriott, 2011). Using molecular diagnostics, Dowd et al surveyed 915 clinical specimens taken from chronic wounds. Their study revealed that 23% were positive for fungal species and the most abundant were of the genus Candida. Quantification of bacteria versus fungi in these chronic wounds demonstrated that fungi contributed to >50% of the microbial burden in the majority of the wounds (Dowd SE D. H., 2011).

Laboratory diagnosis of infection by Advanced Molecular Detection

Advanced molecular detection AMD has benefits compared to traditional culture. The turnaround time is significantly shorter, hours to days vs. days to weeks for culture, and antimicrobial resistance can be detected at the same time. A limitation as well as a benefit of AMD is that it will only detect the organisms you test for. There is less detection of commensal bacteria and fungi such as Propionobacteria, Dermabacter, Corynebacterium, and Malasezzia because they are usually not tested for by molecular techniques. AMD will detect more fastidious anaerobes, and gram negatives than culture (D.D. Rhoads, 2012). In addition there will be more detection of symbiotic groups of microbes or FEPs (Dowd SE W. R., 2008). The increased number of pathogenic species identified by AMD may be related to the limitations of traditional culture, which favors the recovery of non-fastidious organisms and a dominant culture, and may represent a more accurate snapshot of the polymicrobial nature of the infection.

Recommendations

For testing by AMD, only select wounds which appear clinically infected and require antimicrobial treatment. Antibiotic therapy is required for most clinically infected wounds, but not for uninfected ulcers. Test for likely infectious agents and most common antibiotic resistant genes. Do not test for microbes for which no treatment is indicated. Use clinical judgment to decide whether or not to treat organism which could be commensal or pathogenic such as S. epidermidis. Treat all pathogenic organisms detected by AMD. If multiple bacterial species are detected, it may be possible to cover all with one broad spectrum antibiotic. Antibiotic and antifungal coverage may include systemic (IV or oral) or topical therapies. Consider topical treatments for anaerobes (such as off-label topical Metronidazole, especially in malodorous wounds) when systemic antibiotics may be contraindicated. Candida or other fungal species present may warrant treatment with antifungals and topical therapies are available.

Optimal treatment of diabetic foot problems requires a multidisciplinary approach, including wound debridement, pressure off-loading, glycemic control, sometimes surgical interventions and other adjunctive measures. Assess and treat perfusion issues.

Conclusion

Chronic wounds are host to biofilm-based communities of bacterial and sometimes fungal co-infectors. PCR for identification of wound infection is new and the more detailed results are potentially confusing. Benefits include identifying more pathogenic microbes and much faster turnaround time than culture. Expanding antimicrobial coverage to include detected fungi, gram negatives, and anaerobes can improve treatment outcomes.

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