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EDITORIAL

Use of cultures in cellulitis: when, how, and why?

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Correct management of patients with cellulitis poses both diagnostic and therapeutic challenges. Unless a wound is present, obtaining a specimen for culture to determine the causative organism may be difficult. Thus, initial therapy of cellulitis is usually empirical and based on clinical presentation, epidemiological clues, and statistical probabilities. In most cases, initial antimicrobial therapy targets the two most common etiologic agents – beta-hemolytic streptococci and *Staphylococcus aureus* [1]. Resistant organisms may occasionally be present, however, and unless they are identified, the prescribed antimicrobial therapy may be inadequate. An incorrect choice of initial treatment of cellulitis may delay discharge from the hospital and potentially increase morbidity and mortality.

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What type of culture to obtain?

To treat cellulitis most effectively, the clinician should attempt to isolate the causative pathogen. For open wounds, tissue specimens (obtained by biopsy or curettage) grow pathogens in 20–40% of cases and are usually preferable to swabs [2]. When there is no open wound, the clinician should consider obtaining material for culture by one of two other methods. A punch biopsy of the skin may yield a positive culture in 20–30% of cases [3, 4]. Needle aspiration of the erythematous border of cellulitis has been reported to yield a positive culture in as few as 2% to as many as 40% of cases [5, 6]. Higher culture positivity rates may be obtained by aspirating with a large-bore needle (≤18 gauge) and first drawing ~1 ml of air into the barrel of the syringe to later help expel small amounts of tissue fluid [2, 7]. In immunocompetent individuals, blood cultures are generally positive in only about 2% of cases [8], but they may be positive in up to 60% of cases with infections such as necrotizing fasciitis [9, 10]. Serological tests show evidence of group A streptococci in 80% of cases of uncomplicated cellulitis [11]. So, when should a clinician obtain a culture or serological tests in a patient with cellulitis, and which types of tests are most appropriate?

Risk factors for bacteremia

Because blood cultures in patients with uncomplicated cellulitis may be of very low yield [8, 12, 13], many conclude that obtaining them is pointless [14, 15] unless the infection is "particularly severe" [6]. In fact, the rate of specimen contamination often equals that of true-positive blood cultures. These false-positive cultures add additional

costs by prolonging the length of hospitalization, provoking extra testing, and prompting unnecessary antimicrobial therapy [16, 17]. However, with increasing rates of antibiotic resistance among both gram-positive cocci (especially methicillin-resistant *S. aureus*) and gram-negative bacilli, clinicians must rely on culture-directed therapy wherever possible. These competing interests highlight the importance of studies such as that of Peralta et al. [18]. Their findings help predict which patients with cellulitis are likely to be bacteremic and thus to benefit from having blood cultures taken. By comparing patients with and without bacteremia, they showed that the following were independent risk factors for a positive blood culture: multiple comorbid factors, lack of pretreatment with antimicrobial agents, cellulitis involving the proximal limb, and duration of infection for less than 2 days. Unfortunately, they did not make clear how they decided which cultures were "true" positives.

Peralta et al. [18] also found that patients with bacteremia were significantly more likely to be febrile and to have extension of cellulitis and signs of severe infection. While the presence of severe cellulitis was predictive of positive blood cultures, the number of patients meeting this criterion in the study is unclear. Of note is that only a minority of patients with cellulitis had a blood culture in this retrospective study. Presumably, the decision to obtain blood cultures from patients was based on how sick they initially appeared. However, 68 of the 308 (22.1%) patients from whom blood cultures were obtained were not hospitalized. Although the frequency of bacteremia was significantly higher in patients who were hospitalized, six patients who were found to be bacteremic were treated as outpatients. Thus, the presence of bacteremia did not reliably identify patients ill enough to be hospitalized. Similarly, there was no difference in the lengths of hospitalization (almost 11 days) between those with and those without bacteremia.

Do blood cultures make a difference?

These data suggest that obtaining blood cultures in patients with severe cellulitis or any of the cited risk factors may be reasonable, but does it make a difference in outcomes? In the study by Peralta et al. [18], antimicrobial treatment in 28 of the 57 (49.1%) bacteremic patients was changed on the basis of blood culture results. In approximately half of these patients, a causative organism was identified that was inadequately covered by the antimicrobial agent initially chosen. In the other half, the culture results permitted clinicians to narrow the antimicrobial spectrum of treatment. Narrowing the breadth of coverage of the antimicrobial agents used may lessen the selection pressure on nosocomial flora, thereby generating less resistance.

While reducing antibiotic resistance is laudable, we wonder whether a change in antimicrobial therapy after 24–48 h improves patient outcomes. In a study of patients with ventilator-associated pneumonia, only an initially correct choice of antimicrobial agent, not a change based on culture results, lowered mortality. [19]. Presumably, the requisite 24–48 h delay in obtaining the results of a culture may negate any benefit of the adjustment of antimicrobial treatment. In the study of Peralta et al. [18], only two patients died (1 bacteremic, the other nonbacteremic), precluding an analysis of the mortality benefit of adjusting initial antimicrobial choices on the basis of blood culture results. The study also did not analyze whether *adjusting* antimicrobial therapy on the basis of culture results reduced the need for surgical debridement, or the duration of hospitalization. Unfortunately, there are few data that help clarify what role, if any, blood cultures play in managing patients with cellulitis.

Microbiological surprises

The study by Peralta et al. [18] also reported several unexpected results. The frequency of positive blood cultures in patients with cellulitis (18.5%) was unusually high. While we do not know the criteria clinicians used for obtaining blood cultures, it is likely that more severely ill patients underwent cultures more often. Only 308 of the 2,232 (13.8%) patients with limb cellulitis actually had blood cultures drawn. Also unanticipated was the high frequency of isolates of gram-negative bacilli (24.6%) and the low percentage that were *S. aureus* (2.1%). These results may reflect peculiarities of the study population or the types of infections in the study patients.

Finally, group A *Streptococcus* has long been considered the dominant cause of uncomplicated cellulitis, but in the study by Peralta et al. [18], there were 33 isolates of non-group-A streptococci (groups C, G, B, and viridans streptococci) compared to only 2 isolates of group A *Streptococcus*. By comparison, in one hospital in Hawaii in 2005, 26 of 46 (56.5%) patients with lower limb cellulitis who had bacteremia grew group A *Streptococcus*, while 16 grew group B and 4 grew group G (L.J.E., unpublished data). Discrepancies of this sort between hospitals are likely related to differences in the demographics and comorbidities of the patients and to the types of infections seen at the institutions. For example, non-group-A streptococcal cellulitis has been reported to be more frequent than that caused by group A streptococci when the cellulitis is associated with tinea pedis, venous insufficiency, or lymphatic compromise [20, 21].

The bottom line

As a general principle, when treating serious infections like bacteremia, it's best to "hit early and hit hard". Unfortunately, initial antimicrobial therapy must usually be selected empirically at the inception of treatment. In the future, new techniques, like DNA hybridization, may help in rapidly identifying the causative organisms of cellulitis and in reducing the delay in choosing appropriate antimicrobial therapy. In the meantime, it is important for clinicians caring for patients with cellulitis to understand some of the limitations of the diagnostic techniques presently employed, as well as how to utilize them most effectively.

This study by Peralta et al. [18] has provided useful information about the risk factors for bacteremia in patients with cellulitis. Nevertheless, important questions remain as to the value of blood cultures in this common disorder. While a positive blood culture result may be helpful in narrowing the breadth of antimicrobial coverage, it cannot provide guidance until 1–2 days after the initiation of therapy. The value of this information remains to be clarified. Current guidelines [6] suggest that obtaining blood cultures "is not fruitful for the typical case of cellulitis unless the illness is severe or the patient has one of several predisposing factors". Meanwhile, we advocate obtaining blood cultures (using optimal techniques to avoid specimen contamination) for most patients with cellulitis who have severe disease. In addition, on the basis of the work of Peralta et al. [18], we would suggest obtaining cultures for those not recently treated with antibiotics, with underlying comorbid factors, with an acute onset of disease, or with proximal limb involvement.

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