

Lack of Antibiotic Efficacy for Simple Abscesses: Have Matters Come to a Head?

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When the *New England Journal of Medicine* conducted an international survey of the management of a healthy 20-year-old basketball player with a 5-by-3-cm buttock abscess and a temperature of 37.7°C (98.6°F), most respondents indicated that they would prescribe antibiotics in addition to performing incision and drainage.¹ The belief that antibiotics are necessary for simple abscesses persists despite mounting scientific evidence, including the study by Duong et al² in this edition of *Annals*, that drainage is sufficient. Indeed, a good number of persons who never become patients successfully treat these infections with warm compresses at home. The authors conclude that antibiotics are not required and the accompanying editor's summary asserts, "Antibiotics should not be considered the standard of care in the treatment of skin abscesses." But how can so many be so wrong about so common a problem?

We should acknowledge that abscesses in patients who wind up in the ED are likely to be more severe than abscesses in those who do not. As opposed to other infections for which physicians are panned for prescribing antibacterials inappropriately, such as colds and acute bronchitis, at least there's no doubt that abscesses are bacterial infections. And abscesses, by their nature, have associated redness and induration. These are also characteristics of cellulitis, an infection that in the absence of a drainable lesion certainly requires antibiotics.

Recently, the number of patients treated in EDs for abscesses has dramatically increased,³ coincident with the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) as the most common cause of these infections in many parts of the United States.⁴ CA-MRSA has attained some notoriety. Aside from patients' suspicions of arachnid origin and dramatic tabloid infamy, it is suspected to be more contagious and invasive than methicillin-susceptible *S aureus*, which may surely influence physicians' antibiotic decisions.^{5,6}

Duong et al² should be congratulated on conducting the first adequately powered, randomized, placebo-controlled trial in the MRSA era of patients with a simple cutaneous abscess in which an antibiotic with in vitro activity against the predominant pathogen was used, trimethoprim-sulfamethoxazole. Previous

investigations of which I am aware consist of case series and case-control investigations, and small, randomized, placebo-controlled trials in the pre-MRSA era.⁷⁻¹³

Whereas the present investigation involved children, Rajendran et al¹⁴ recently conducted another randomized, placebo-controlled trial of simple abscess in 166 stable adults, which included some patients with comorbidities, and about 20% of lesions were greater than 5 cm in diameter.¹⁴ Their trial, unfortunately, used an antibiotic lacking MRSA activity (ie, cephalexin) and MRSA accounted for 76% of infections. Still, the study was informative in that all patients had incision and drainage, and cure rates in the placebo and treatment arms were high, 90.5% and 84.1%, respectively.

Duong et al² attempted to determine among children with an abscess that was drained whether treatment with placebo was associated with a cure rate 7% less than that of trimethoprim-sulfamethoxazole. They found that placebo was noninferior compared with trimethoprim-sulfamethoxazole, with 10-day cure rates of the primary lesion of 94.7% and 95.9%, respectively, and the upper bound of the 95% confidence interval of the difference of 6.8%. So can the general practice of antibiotic treatment for drained simple abscesses now be confidently abandoned in favor of a new standard of care, as suggested?

Studies of the effect of antibiotics on uncomplicated abscess outcomes pose unique challenges. Because cure rates of the primary lesion with drainage alone are in the neighborhood of 90%, any differences in cure rates associated with antibiotic treatment must be small. Large studies are required to detect these small differences in cure rates. CA-MRSA is generally susceptible to several inexpensive and relatively safe generic oral antibiotics, such as trimethoprim-sulfamethoxazole, tetracyclines, and clindamycin. So even small increases in cure rates, such as the somewhat arbitrarily chosen 7% difference in the present study, may lead to reduced costs of additional visits, procedures, antibiotics, and loss of work in a few that offset the costs of unnecessary antibiotics in the majority.

Of course, additional studies would be necessary to test various notions about antibiotic indications in otherwise stable patients, including fever, comorbidities, and large abscess size and area of surrounding cellulitis, provided clinicians would allow patients to be randomized to placebo. Presently, many would consider fever with an abscess in such patients a

justification not only for antibiotics but also hospital admission, even though we routinely treat febrile women with acute uncomplicated pyelonephritis as outpatients with oral antibiotics and we certainly can't incise and drain their kidneys.

Abscess management also has a surgical component, and Duong et al² appropriately attempted to standardize this management and ensure complete drainage, which would seem essential. The *New England Journal of Medicine* published a description of abscess incision and drainage, including an Internet-based video that was produced by a group of emergency physicians.¹⁵ However, despite the definitive nature of this review, in fact, the components of incision and drainage have generally not been subjected to scientific evaluation. For example, only recently has the need for abscess packing been examined.¹⁶

Because potential cure rate margins are so narrow, abscess studies are particularly prone to methodological limitations that threaten their internal validity. Case-control studies of abscess treatment, in which data are incomplete and inaccurate, outcome assessments are neither standardized nor done in an unblinded fashion, biases cannot be completely identified, are particularly unreliable and have found associations that have contributed to abscess mythology, such as that abscess size greater than 5 cm alone is an antibiotic indication.¹¹⁻¹³

Randomized, placebo-controlled trials address many of the limitations of case-control studies; however, they may also be affected by biases. In this trial, many eligible patients must have been missed because only 161 of 1,305 patients (12%) with a skin and soft tissue infection diagnosis were enrolled. The expected bias toward enrollment of lower-risk cases cannot be excluded. In this regard, by design patients with comorbidities and fever were excluded, and less than 10% of abscesses measured by ultrasonography were more than 5 cm. Remarkably, 92% of subjects had follow-up; however, follow-up could be obtained only by telephone for 40%. Because cure required resolution of all signs of infection, one wonders how well a parent could discern and describe signs of infection over the telephone. If the cure rate with placebo is almost 95%, you can be fairly certain a randomized, placebo-controlled trial won't find a trimethoprim-sulfamethoxazole cure rate to be 7% higher (ie, 102%).

Compliance is critical in placebo-controlled trials because only one group receives active treatment. In this study, compliance was defined as only 50% or more of the dispensed treatment, a threshold well below that of standard registration trials for new antimicrobials. Only two thirds of the patients met this minimal compliance threshold, which may have introduced a bias toward a lower cure rate in trimethoprim-sulfamethoxazole-treated patients.

These potential biases may have conspired to increase the likelihood of finding placebo noninferiority. On the other hand, one can understand the extra degree of caution imposed by conducting the first placebo-controlled study of abscesses involving young children, and even though primary lesion failure rates were low, the rates of new infected lesions more than 5 cm from the primary abscess were higher.

Finally, for abscess studies, there's the question of which outcomes should be examined. Appropriately, the study was designed to test for placebo noninferiority for the primary outcome of resolution of the primary lesion. It appears that patients who have been infected with CA-MRSA are prone to recurrent infections at the same site and different sites from that of original infection.¹⁷ This is an area for which little information exists, and therefore, it is to the authors' credit to have included the development of new lesions more than 5 cm from the primary abscess as a secondary outcome of interest. At 10 days, new lesions were more frequent in the placebo than antibiotic group, 26.4% and 12.9%, respectively.

The meaning of this observation is unclear because no previous studies have examined this outcome, to my knowledge, and the rate of new lesion development at 90 days, albeit limited by significant patient dropout and telephone follow-up, was similar between treatment groups. Rajendran et al¹⁴ did not report new lesion development in their population of adults with predominantly extremity abscesses. The high rate of new lesion development in the present study may be unique to this lower socioeconomic pediatric population in which the predominant abscess site was the "diaper region" and was perhaps also affected by fungal coinfection or enhanced acquisition risk associated with care environments.

It is assumed that colonization with MRSA precedes infection and that the rate of nasal colonization of infected patients is much higher than that of the general population.¹⁷⁻¹⁹ In the present study, it is possible that systemic antibiotic treatment prevented new lesions by reducing colonization. A placebo-controlled randomized trial of nasal mupirocin in soldiers found that although mupirocin was nearly 90% effective at eliminating CA-MRSA nasal colonization, it did not reduce the skin infection rate during a 16-week period.²⁰ However, the importance of nasal colonization in the pathogenesis of CA-MRSA skin infections is unclear. I am also unaware of published studies of secondary prophylaxis of patients who have experienced a previous MRSA skin and soft tissue infection. The finding of reduced frequency of new lesions while receiving treatment is intriguing and should be further pursued.

Some physicians are undoubtedly motivated to prescribe antibiotics for simple abscesses because of concern for serious septic complications. Because of their rarity, studies are unlikely to be of adequate size to address whether antibiotics can reduce this risk and provide sufficient benefit that outweighs other extraordinary but potentially catastrophic antibiotic risks, like Stevens-Johnson syndrome. Two large, randomized, placebo-controlled trials of simple abscesses, sponsored by the National Institutes of Health, are ongoing. Through these and other studies, it may be possible to get some better quantification of this consequence. It remains to be determined whether the risk of septic complications is similar to the small chance of developing bacterial pneumonia after a bout of acute bronchitis, an infection for which academic and public health standards and antibiotic prescribing practices have yet to become successfully aligned.

So should antibiotics for drained simple abscesses not be considered the standard of care? I believe this would be better stated as, “Antibiotics for drained simple abscesses are not required to meet the standard of care,” along the lines of the conclusion of Duong et al.² In other words, the standard of care allows the use and nonuse of antibiotics. The study by Duong et al² moves the ball and further supports the nonuse of antibiotics by demonstrating in healthy afebrile children with a small simple abscess that drainage alone is sufficient to achieve a cure rate of about 95% for the primary lesion. The study, however, does not provide convincing evidence that antibiotics are nonefficacious, and it opens a new door in terms of the possibility that antibiotics reduce new lesion development. It remains to be seen through additional studies of a fuller range of patients and abscess severity whether the cost and risk of antibiotics for drained simple abscesses are outweighed by the benefits derived from an increase in primary lesion cure rates, reduced frequency of new lesions, and improvement in other outcomes of interest.

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