

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Pollara, G; Marks, M; (2016) Trimethoprim-Sulfamethoxazole for Uncomplicated Skin Abscess. The New England journal of medicine, 375 (3). p. 285. ISSN 0028-4793 DOI: <https://doi.org/10.1056/NEJMc1605392SA3>

Downloaded from: <http://researchonline.lshtm.ac.uk/2697236/>

DOI: <https://doi.org/10.1056/NEJMc1605392#SA3>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Copyright the publishers

<https://researchonline.lshtm.ac.uk>

latter considered to be a “true” treatment failure. Our main hypothesis was that the four treatments would have similar efficacy, and indeed the differences between the PCR-adjusted cure rates were within the prespecified equivalence margin of 5 percentage points. Genotyping was carried out according to standard methods,¹ whose limitations, particularly where transmission is intense, were mentioned in the Discussion section of our article. Adekunle et al. state that the recrudescence rate equates to resistance. However, it is well known that this is not true, because observed therapeutic failure may be due to factors other than parasitologic resistance (e.g., malabsorption and rapid or abnormal metabolism),² and this may be particularly true for pregnant women.³ We have also stated that there are major differences in the duration of the post-

treatment prophylaxis between treatments, and this is shown by the PCR-unadjusted cure rates.

Umberto D'Alessandro, M.D., Ph.D.

Medical Research Council Unit
Fajara, Gambia
udalessandro@mrc.gm

for the PREGACT Study Group

Since publication of his article, the author reports no further potential conflict of interest.

1. Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations: informal consultation organized by the Medicines for Malaria Venture and cosponsored by the World Health Organization. Geneva: World Health Organization, 2008:29-31.

2. Talisuna AO, Boland P, D'Alessandro U. History, dynamics, and public health importance of malaria parasite resistance. *Clin Microbiol Rev* 2004;17:235-54.

3. Ward SA, Sevene EJP, Hastings IM, Nosten F, McGready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. *Lancet Infect Dis* 2007;7:136-44.

DOI: 10.1056/NEJMc1604709

Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Abscess

TO THE EDITOR: Talan et al. (March 3 issue)¹ slightly misstate the findings of an earlier summary to which I contributed.² My fellow authors and I concluded that prior studies of antibiotics administered in patients with uncomplicated abscesses were underpowered because the authors of those studies could not rule out the 5 to 10% superiority of antibiotics suggested in our review. The current study was well designed to address this concern. Comment is also warranted regarding the trial guidance provided by the Food and Drug Administration (FDA) on an early end point that is required as the primary end point for registrational studies and was a secondary end point in the study by Talan et al. The FDA guidance indicates that patients are considered to have been treated successfully even if 80% of their infection remains unresolved after 3 days of therapy. Space limitations here preclude a thorough discussion of this objectionable end point.³ The trial by Talan et al. is at least the second randomized, controlled trial (RCT) that has shown that the early end point does not correlate well with test-of-cure success.⁴ Furthermore, the current trial adds to the data that show that an “end-of-therapy cure” end point is sensitive to the efficacy of the antibiotic for skin infections.⁵ In my

opinion, the early end point should be abandoned.

Brad Spellberg, M.D.

LAC+USC Medical Center
Los Angeles, CA
bspellberg@dhs.lacounty.gov

Dr. Spellberg reports receiving consulting fees from Adenium Biotech, Cempra, the Medicines Company, MedImmune, PTC Therapeutics, Tetrphase, AstraZeneca, and Merck, serving as a member of a data safety and monitoring board for Dipexium, and holding stock in Motif, BioAim, and Synthetic Biologics. No other potential conflict of interest relevant to this letter was reported.

1. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim–sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med* 2016;374:823-32.

2. Spellberg B, Boucher H, Bradley J, Das A, Talbot G. To treat or not to treat: adjunctive antibiotics for uncomplicated abscesses. *Ann Emerg Med* 2011;57:183-5.

3. Spellberg B. Acute bacterial skin and skin structure infection trials: the bad is the enemy of the good. *Clin Infect Dis* 2011;53:1308-9.

4. Spellberg B. End points in trials of treatments for skin infections. *JAMA* 2013;309:2091-2.

5. Spellberg B, Talbot GH, Boucher HW, et al. Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials. *Clin Infect Dis* 2009;49:383-91.

DOI: 10.1056/NEJMc1605392

TO THE EDITOR: Talan et al. reported higher per-protocol cure rates for abscesses treated with tri-

methoprim–sulfamethoxazole in addition to incision and drainage than for abscesses treated with incision and drainage alone (92.9% vs. 85.7%). However, the dimensions of the abscesses varied greatly, ranging from a few millimeters up to 16 cm in their largest measure, and the dimensions of associated erythema ranged from 1 to 49 cm. Stratifying the success rates for incision and drainage according to lesion size could help clinicians determine when antibiotics may not be useful. In addition, it would be interesting to know the location of the erythema with respect to the abscess (e.g., a patch of cellulitis extending entirely proximal to the abscess may be more likely to warrant antibiotic coverage than a patch that shows concentric extension). Guidelines from the Infectious Diseases Society of America note that “For simple abscesses or boils, incision and drainage alone is likely to be adequate, but additional data are needed to further define the role of antibiotics, if any, in this setting.”¹ It would be unfortunate if clinicians were to interpret the findings of Talan et al. as implying that antibiotics should now be routinely prescribed.

Steven Leiner, N.P.

Mission Neighborhood Health Center
San Francisco, CA
steven.leiner@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52(3):e18-55.

DOI: 10.1056/NEJMc1605392

TO THE EDITOR: The study by Talan et al. supports the use of antibiotics as an adjunctive treatment for uncomplicated skin abscesses, but this recommendation runs contrary to current efforts to reduce antibiotic use in the face of the rising threat of antimicrobial resistance.^{1,2} We note that up to a quarter of the swabs processed in the study showed either no growth or coagulase-negative staphylococcal growth. Did the authors find a difference in response rate stratified according to these culture results? In addition, since high adherence to antibiotic therapy was achieved in only 64.7% of study participants, was a subanalysis performed for those who received courses that were shorter than prescribed? When antibiotics are used as an adjunct to drainage,

the majority of bacteria are probably removed during surgery, and recent studies have shown that adequate source control can shorten the standard course of antibiotics without reducing clinical efficacy.³ Therefore, it is likely that when antibiotics are used as an adjunctive treatment, a shorter course would provide equivalent clinical benefit and would also reduce the risks of adverse effects, limit total antibiotic consumption, and decrease the selective pressure toward the development of resistance.

Gabriele Pollara, M.B., B.S., Ph.D.

University College London
London, United Kingdom
g.pollara@ucl.ac.uk

Michael Marks, M.B., B.S.

London School of Hygiene and Tropical Medicine
London, United Kingdom

No potential conflict of interest relevant to this letter was reported.

1. Antibiotic resistance threats in the United States, 2013. Atlanta: Centers for Disease Control and Prevention (<http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>).

2. European Antimicrobial Resistance Surveillance Network (EARS-Net) home page (<http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx>).

3. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015;372:1996-2005.

DOI: 10.1056/NEJMc1605392

THE AUTHORS REPLY: Spellberg emphasizes that in our study, unlike previous RCTs, we powered our superiority trial to detect a difference of 5 to 10 percentage points in primary outcome.¹ Our primary outcome was clinical cure of the abscess such that no new antibiotic was indicated according to standardized criteria. We evaluated cure between 7 and 14 days after treatment, a period of time that was consistent with FDA industry guidance until 2010. Subsequently, the FDA recommended the use of early response as the primary outcome — that is, there should be no increase in lesion size within 48 to 72 hours after treatment.² The FDA then revised this criterion, recommending a decrease in lesion size of 20%. We developed our protocol before this guidance was available. Considering the persistent and recurrent nature of some abscesses, we believed that differences in clinical care would probably be detected later. We also evaluated rates of new infections and additional surgical procedures.

As Spellberg indicates, whereas we found no significant between-group difference in early response rates, at 7 to 14 days after treatment, the participants who received treatment with trimethoprim–sulfamethoxazole had an abscess cure rate that was significantly higher (by 7 percentage points) than that of participants treated with placebo. At 6 to 8 weeks after treatment, these participants had significantly lower rates of new infections and drainage procedures. An alternative primary outcome, composite clinical cure, was lesion resolution without the addition of a new antibiotic or further drainage; the use of trimethoprim–sulfamethoxazole was also favored for this measure, by 12 percentage points. Our results elucidate the history of treated skin abscesses and challenge current FDA guidance, particularly the guidance for noninferiority registration trials.

Leiner has concerns about the use of antibiotics becoming routine, and Pollara and Marks raise stewardship questions. Our findings are appropriately applied only to patients similar to our trial participants (i.e., those who have an abscess measuring at least 2 cm in diameter and whose clinician intends outpatient treatment). In our study, most abscesses measured 2 to 3 cm in diameter (with a median erythema length of 7 cm), but some were much larger. We agree that subgroup analyses of conditions for which there is a theoretical association with a greater antibiotic effect, such as larger size, could be informative. We will see whether another multicenter RCT (ClinicalTrials.gov. number NCT00730028) in which antibiotics are compared with placebo supports our findings and hope to validate subgroup treatment associations to further inform

decision making. However, we have shown that trimethoprim–sulfamethoxazole (which typically has a cost of less than \$5 per course) leads to superior outcomes and is generally safe, which justifies discussion of this option with patients at the least. The risk of promotion of bacterial resistance is probably small with our regimen, since it involves the use of high-dose trimethoprim–sulfamethoxazole (320 mg and 1600 mg, respectively, twice daily) for 7 days in healthy, community-dwelling patients with an identifiable bacterial infection. We do not know whether a shorter regimen would be efficacious. The fact that some lesions were culture-negative or grew coagulase-negative staphylococci is probably due to the limitations of culture technique and not the presence of a nonbacterial cause of infection.

David A. Talan, M.D.

Olive View–UCLA Medical Center
Los Angeles, CA
dtalan@ucla.edu

William R. Mower, M.D., Ph.D.

Ronald Reagan–UCLA Medical Center
Los Angeles, CA

Anusha Krishnadasan, Ph.D.

Olive View–UCLA Medical Center
Los Angeles, CA

Since publication of their article, the authors report no further potential conflict of interest.

1. Spellberg B, Boucher H, Bradley J, Das A, Talbot G. To treat or not to treat: adjunctive antibiotics for uncomplicated abscesses. *Ann Emerg Med* 2011;57:183-5.

2. Guidance for industry: acute bacterial skin and skin structure infections: developing drugs for treatment. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 2013 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf>).

DOI: 10.1056/NEJMc1605392

Kidney Transplants from HLA-Incompatible Live Donors and Survival

TO THE EDITOR: Orandi et al. (March 10 issue)¹ report a survival benefit among patients who received a kidney transplant from an HLA-incompatible live donor, as compared with those who did not undergo transplantation and those who waited for a transplant from a deceased donor. However, three variables could distinguish patients who underwent desensiti-

zation before HLA-incompatible transplantation from those in the two other study groups, despite the efforts that were made to find the most effective matches.

First, patients receiving an HLA-incompatible live-donor transplant appeared to have higher survival rates as early as 0.02 months (0.6 days) after transplantation. Such immediate differ-