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Therapy for cellulitis

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In Reply Dr Goldman and colleagues highlight aspects of the phylogenetic analyses used to investigate HIV transmission events in the PARTNER study.[1] Previous studies have taken advantage of the now-discontinued Roche 454 deep-sequencing platform to obtain sequence reads of sufficient length to allow reliable phylogenetic analyses of minority viral species. We have been conducting work to optimize the Illumina deep-sequencing platform to perform an analysis of minority species in couples in our study. The reconstruction of HIV haplotypes presents notorious technical and interpretative challenges when applied to the short sequence reads currently obtained by Illumina. We are also using conventional limiting dilution techniques to obtain single and near full-length genomes using established methods.[2] These further analyses will be submitted for publication once completed.

Also, Goldman and colleagues propose that some *env* pairwise genetic distances in samples from the PARTNER study were similar to those of samples found to be linked in another study.[3] The proposed comparison of genetic distances is complicated by the fact that the sequences in the PARTNER study were considerably longer (2000 base pairs) than those reported in the other study (approximately 516 base pairs). Nonetheless, as shown in eTable 2 in the article Supplement, the median pairwise distance of *env* control sequences was at least 5 times lower than the median pairwise distance of the partners' *env* sequences. When considering sequences falling within the upper limit of the previously reported range,[3] the *env* phylogeny did not support linkage. Detailed analyses of the *env* sequences were made available to selected expert reviewers from *JAMA* and deemed robust. All phylogenies will be submitted for publication once study is completed.

Goldman and colleagues are correct that phylogenetic analyses of putative transmission events should include control sequences drawn from epidemiologically relevant settings and take into account time since seroconversion.[4] These factors were taken into account in the PARTNER study. The study design was such that patients were sampled never later than 6 to 8 months from seroconversion. Constraints dictated by the terms of the ethical approvals and need to protect patients' confidentiality mean that the phylogenetic investigations must not reveal the geographic origin of the specimens undergoing analysis. Although we recognize the importance of disclosing to public scrutiny our detailed analyses, the confidential data we hold in this respect are entirely consistent with the reported conclusions of the PARTNER study.

We are confident that clinicians are able to interpret the data and counsel patients appropriately, taking into account individual circumstances and tolerance of any risk, however small.

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Therapy for Cellulitis

To the Editor In their comprehensive review of cellulitis, Drs Raff and Kroshinsky discussed the limited role of culture in making the diagnosis.[1] Although a majority of cases of severe nonsuppurative cellulitis (even those presenting with sepsis) are due to β-hemolytic streptococcus,[2] antibiotic therapy in the inpatient setting often is unnecessarily broad, covering methicillin-resistant *Staphylococcus aureus* (MRSA) and various gram-negative bacteria. The lack

of culture data can lead to continued extended broad-spectrum antimicrobial use in these patients. The use of serological testing for β-hemolytic streptococcus is underused in this setting but can lead to diagnosis of an etiological agent in up to 40% of these patients, and subsequently, to the fairly rapid simplification of treatment regimen to a narrow-spectrum agent such as penicillin G.[2-4] Use of serologic testing thus has implications both for cost of antimicrobials and effective antimicrobial stewardship.

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To the Editor There are several statements in the review of cellulitis[1] that require discussion. First, the authors stated that MRSA should be considered as the causative organism of purulent infections in known high-risk populations, such as athletes, men who have sex with men, prisoners, etc. However, the concept that patients in the United States with community-associated MRSA have risk factors for acquiring an *S aureus* isolate with methicillin resistance is outdated, as most children and adults with community-associated MRSA infection lack any risk factors and have not had contact with persons with such exposures.[2] MRSA should not be excluded based on the lack of such risks.

Second, for nonpurulent cellulitis, both clindamycin and trimethoprim-sulfamethoxazole should be considered as alternative first-line treatments. In a clinical trial of 524 patients with purulent and nonpurulent cellulitis, these 2 agents had similar efficacy and tolerability in the subgroup of 280 patients with nonpurulent cellulitis.[3] Many of these patients had 1 or more signs of systematic inflammatory response syndrome; data on patients with severe infection treated with these agents are lacking, and thus, these agents may not be appropriate for this population. Although the efficacy of these agents compared with other recommended antibiotics for cellulitis are lacking, in patients with mild to moderate nonpurulent cellulitis, trimethoprim-sulfamethoxazole and clindamycin should be considered acceptable agents.

Third, for purulent cellulitis, it is unclear why clindamycin should be relegated to being an alternative antibiotic for patients with penicillin allergy. The efficacy, tolerance, and safety of clindamycin are undistinguishable to those of trimethoprim-sulfamethoxazole for purulent cellulitis.[3] Concerns over *Clostridium difficile* were cited by the authors, but *C difficile* is uncommon in patients with mild-to-moderate disease. In the trial cited above,[3] none of the 264 patients receiving clindamycin acquired *C difficile* as a complication (95% CI, 0.0%-1.4%). *C difficile* incidence is influenced by patient characteristics, such as recent hospitalization and advanced age,[4] and the majority of patients with skin infections are not hospitalized[5] and thus are at relatively low *C difficile* risk.

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To the Editor We would like Drs Raff and Kroshinsky[1] to comment on 3 additional issues in the management of cellulitis. First, we were surprised by their omission of the beneficial role of adjunctive corticosteroids, which in a randomized double-blind trial of erysipelas (the European synonym for cellulitis) accelerated clinical response, shortened hospital stay, and may have reduced recurrence rates.[2,3]

Second, we wonder if 24 hours is too soon to assess response to therapy, because the inflammation of many patients worsens temporarily, presumably from the release of streptococcal toxins into the dermis and subcutaneous tissue. Third, we would like the authors to comment on the utility of the common clinical practice of outlining the erythema with a pen, a practice we believe is fundamentally flawed because the border is often indistinct with skip areas and because erythema often extends beyond this border in patients who eventually respond to therapy.

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In Reply Dr Kak highlights the challenge of treating cellulitis given the lack of culture data and the possibility of using surrogate biomarkers instead. In patients with group A streptococcal infections, although the antistreptolysin O response usually appears within 1 week and peaks 3 to 6 weeks after the infection, the decline in titers is less well characterized,[1] and elevated titers can persist long after initial infection. Also, many patients have recurrent bouts of cellulitis, which may further complicate titer results. These difficulties in interpreting a single antistreptolysin O titer led the World Health Organization to recommend that 2 assays performed 10 to 14 days apart with a 4-fold rise in titer between samples be used to diagnose recent group A streptococcal infection,[2] which is impractical for patients with acute cellulitis.

Dr Miller notes the high prevalence of community-acquired MRSA in children and adults even without known risk factors. We agree that MRSA should not be excluded based on the absence of risk factors alone and advocate for use of hospital antibiograms,[3] which are compilations of aggregate antimicrobial susceptibility data, along with risk factors to influence empirical treatment.

Miller cites a trial of treatment of nonpurulent cellulitis with clindamycin or trimethoprim-sulfamethoxazole that demonstrated similar cure rates and adverse event rates. However, another trial found that the addition of antibiotics against community-associated MRSA did not improve outcomes in nonpurulent cellulitis,[4] suggesting that although antibiotics against community-associated MRSA can be effective, the organism does not cause nonpurulent cellulitis to a significant degree. Therefore empirical treatment with antibiotics against streptococci and methicillin-sensitive *S aureus* is reasonable. Community-associated MRSA is more commonly found with abscess or purulent cellulitis; however, purulent cellulitis accounts for less than 10% of all purulent skin infections.[6] The Infectious Diseases Society of America guidelines recommend treatment of most cases of cellulitis with antibiotics against streptococci, not MRSA.

In our review, clindamycin was listed as an alternative for purulent cellulitis in patients who were allergic to penicillin primarily due to the concern for clindamycin resistance in MRSA, which was found in nearly 27% of MRSA isolates in 43 US medical centers.[5] In contrast, only 2% of MRSA isolates were resistant to trimethoprim-sulfamethoxazole. Ultimately, the use of clindamycin alone for MRSA should be based on local resistance patterns.

Our review focused on nonerysipelas and we were unable to comment on several interesting aspects of cellulitis and its treatment, including the role of systemic steroids. Data support the adjunctive use of steroidal and nonsteroidal anti-inflammatory medications to address the strong inflammatory response to the organisms.[6] Timing, dosage, and duration of use of these agents require further exploration.

Some, but not all, patients respond within the first 24 hours of therapy, and as such we recommended a range for the window to reevaluate of 24 to 48 hours. We agree that by definition nonerysipelas cellulitis has indistinct margins. However, outlining the border of inflammation has value because there is a margin that can be identified between involved and uninvolved skin, and more clearly defining this can be helpful to monitor disease progression vs improvement with treatment, especially in situations of physician turnover or patient-led assessment. Skip areas do arise, and we outline these areas as well. In the age of electronic medical records, this practice may be replaced with the inclusion of serial, high-quality photographs.

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CORRECTION

Error in Abstract: In the Original Investigation entitled "Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial,"[1] published online October 5, 2016, and in the October 18, 2016, print issue of *JAMA*, there was an error in the wording of the second sentence of the abstract's Results section. The sentence should read as follows: "Sixty-six patients (22.8%) in the high-flow group vs 60 (19.1%) in the NIV group were reintubated (absolute difference, −3.7%; 95% CI, −9.1% to ∞); 78 patients (26.9%) in the high-flow group vs 125 (39.8%) in the NIV group experienced postextubation respiratory failure (risk difference, 12.9%; 95% CI, 6.6% to ∞)." This article was corrected online.