Reply to Eisen and Denholm, Dauchy et al, Fierer, and Nguyen and Jones

We appreciate the opportunity to reply to the letters of Fierer [1], Eisen and Denholm [2], Dauchy et al [3], and Nguyen and Jones [4]. We are also glad that the publication of the Infectious Diseases Society of America (IDSA) guidelines on prosthetic joint infection (PJI) has prompted additional discussion and hope that this eventually manifests as further research [5].

Fierer [1] raises the important question of rifampin dosing in PJI due to susceptible staphylococci treated with debridement and retention. We recommended the dose as outlined in the only randomized clinical trial to address this issue [6]. In that trial, a dose of 450 mg orally twice daily was used initially and decreased to 300 mg orally twice daily if toxicity occurred that did not require drug discontinuation. With oral rifampin doses of 300 mg or 450 mg, peak concentrations of 4.0 μg/mL or 6 μg/mL, respectively, are reached. The trough level of both doses is >0.25 μg/mL at 12 hours (half-life: 2.5 hours). The 600-mg dose results in a peak of 10 μg/mL, with a trough level at 24 hours of about 0.08 μg/mL (half-life: 3 hours) [7]. In view of the minimum inhibitory concentration (MIC) values of *Staphylococcus aureus* (0.008–0.15 μg/mL, MIC 90% [MIC_{90}]: 0.015 μg/mL) and *Staphylococcus epidermidis* (0.004–0.15 μg/mL, MIC_{90}: 0.015 μg/mL), all these regimens may be adequate [8]. The dose of 300–450 mg orally twice daily as well as 600 mg orally once daily was also recently recommended in

the IDSA guidelines for treatment of methicillin-resistant *S. aureus* [9].

Eisen and Denholm [2] raise the question of the A1-level ranking of the recommendation for the use of rifampin for staphylococcal PJI treated with debridement and retention. We followed the ranking system as recommended by IDSA and the Canadian Task Force on the Periodic Health Examination [5]. That document states there must be at least 1 randomized trial to give it a rank of A1. We regret the typographical error in table 1 of the PJI guidelines [5], which states >1 rather than ≥1. The panel believes there is ample evidence to support the use of rifampin for this indication as outlined in the PJI guidelines.

Dauchy et al [3] raise multiple questions. The panel did not recommend cutoffs for C-reactive protein and sedimentation rate, as different authors have used different cutoffs. We believe what is abnormal for these tests should be left to the clinician and the laboratory they are utilizing. We state in the footnote of table 2 [5] that the vancomycin dose should be based on serum levels and that optimal serum levels will depend on the pathogen. In addition, optimal serum levels are unknown if local antimicrobial therapy is used, such as when a spacer is used during 2-stage exchange or when vancomycin is used in conjunction with rifampin. We believe we clarified the issue of duration of therapy as best we could based on the available evidence and expert opinion. We clearly stated where there was and was not consensus regarding the use of chronic oral suppression given the data available for the various surgical procedures including debridement and retention and 1-stage exchange. We think more research is warranted to clarify this issue further and stated so in the "research gaps" section of the guidelines. It is true we did not make a definitive recommendation for 1-stage exchange for joint arthroplasties other than for hip arthroplasty. We agree with the authors that, since our literature review was completed, additional information has become available to suggest that 1-stage exchange for total knee arthroplasty infection may be useful [10, 11]. We look forward to additional information becoming available.

Last, Nguyen and Jones [4] raise the important question about the optimal dose of ceftriaxone for the treatment of oxacillin- and ceftriaxone-susceptible staphylococci based on the oxacillin MIC. We understand the argument for the 2- to 4-g dose of ceftriaxone every 12–24 hours as outlined by the authors in their letter but also recognized, based on the references cited by the authors as well as additional references included in the PJI guidelines [12, 13], that a dose of 1–2 g every 24 hours has been successfully used by investigators to treat PJI due to susceptible staphylococci. It was on the basis of this information that we recommended a dosing range of 1–2 g every 24 hours. We also clearly state that we could not reach consensus about the use of ceftriaxone in general for the treatment of methicillin-sensitive, ceftriaxone-susceptible staphylococci. Certainly where ceftriaxone has formed a significant component of intravenous antibiotic therapy, we are aware that it was commonly used to support outpatient parenteral antibiotic therapy (OPAT) and would mainly have been preceded by a period of high-dose anti-staphylococcal penicillin therapy in the immediate postoperative period and for some days prior to patient discharge into a OPAT program. Initiating treatment with ceftriaxone in the face of high bacterial burdens may pose different risks to doing so after a formal surgical debridement either as part of a debridement and implant retention (DAIR) procedure or at revision surgery, when the bacterial burden has been dramatically reduced. Furthermore, when used as part of a DAIR strategy, ceftriaxone was itself followed by extended therapy with, usually, a fluoroquinolone and rifampin. These complexities, and the fact that failures of treatment have been seen to occur both during therapy (of any kind) and when antibiotics are stopped, do make it hard to be certain whether the theoretical concerns from Nguyen and Jones, based as they are mainly on MIC data, give a genuine cause for concern in the real world.

We agree that clinicians should consider all information, including the guidelines and the information outlined by Nguyen and Jones [4] (as well as the fact that pharmacokinetic/pharmacodynamic predications may not reflect the dosage of a particular drug required in the setting of the use of combination therapy with rifampin or procedures where antibiotic-impregnated spacers are used), when they are making treatment decisions for individual patients.

As with many aspects of the diagnosis and treatment of PJI, there may be multiple ways to successfully manage these most difficult infections; additional research is needed to define optimal treatment strategies.

Note

Potential conflicts of interest. The following list is a reflection of what has been reported to IDSA. In order to provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. The reader of these guidelines should be mindful of this when the list of disclosures is reviewed.

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