et al. [5] that we analyzed for our review. In our article, we tried to select papers that included a considerable number of patients, allowing us to describe the characteristics of the disease. We found many interesting reports of single cases, such as the one by Dr. Meyers’s on intracranial tuberculosis [6]; however, space limits and relevance for the purpose of our article did not allow us to include all of them. At this point, we would like to mention that the first case of tuberculoma in a liver recipient that we were able to find was not reported Dr. Meyers but was reported by Grauhan et al. [7] in 1995.

In his letter, Dr. Meyers mentions 2 of his 5 patients in whom tuberculosis was diagnosed at the time of the surgical procedure or very soon after transplantation [3]. By referring to these 2 patients, the implication seems to be that active tuberculosis does not preclude the transplantation procedure. However, although we agree with Dr. Meyers, we feel that these 2 patients also represent the difficulties in diagnosis of this disease.

Regarding antituberculous drugs, Dr. Meyers agrees with us on the lack of evidence of the utility of a 2-drug regimen (ethambutol and a quinolone) as prophylaxis. However, he points out that he uses this treatment for patients who have developed hepatotoxicity [8]. We were not able to find any evidenced-based recommendation that supports this practice, and we do not usually treat patients in this way.

Of course, we apologize for not including any of the articles by Dr. Meyers’ group in our review, giving the important contributions he has made in this and other fields. We also apologize to the other authors of the remaining 1168 papers that were not mentioned in our review.

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The Clinical Relevance and Correct Designation of Isolates Nonsusceptible to Daptomycin

Sir—We read with interest the article by Mangili et al. [1] that described “daptomycin resistance” in Staphylococcus aureus bacteremia during prolonged therapy. The isolate labeled as “resistant” had a daptomycin MIC value of 2 μg/mL, which is only 1 dilution over the breakpoint of 1 μg/mL. Daptomycin MIC values of 2 μg/mL are found, although uncommonly, in the wild-type distribution of S. aureus [2]. Although the baseline isolate tested as “susceptible” by disk diffusion (and was unavailable for MIC testing), a shift of as little as 2 mm in zone size (or a 1-dilution tube increase in MIC value) could have caused the interpretation to change from susceptible to nonsusceptible.

Importantly, daptomycin does not have a “resistant” category, according to the US Food and Drug Administration or Clinical Laboratory Standards Institute criteria; the correct designation is “nonsusceptible”—which is the designation applied when there is insufficient clinical information on resistance, as is typically the case with new classes of antibiotics. The daptomycin S. aureus breakpoints were set at 1 μg/mL, which abuts the MIC90 value of 0.5 μg/mL in a unimodal distribution curve [2]. In contrast, vancomycin susceptibility is designated as intermediate at 8 and 16 μg/mL and resistant at ≥32 μg/mL, values that are placed well above the MIC90 value of 1 μg/mL, despite the fact that vancomycin is not as bactericidal as daptomycin and has a lower maximum serum concentration and a shorter half-life than daptomycin. The high breakpoint values for vancomycin, relative to its MIC90 value, undoubtedly have contributed to the dearth of resistance reports (n = 4). Vancomycin breakpoints were set in a different era. Additional data on the relationship between isolate MIC values and clinical outcomes, along with surveillance, pharmacokinetic, and pharmacodynamic data, can lead to the assignment of true intermediate and resistant breakpoints. Thus, it is a misnomer at this stage to designate a strain of S. aureus as “resistant” to daptomycin.

All antibiotics, under the right circumstances, can select for increasingly less susceptible bacteria. Selection for relatively more-resistant bacteria by daptomycin is difficult to achieve in the lab and is clinically rare. The only consistent method of selecting bacteria less susceptible to daptomycin in the lab is by serial passage under conditions of subinhibitory concentrations of antibiotic [3]. Under such circumstances, we have found that 4–8-fold increases in MIC values occur equally.
with vancomycin and daptomycin and require 25–30 serial passages. This is in sharp contrast to some other antibiotics, such as rifampin, which can select for high-level resistance by a single mutation at high frequency ($1 \times 10^{-7}$) after a single exposure above MIC levels, an unfortunate property of clinical significance [4].

During the ongoing pharmacovigilence of daptomycin, Cubist Pharmaceuticals has been informed of a handful of cases in which the MICs of S. aureus have increased to 1–2 μg/mL, most often in difficult-to-treat infections with undrained pus or retained material and/or with antibiotic underdosing [5, 6]. Several of these nonsusceptible organisms have been successfully treated in a mouse model of infection with doses of daptomycin equivalent in exposure to the human 4-mg/kg dose [7]. These data, together with future clinical outcome reports of S. aureus infections treated with daptomycin when MICs start in the nonsusceptible range, will allow determination of breakpoints for true resistance.

It would be incorrect to infer that daptomycin was closer to rifampin than to vancomycin in its selection of resistance behavior, which has been a mainstay of antistaphyloccocal therapy for several decades. Successful selection of S. aureus isolates that are nonsusceptible to daptomycin in the clinic appears to be relatively difficult to accomplish, requiring a combination of treatment events.

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Reply to Alder and Eisenstein

Sir—We appreciate the clarification of Alder and Eisenstein [1] with regard to the designation of isolates as “nonsusceptible” to daptomycin and the fact that the US Food and Drug Administration has not yet defined the breakpoint for daptomycin resistance. However, from a clinical perspective, most clinicians would regard an isolate that is nonsusceptible as “resistant,” and, in the face of clinical failure, that is how we classified our case. Additional clinical data will need to be collected to establish a breakpoint for defining resistance to daptomycin.

There is no way to know whether the original isolate was misclassified as susceptible, because we did not have the isolate to test ourselves; however, the outside laboratory used Kirby-Bauer methodology, and the zone size reported by that laboratory clearly placed the isolate within the susceptible range. In support of our use of the term “resistant,” we found that, in contrast to previous descriptions of the susceptibility of methicillin–resistant Staphylococcus aureus to daptomycin, our isolate not only showed a smaller Kirby-Bauer zone size and a rarely reported MIC value of 2 μg/mL but also demonstrated an unexpected bacteriostatic effect at 1, 2, and 4 μg/mL with the use of in vitro time-kill studies. Bactericidal activity was observed only at 8 μg/mL. This reduced in vitro activity is consistent with the persistence of bacteremia in our patient and the poor clinical outcome.

The reduction in susceptibility of our patient’s isolate occurred in a context similar to that described by other authors and referenced by Alder and Eisenstein [1]—that is, difficult-to-treat infections with undrained pus (i.e., an infected clot) and initial antibiotic underdosing after a prolonged course of the drug (28 days after the initiation of daptomycin). Despite a possible misclassification of the initial isolate, this case underscores the need for vigilance and surveillance of bactericidal activity and the potential failure of therapy in complex cases. This case report was primarily meant to alert the medical community of the potential for the emergence of isolates with reduced daptomycin susceptibility and the consequent clinical implications.

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