Editorial Response: A Silver Bullet for Colonization and Infection with Methicillin-Resistant *Staphylococcus aureus* Still Eludes Us

Within a relatively short period of time following the first uses of penicillin for the treatment of staphylococcal infection and streptomycin for the treatment of tuberculosis, the emergence of bacterial strains resistant to these antimicrobial agents was recognized. As we now know but did not then, the emergence of these two types of resistance represented two completely different phenomena. In the case of tuberculosis, resistance represented the selection of a small subpopulation with mutations in the ribosomal RNA genes that prevented the binding of streptomycin to the ribosome. Resistance of *Staphylococcus aureus* to penicillin resulted from the acquisition of a β-lactamase-encoding transposon, one that could subsequently be transferred to other members of the same species. One thing that was clear at the time, and remains clear today, is that the appearance of new resistance phenotypes in bacteria is closely linked to the clinical use of compounds against which resistance is expressed.

See article by Landman et al. on pages 1062–6.

The recognition that antimicrobial resistance is related to antimicrobial use led to the logical hypothesis that reducing antimicrobial use would reduce antimicrobial resistance. If this hypothesis is true, then simply altering antibiotic formularies may be effective at reducing resistance. Such strategies have intrinsic appeal, especially since the past 3 decades have witnessed the introduction of a variety of alternative antibiotics for the treatment of common infections and since the only other method for controlling the spread of resistant bacteria—strict adherence to cumbersome and expensive infection surveillance and control practices—is very difficult to institute and enforce in the modern hospital setting.

At least two important facts about antimicrobial-resistant bacteria raise doubts about antimicrobial-switching strategies. The first is that antimicrobial-resistance determinants rarely travel alone. Determinants conferring resistance to several different classes of antibiotics are often found together on the same plasmid or mobile element, in some cases lined up within resistance-gene collection devices, known as integrons [1]. The result of this condensation is that a single antimicrobial agent may select for resistance to many different classes of agents. The second important fact is that resistance determinants exist for virtually every known antibiotic. Over the years, many human pathogens have proved remarkably resourceful at scavenging these determinants from their natural producers. As such, there is real concern that switching from one antimicrobial agent to another will simply result in the emergence of different and perhaps more troublesome resistance determinants.

Published data in support of the effectiveness of antibiotic changes in reducing rates of antimicrobial resistance in nosocomial pathogens are far from plentiful, but those that are available offer some hope for these strategies, at least in certain settings. Several studies published in the late 1980s or early 1990s suggested that changing from gentamicin to amikacin as the primary aminoglycoside was associated with a statistically significant decline in resistance of gram-negative bacilli to gentamicin [2]. In several studies, reintroduction of gentamicin was associated with a reappearance of the gentamicin-resistant strains. In most cases, significant increases in amikacin resistance were not observed. Whether increased amikacin resistance would have been observed over time is difficult to determine, since the proliferation of less toxic antimicrobial alternatives to aminoglycosides has been associated with a general decline in their use in many institutions over the past decade.

Antibiotic switches appear to be important components of strategies to control outbreaks of ceftazidime resistance in *Klebsiella pneumoniae*. Virtually all reported outbreaks of infection and colonization with these important pathogens involved widespread and often indiscriminate use of ceftazidime. In the largest published study of such strains to date, Meyer et al. [3] reported a reduction in the rate of ceftazidime resistance in *K. pneumoniae*, from >30% to <10%, in association with control of ceftazidime use and replacement of this antibiotic with imipenem. Peña et al. [4] reported a similar reduction in resistance associated with a reduction in ceftazidime usage in an intensive care unit. In this instance, ceftazidime was replaced initially with imipenem and subsequently with piperacillin/tazobactam.

Assessment of the contribution of antibiotic switches to the reduction in resistance in these studies is made problematic by the concomitant introduction of infection-control measures specifically designed to address patients colonized or infected with resistant isolates. My colleagues and I reported the only study published to date that altered antimicrobial prescribing practices without concomitant infection-control measures to address an outbreak of ceftazidime-resistant *K. pneumoniae* [5]. In our study, a rate of ceftazidime resistance that persisted at >25% for 6 months was rapidly reduced in association with decreased ceftazidime use and introduction of piperacillin/tazobactam for the treatment of serious nosocomial infections.
Four years after this change in practice, rates of ceftazidime resistance in *K. pneumoniae* isolates at our institution remain at ~5% (author’s unpublished data).

More recently, antimicrobial usage has been implicated in the emergence and spread of vancomycin-resistant enterococci (VRE). Published studies have associated use of several different classes of antibiotics with increased risk for infection and colonization with VRE, among them vancomycin, extended-spectrum cephalosporins, and antibiotics with potent activity against anaerobic bacteria [6–8]. It is interesting that control of vancomycin usage, when it is achievable, has had little if any impact on the prevalence of VRE within institutions. In one study, reduced use of vancomycin, cephalosporins, and clindamycin, increased use of ampicillin-sulbactam and piperacillin/tazobactam, and strict infection-control measures that isolated all patients with diarrheal illnesses were associated with a decrease in the prevalence of VRE colonization, from 47% to 15%, over a 9-month period [8]. The authors emphasized the role played by reduced cephalosporin use in the decline of VRE prevalence.

The correlation between aminoglycoside or ceftazidime use and resistance to these agents is logical and readily understandable. It is not so obvious why cephalosporin use may be associated with increased prevalence of VRE. If there is a correlation between the use of cephalosporins and prevalence of VRE, it may be due to the fact that virtually all VRE are *Enterococcus faecium* and the vast majority express high levels of resistance to ampicillin [9]. MICs of ampicillin for most VRE range from 64 µg/mL to 512 µg/mL, and MICs of piperacillin generally fall one doubling dilution higher. MICs of extended-spectrum cephalosporins for these strains commonly are >10,000 µg/mL (author’s unpublished data). Whereas piperacillin, which can achieve concentrations in bile of >1,000 µg/mL, may inhibit even a resistant *E. faecium* strain in the gastrointestinal tract, ceftriaxone, which can achieve concentrations of 5,000 µg/mL or greater, will not. At the same time, such high concentrations of ceftriaxone will inhibit just about anything else. It is therefore not surprising but very instructive that the use of extended-spectrum cephalosporins was associated with colonization by ampicillin-resistant *E. faecium* even before the emergence of VRE as significant pathogens [10].

In summary, there is a growing body of data to suggest that, in some instances, general antimicrobial usage practices can exert a significant impact on the nature and prevalence of certain resistance determinants in certain bacteria. It should be noted that all of the instances cited above involve transferable determinants found in bacterial species whose primary sites of colonization are the gastrointestinal and urinary tracts—areas where antimicrobial agents can be expected to achieve significant concentrations, where many different species may mix, and where the opportunities for the transfer of resistance determinants are frequent.

In this issue of *Clinical Infectious Diseases*, Landman and colleagues [11] report on the changing patterns of resistance in three pathogens (*Staphylococcus aureus*, *K. pneumoniae*, and *Acinetobacter* species) during a time in which the antimicrobial formulary was changed to reduce the use of cefotaxime, clindamycin, and vancomycin. At the same time, ampicillin-sulbactam and piperacillin-tazobactam were introduced and used widely. These investigators previously reported a reduction in prevalence of VRE colonization and infection in association with the same formulary changes [8]. In the present report [11], Landman and colleagues describe a decline in the incidence of infection with ceftazidime-resistant *K. pneumoniae*. Equally important, and perhaps more indicative that the effect they observed was due to the antibiotic changes, they also report a marked decline (from 34% to 12%) in the percentage of clinical *K. pneumoniae* isolates that expressed resistance to ceftazidime. The decrease in incidence of ceftazidime-resistant *K. pneumoniae* infection is modest, and the graph presented raises questions about whether it will persist, but these data are in general agreement with those from other studies and provide further evidence supporting the effectiveness of minimizing use of extended-spectrum cephalosporins in controlling extended-spectrum β-lactamase (ESBL)–producing *K. pneumoniae*.

Landman and colleagues [11] also suggest that the antimicrobial formulary change, specifically the decline in use of extended-spectrum cephalosporins, was responsible for a modest but statistically significant decrease in the incidence of methicillin-resistant *S. aureus* (MRSA) infection. Since MRSA is among the most important and dangerous pathogens in the nosocomial setting, this conclusion warrants close inspection. MRSA differs from the pathogens discussed above in several important respects. The determinant that confers methicillin resistance in staphylococci, the meca region, is chromosomally determined and has never been shown to be transferable between *Staphylococcus* [12]. As a result, the spread of these strains is almost entirely clonal and is due primarily to person-to-person transmission. Second, the primary sites of staphylococcal colonization are not the gastrointestinal and urinary tracts but the anterior nares, the skin, the axillae, and open wounds. In contrast to levels of antibiotic achievable in the gastrointestinal and urinary tracts, concentrations of antimicrobial agents achievable in these areas are often negligible.

Landman and colleagues [11] emphasize the statistically significant relationship between declining use of extended spectrum cephalosporins and the lower incidence of MRSA infection. These findings, if generally applicable, suggest that institutions may be able to reduce their burden of MRSA by decreasing use of cephalosporins in favor of β-lactam-β-lactamase-inhibitor combinations. Before reaching such a conclusion, however, one must consider several features of the data as presented. The first is that there appears to have been a marked decrease in the overall use of antimicrobial agents, when the two study periods are compared (table 1). In addition to a reduction in use of ceftriaxone, clindamycin, and vancomycin, the authors report statistically significant reductions in the
use of cefazolin, ceftazidime, imipenem, and gentamicin. If the mean decline or increase in the use of each antibiotic is presumed, then the defined daily dose of antimicrobial agent administered per month was reduced by >50% in the second period, compared with that in the first (table 1). This apparent decrease in overall antimicrobial use, if it is accurate, is truly enviable.

A second feature of this study that is worth considering is that the antimicrobial changes occurred during a time when many other changes were taking place, most of which had little to do with the use of specific antibiotics but could have significant impact on the incidence of MRSA infection. These changes include the significant decrease in the number of monthly discharges from the medical and surgical services. If fewer patients were housed in the same number of beds over the same number of units in the hospital—and there is no indication otherwise—then the average density of the patient population must have decreased over the study period. Lowering the patient density would be expected to decrease the rate of MRSA colonization and infection, since it is well established that this pathogen is transmitted person-to-person.

In the same vein, the decrease in the average length of stay would also be anticipated to impact the transmission of MRSA, since it would decrease the duration for which colonized patients could transmit the organisms, as well as reduce the time during which noncolonized patients are exposed. In summary, if fewer patients are admitted to the (presumably) same numbers of beds and if they stay for shorter periods, the patient density and risk of cross-transmission of bacteria are bound to be reduced.

The decline in new MRSA infections would be more compelling if it was associated with a more impressive decrease in the rate of resistance to methicillin, when compared with the 23% reduction in the number of new MRSA infections per month, suggests that the reduction in MRSA infections reflects an overall reduction in S. aureus infections at this institution.

Personal experience has taught me that caution is warranted when interpreting year-to-year variability in MRSA percentages. I was impressed by a decrease in the rates of MRSA in the years following reduction of extended-spectrum cephalosporin use at my hospital. The percentage of S. aureus expressing resistance to methicillin at the time of the switch was roughly 65%; in the first and second years following the switch, the rates declined to 57% and 45%, respectively. Unfortunately, the next 2 years saw a rise in percentage of MRSA back to preswitch levels, despite continued low-volume use of cephalosporins. The rises in incidence of MRSA in the months of December 1996 and April 1997, as shown in figure 1A of the article by Landman and colleagues [11], raise questions about the durability of the reported decline.

It is difficult to know whether ampicillin/sulbactam is likely to exert a preventive effect against MRSA infection, as Landman and colleagues suggest. They correctly point out that β-lactam/β-lactamase-inhibitor combinations have shown activity against MRSA in the treatment of experimental endocarditis. However, results of animal studies in which sulbactam was used as the β-lactamase inhibitor are conflicting. One study showed no effect of ampicillin/sulbactam in the treatment of experimental endocarditis caused by MRSA strains expressing heterogeneous or homogeneous resistance [13]. In another study, sulbactam was shown to be a potent inducer of the staphylococcal β-lactamase [14]. This type of borderline (at best) activity is unlikely to exert any effect at typical sites of MRSA colonization. Whether it is enough to prevent initial, low-inoculum colonization of open wounds remains to be determined. To my knowledge, there are no published data assessing the in vivo efficacy of cephalosporin-containing combinations against MRSA.

The desire to identify antimicrobial silver bullets for problematic antibiotic-resistant bacteria is a strong and understandable one. The inconvenience and expense associated with instituting strict infection-control measures are considerable, and long-term compliance is difficult to achieve. Landman and colleagues [11] are to be commended for providing further evidence that ceftazidime-resistant K. pneumoniae isolates decline in association with decreased use of extended-spectrum cephalosporins, as well as for sounding a cautionary note that no antibiotic is free from the risk of helping to select out particularly resistant bacteria such as Acinetobacter species.

The possibility that reducing cephalosporin use in favor of β-lactam/β-lactamase-inhibitor combinations will help control MRSA is an enticing one, but more long-term studies from a variety of institutions will be required. Until such time as a silver bullet is identified, however, there remains no substitute for the use of strict and comprehensive infection-control mea-

### Table 1. Defined daily doses of antibiotics.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Increase (decrease) in g/mo</th>
<th>Daily dose (g/d)</th>
<th>Increase (decrease) in daily dose per mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/sulbactam</td>
<td>3,326</td>
<td>12</td>
<td>277</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>1,898</td>
<td>16</td>
<td>119</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>(193)</td>
<td>3</td>
<td>(64)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>(1,268)</td>
<td>6</td>
<td>(211)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>(448)</td>
<td>6</td>
<td>(75)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>(486)</td>
<td>2.7</td>
<td>(180)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>(29.7)</td>
<td>0.2</td>
<td>(148)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>(47)</td>
<td>2</td>
<td>(23.5)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>(275)</td>
<td>2</td>
<td>(137.5)</td>
</tr>
<tr>
<td>Total</td>
<td>...</td>
<td>...</td>
<td>(443)</td>
</tr>
</tbody>
</table>

NOTE. Data are from [11].
sures to minimize the prevalence of MRSA. The tools to control MRSA are within our reach. The real question is whether we have the will, and the pocketbook, to use them.

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References