Genesis of Methicillin-Resistant Staphylococcus aureus (MRSA), How Treatment of MRSA Infections Has Selected for Vancomycin-Resistant Enterococcus faecium, and the Importance of Antibiotic Management and Infection Control

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We extensively studied the epidemiology and time course of endemic methicillin-resistant Staphylococcus aureus (MRSA) in the Millard Fillmore Hospital, a 600-bed teaching hospital in Buffalo. The changeover from methicillin-susceptible S. aureus to MRSA begins on the first hospital day, when patients are given cefazolin as presurgical prophylaxis. Under selective antibiotic pressure, colonizing flora change within 24 to 48 hours. For patients remaining hospitalized, subsequent courses of third-generation cephalosporins further select and amplify the colonizing MRSA population. Therefore, managing antibiotic selective pressure might be essential. Other strategies include attention to dosing, so that serum concentrations of drug exceed the minimum inhibitory concentration, and antibiotic cycling. Although there are some promising new antibiotics on the horizon, it is necessary to deal with many resistance patterns by using the combined strategies of infection control and antibiotic management.

Scope of Staphylococcal Resistance

The dawn of the antimicrobial era in the late 1930s dramatically altered the focus of clinical medicine, at least for the next several decades [1, 2]. With the introduction of the sulfonamides and penicillin, practicing clinicians could remedy many infectious diseases. The early success of anti-infective therapy was evidence that the battle against infectious diseases had been won, and more time and energy could be devoted to chronic diseases. The optimism ultimately proved fallacious because bacteria such as Staphylococcus aureus acquired resistance to penicillin soon after its introduction in the early 1940s. The problem of methicillin-resistant S. aureus (MRSA) broadened to include the concept of multidrug-resistant S. aureus, which is now synonymous with MRSA [2, 3].

MRSA was first observed in the United States in the mid 1980s [4, 5], as exemplified in the epidemiologic data collected by the National Nosocomial Infection Surveillance System. Among S. aureus isolates, resistance increased from 2.4% in 1975 to 29% in 1991 [5]. Institutional surveillance studies conducted over the past 15–20 years have chronicled the rise of MRSA [6, 7]. The organism is also endemic in nursing homes, in outpatients who are iv drug abusers, or in those undergoing hemodialysis. In hospitals, the first reports of rapidly increasing resistance in S. aureus appeared in large hospitals (>500 beds) in the mid 1980s [5]. Later, the organism appeared in smaller hospitals and nonteaching hospitals.

MRSA—An Import or Homegrown?

Most investigators who study the incidence and pathogenesis of MRSA practice in hospitals. Perhaps as a direct consequence, the focus of publications on MRSA epidemiology and transmission has also been on hospitals [5, 7, 8]. Surveillance studies track MRSA where it can be easily found, and in this case the hospital appears to be a highly appropriate target. MRSA is not endemic in healthy individuals living in the community, given that they are not treated with antibiotics [9–12]. At Millard Fillmore Hospital, a 600-bed teaching hospital in Buffalo, where the frequency of endemic MRSA is >40%, our group noted that in the adjoining outpatient community, nasal carriage consists predominantly of methicillin-susceptible S. aureus (MSSA) (authors’ unpublished observations). This finding largely refutes the notion that the MRSA strains infecting Millard Fillmore Hospital’s newly admitted surgical patients are being replenished from an existing community reservoir of MRSA.

In the Netherlands, where MRSA is rare and cross-transmission is therefore readily detected by simple procedures such as phage typing, there was 92% homology in MSSA postsurgical wound infections with the patients’ own nasal isolates, and 86% of MSSA infections were due to a unique strain [13]. Postsurgical infections were therefore caused by the patients’ own flora.

Further study of the emergence of MRSA should focus on the selective factors that have acted on the MSSA in the pa-
patients’ anterior nares, resulting in a population of MRSA. The transformation of colonizing MSSA to MRSA occurs very rapidly (i.e., 24–48 hours) in hospitalized patients [14–16]. Therefore, both the characteristics of the organism and the onset and time course of subsequent infection argue against cross-transmission as the major initial cause of the emergence of MRSA in hospitals. Furthermore, the very high frequency of this change and the wide variety of different strains that are found make cross-transmission even less likely [16].

In view of the strong evidence against importation of MRSA and against MRSA cross-transmission [17], antibiotic selective pressure might play a larger role in the genesis of endemic MRSA than previously suspected. Thus MRSA is not often imported. Rather, it is typically homegrown. The rapid worsening of this problem, despite highly effective infection-control programs [18], illustrates the need for a focus on the impact of antibiotic selective pressure. No one is arguing for the abandonment of infection control procedures, since they are generally effective in preventing cross-transmission [18–20], and they minimize the chances of importation of MRSA. However, infection control procedures only protect other patients from acquiring MRSA via cross-transmission. Such procedures are designed to prevent epidemic spread and are unable to eradicate an endemic population of organisms. In most institutions, MRSA has become endemic rather than epidemic.

The Link Between Outpatient MSSA Colonization, Inpatient Antibiotics, and MRSA

All of the major elements of the link between susceptibility on the outside, antibiotic-mediated shifts in colonization in hospitals, and subsequent infection were described clearly in McGowan’s 1983 review [8]. Although these elements clearly apply to MRSA, it is unfortunate that little was added to the basic knowledge about endemic MRSA, in contrast to epidemic MRSA, during the subsequent 14 years. For a time, studies of endemic resistance in many organisms were subordinated to excitement over the deluge of new cephalosporin and quinolone antibiotics in the mid 1980s. Victory was declared briefly, and drug development ceased. Now, of course, the resistance problem is back with a vengeance.

In the case of MRSA, there seems little doubt that the antibiotic selection process acting on MSSA begins after patients reach the hospital environment [8, 15, 21]. Patients arrive with *S. aureus* as MSSA. The first action that transforms these MSSA to MRSA in hospitalized patients is antibiotic treatment. The action of antibiotics on the endogenous MSSA selects MRSA from the initially heterogeneous culture [22–24]. This selection process can act on a phenotypic MSSA, i.e., one that reads as MSSA on an 18-hour incubation screen for identification and susceptibility [23, 25]. In a small subgroup of patients with complications or risk factors, subsequent infections with MRSA are likely to occur following colonization with MRSA [17, 26].

In seeking evidence that better antibiotic management strategies are needed, consider a worst-case scenario. Use of an antibiotic selects a small multiresistant subpopulation from the MSSA population. The selected organisms survive attack by a patient’s WBCs. The patient remains in the same semiprivate room, is attended by the same caregivers, and the other patient in the room is given the same antibiotic. In the real world, if a patient is already receiving an antibiotic active against MSSA but not MRSA, the same antibiotic facilitates cross-transmission of this multiresistant organism between patients [27, 28].

The Rise and Fall of MRSA in Millard Fillmore Hospital

We have spent considerable time tracking both antibiotic use patterns and the course of MRSA in Millard Fillmore Hospital [29, 30]. As shown in figure 1, MRSA, which is now polyclonal, appeared at our hospital at about the same time as it appeared in most of the >500-bed hospitals reporting to the National Nosocomial Infection Surveillance System. Of particular interest to us was the fact that the appearance of MRSA coincided with our change from cephalothin prophylaxis to cefazolin prophylaxis, which occurred in 1983–1984.

This temporal pattern was not unique to Millard Fillmore Hospital. Throughout the United States, most prophylaxis with cephalosporins changed to that with cefazolin between 1982 and 1984 [31]. This almost universal changeover to cefazolin might represent the greatest monopolistic adoption of an antibiotic regimen of all time. Widespread formulary adoption of cefazolin was driven by marketing efforts, as cephalothin, the previously dominant agent, lost its patent protection. In addition, at about this time, the hospital formulary began to play a prominent role in the control of antibiotic selection [32]. Even

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**Figure 1.** Percentage of methicillin-resistant *Staphylococcus aureus* at Millard Fillmore Hospital (Buffalo), a 600-bed hospital (■), and at a representative 500-bed hospital in the National Nosocomial Infection Surveillance System (□). The conversion to cefazolin for prophylaxis at Millard Fillmore Hospital (arrow) occurred in 1983–1984.
Cefazolin and MRSA: The Impact of Antibiotic Exposure on Nasal MSSA

There are reasons to speculate that exposure to cefazolin, a central component of the surgical admission process, exerts a great measure of early selective pressure on MSSA and therefore plays a central role in the origin and endemicity of MRSA in hospitals. Even more attention would be focused on this hypothesis if it was clearly demonstrated that MRSA colonizes MSSA carriers extremely rapidly after they are admitted to the hospital and given prophylactic antibiotics before elective surgery.

A convenient means to evaluate the impact of this in vivo antimicrobial exposure on \textit{S. aureus} resistance would be to study the impact of exposure to antibiotics on MSSA in the anterior nares, a common reservoir for \textit{S. aureus} [38]. In a case-control study by Kluytmans et al. [13], nasal carriage of \textit{S. aureus} was found to be a significant risk factor for the development of sternotomy wound infection following cardiac surgery. Similarly, in clinical trials [39] the risk of sternotomy infection was found to be four-to-six times higher among patients who were nasal carriers of \textit{S. aureus}.

We used the staphylococcal nasal carriage model for a study in healthy volunteers. The results showed that there is an extremely rapid shift in nasal staphylococcal populations when cefazolin is used (authors’ unpublished observations). In fact, it takes $<48$ hours to change the nasal colonization profile from that of MSSA carriage to that of MRSA carriage.

Serial microbiological studies in surgical patients [16] have also shown that the colonizing MSSA isolates react dramatically to the antibiotics introduced into their microenvironment. During the first 48 hours, cefazolin might either eradicate nasal MSSA (the outcome for 50% of patients), or the MSSA might be replaced by MRSA because of antibiotic selection (the outcome for $\sim 15\%$ of patients). In the remaining 35% of patients, the MSSA persists as MSSA, albeit at a lower inoculum.

All of these changes occur too rapidly to allow the assumption that MRSA has been introduced from the surgical environment or is the result of a mutation in the original MSSA. Rather, what was thought to be pure MSSA most likely contained a small subpopulation of \textit{mecA}-positive \textit{S. aureus}. Thus, \textit{mecA} was always present in the MSSA, but initially the numbers of MRSA subpopulation isolates were too low to manifest as a cloudy well after an 18-hour MIC test. Given a longer in vitro incubation time, we would detect more MRSA than MSSA, a well-described [22, 23, 25, 40] but disturbing finding.
How Resistance Develops in Bacteria and the Role of the Antibiotics

Resistance in hospitals is the product of both bacterial heredity and bacterial environment. Bacterial environment consists of nutrients and any antibiotic humans introduce. Bacteria are well versed in their survival-oriented task of developing resistance to antibacterial substances.

For resistance to develop in any bacteria, a genetic mutation must occur or the organism must take up a resistance-conferring plasmid or DNA fragment from the environment. These mutations occur in nature, but not at a frequency such that every case of antibiotic resistance is explained by a new mutation. Thus, the mutations are conserved, which becomes the real impact of antibiotic therapy. Selective pressure from one or more antibiotics can play a central role because the antibiotics preferentially nurture the mutant strain by eliminating any competing flora that are not already resistant. The more competing mechanisms operative in some species of bacteria, the more antibiotics can play a central role because the antibiotics driven altered binding site mechanism is the explanation for the impact of antibiotic therapy. Selective pressure from one or more antibiotics can play a central role because the antibiotics preferentially nurture the mutant strain by eliminating any competing flora that are not already resistant.

Clearly, resistance in hospitals, particularly endemic resistance, is the result of simultaneous mutation and antibiotic therapy [27, 41].

A typical example of a mutation nurtured by antibiotic therapy is the one that selects the β-lactamase genes in Enterobacter cloacae. These strains quickly emerge during therapy and, in most cases, become pathogens [42, 43]. Infections and outbreaks due to these strains can usually be interrupted or controlled by removing the nurturing antibiotic—in this case, cefazidime [44]. The mutated complex is always present and will reemerge when the use of cefazidime is resumed, although measures such as using higher doses of cefazidime along with concomitant aminoglycosides might lessen the chances of emergence of pathogenic E. cloacae in any particular patient.

Highly methicillin-resistant S. aureus contains a 2,130-bp segment of foreign DNA, the meca gene [45]. An altered membrane-bound enzyme, penicillin-binding protein (PBP) 2a, is the gene product of meca. Methicillin, like other β-lactam agents, has poor affinity for PBP2a. With inadequate binding to PBPs, these β-lactam agents have little activity against these strains. Essentially all MRSA strains produce this unique PBP.

Population analysis of MRSA strains demonstrated that resistance can be homogeneous, where most cells produce PBP2a, or heterogeneous, where only a few cells produce this altered PBP [46]. In addition, production of PBP2a can be changed from constitutive to inducible by the insertion of an inducible penicillinase plasmid [47]. Structural similarities shared between the meca gene and the β-lactamase gene make it likely that a repressor gene controls production of PBP2a as well as production of β-lactamase [46]. MecI and mecRI are regulator genes located upstream of the chromosomal meca gene. MecI encodes a repressor of meca transcription, while mecRI is a signal transducer with antirepressor activity. A group of clinical staphylococcal strains contain the meca gene but test susceptible to methicillin. In ~40% of MRSA strains, the mecI is deleted. In the rest of these strains, mecI is present but contains nonsense point mutations. Loss of mecI function, whether as a result of deletion or by mutation, is a necessary step in the production of PBP2a and expression of methicillin resistance [48]. Although cross-transmission plays a role in the spread of MRSA between patients, it seems clear that antibiotic selective pressure on the increasingly heterogeneous MRSA strains, as well as induction of PBP2a production with exposure to β-lactams, are keys to maintaining high-level methicillin resistance in hospitals.

The meca gene, which controls the production of PBP2a, not only confers resistance to β-lactams but also mediates cross-resistance to fluoroquinolones, aminoglycosides, tetracyclines, macrolides, and trimethoprim-sulfamethoxazole. The PBP2a-driven altered binding site mechanism is the explanation for the most current MRSA problems [25, 49, 50]. A third resistance mechanism operative in some species of bacteria, permeability changes, does not appear (at the moment) to be an important factor in the resistance of S. aureus.

Phenotypic expression of methicillin resistance can be either homogeneous or heterogeneous [25, 49, 50]. When this expression of resistance is homogeneous, all organisms in the culture are of identical susceptibility, and they are assumed to be genetically identical. Most staphylococci in cultures are heterogeneous [23, 51]. Thus, an entire array of susceptible-to-highly resistant staphylococcal organisms coexist in the same culture. Even an individual colony of MSSA is heterogeneous, although most individual organisms are susceptible to methicillin at a low MIC [23, 51]. When there are increasing numbers of organisms with increasing resistance (higher MICs), the net effect is expressed as MICs that are above the resistance breakpoint [51]. This effect was reported as early as 1974 by Sabath and Wallace [52], although at that time there was no clear explanation for these results.

A recent surprise has been the frequency of subpopulations of apparently susceptible S. aureus that contain the meca gene [37, 50, 51, 53]. Many apparently susceptible cultured S. aureus populations, regardless of origin, include small subpopulations of organisms that contain meca [37, 49, 53]. These subpopulations can be selected from cultures of apparently susceptible MSSA by exposing the cultures to serially increasing concentrations of antibiotics below the MIC [37].

Nonsusceptible subpopulations that are selected during the antibiotic testing process may be a major reason why MIC testing reveals MRSA at 48 hours of incubation even though the reading at 18 hours reveals MSSA [23, 25, 54]. There are always a few organisms in the inoculum that are resistant to the β-lactam agent [22]. Eighteen hours of incubation is not long enough for them to grow to predominance, but 48 hours is clearly sufficient.

Microbiology laboratories will typically report cultured S. aureus as susceptible after 18 hours of incubation, meaning that the oxacillin-containing test-well broth has remained clear.
If the culture is incubated for another day, the broth in the same well that was read as susceptible to oxacillin on the previous day will be cloudy. The interpretation is that there are always small numbers of more-resistant organisms present at the start in a heterogeneous culture [22]. In the wells of the MIC test, these few organisms require 48 hours of growth in the presence of an antimicrobial exerting selective pressure to become the predominant heterotype [23].

Although the mecA gene might be absent, it is also possible for mecA to be present in small amounts and remain undetected because the detection limit of PCR is above 1,000 bacterial cells [55, 56]. Small numbers of mecA-containing cells in the MSSA culture population before antibiotic exposure could contribute to the higher MIC and yet remain undetected by PCR during the usual genetic analysis [49, 52]. Clearly, both resistance mechanisms are present in some staphylococci, even if these bacteria are phenotypically disguised as MSSA. This finding has been noted at least since 1974 [51], although PCR was not available for discerning the molecular mechanism of the mecA effect until considerably later.

The Importance of Dosing and Area Under the Curve-to-MIC Ratio (AUIC) and Why Bacteria for Which the Antibiotic MICs are High Become Resistant First

The goal of any antibiotic therapy is to cover (exceed) the MIC of the antibiotic for the infecting pathogen for the entire time between doses. There have been numerous references to antibiotic treatment failure when the concentrations do not exceed the MIC [8, 24, 30, 57–61]. This principle of coverage has been studied in in vitro models [59, 62, 63]; in animal models of infection [57, 59]; in healthy volunteers [64, 65]; and in patients with nosocomial pneumonia [60, 61, 66], acute exacerbations of chronic bronchitis [67], or other infections [68].

In each of these settings, concentrations that exceed the MIC <80% of the time are predictive of eradication failure and of resistance [69]. This principle can be quantitated as the AUIC [58, 65]. Each antibiotic exposure or course of therapy in a patient has a unique AUIC. When the AUIC is below 125, the exposure is <80% coverage of the MIC for the organism [58, 60, 61, 70].

The striking observation from these studies is the ability of the AUIC to predict resistance as accurately as it predicts bacterial eradication. The typically observed emergence of resistance in the course of treatment for MSSA infection is a mathematically predictable case of selective antibiotic pressure. These resistant organisms represent neither new nor unique mutations in the strain of infecting bacteria. Mutations do occur, but not every time antibiotics are used. Rather, antibiotic use usually allows a previously mutated subpopulation to emerge. In the case of resistance in *S. aureus*, this mechanism was postulated as early as 1961 [71].

In essence, the coverage described as an AUIC >125 is different for each subpopulation of organisms within the culture. Strains susceptible to low MICs have very high AUICs and thus are subject to excellent antibiotic coverage. For strains susceptible to low MICs, the entire dosing interval is spent above the MIC, and thus they are eradicated. Strains susceptible to higher MICs, a small minority of the initial population, are not covered for the entire dosing interval. Therefore, these strains are selected for survival because they were always resistant.

With sufficient exposure and absence of host defense, all viable organisms become the progeny of the subpopulations that were not exposed to the antibiotic for sufficiently long periods to effect bacterial killing. Even though the subpopulations might be present in very small numbers, they are fully capable of becoming the only survivors if antibiotics are given and if the host response, i.e., WBCs, does not clear these selected survivors [27, 29, 30, 58, 61].

In this scheme, resistance is actually the predictable overgrowth of the surviving organisms that are susceptible to a higher MIC, now the predominant population [27, 54]. They were always present in small numbers; the presence of the antibiotic enabled them to grow to sufficient numbers that their collective susceptibility is usually higher than the laboratory breakpoint for susceptibility even though the MIC value would have indicated susceptibility before antibiotic exposure.

Some examples of the routine occurrence of low AUICs in the patient care setting are provided in table 1. The situations described in this table are common in most hospitals, and in some cases, in the community as well. The approach to these situations is to track both the antibiotic use and the corresponding bacterial resistance in the indicator pair of isolate-antibiotic.

If Selection Is So Common, Why Doesn’t Every Patient Contract an MRSA Infection?

Patients who carry nasal MSSA are admitted every day to hospitals everywhere, and the first act of selective pressure in many of these hospitals is to give an antibiotic before surgery to prevent postsurgical infection. In many areas of the United States, the predominantly used antibiotic is cefazolin, and its use begins the process of selection to MRSA. On the basis of a low AUIC and the presence of a mecA-positive population at baseline, the selective process might be considered a predictable pharmacologic effect of the antibiotic, but obviously not all surgical patients contract postsurgical MRSA infections.

Assuming replacement of nasal MSSA by MRSA in ~15% of patients [21, 39], one reason that more MRSA infections are not observed is the reversion of antibiotic-selected MRSA to heterotypic MSSA. This event follows the cessation of antibiotic therapy. For the majority of patients, cefazolin-mediated selection is obscured by early hospital discharge and the spontaneous reversion of MRSA to MSSA. The normal time required for nasal MRSA to revert to the usual nasal MSSA is ~30 days [38].
Table 1. Antibiotic indicator pairs predictive of resistance.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antibiotic with low AUIC</th>
<th>Indicator organism</th>
<th>Reason for low AUIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>[45]</td>
<td>Ceftazidime</td>
<td><em>Enterobacter cloacae</em></td>
<td>Decrease in dose to 1 g q12h</td>
</tr>
<tr>
<td>[45]</td>
<td>Ceftazidime</td>
<td><em>Staphylococcus aureus</em></td>
<td>High MIC</td>
</tr>
<tr>
<td>[53]</td>
<td>Cefazolin</td>
<td><em>S. aureus</em></td>
<td>Low dose and high MIC</td>
</tr>
<tr>
<td>[67]</td>
<td>Imipenem</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Low dose and high MIC</td>
</tr>
<tr>
<td>[67]</td>
<td>Ciprofloxacin/ofoxacin</td>
<td><em>P. aeruginosa</em></td>
<td>Low dose and high MIC</td>
</tr>
</tbody>
</table>

NOTE. AUIC = area under the curve–to-MIC ratio.

Clearly, if a surgical patient is discharged from the hospital after 3–4 days and is not given additional antibiotics, the entire process of reversion of the initial MSSA colonies to MRSA colonies and back again to MSSA colonies will occur, but it will be undetected in otherwise asymptomatic outpatients. A change in colonizing flora would be noticed if cultures were performed, but cultures are rarely performed for postsurgical patients solely to assess their MRSA carrier status, let alone to periodically monitor susceptibility changes in colonizing flora. Because length-of-stay for surgical patients continues to become shorter, early hospital discharge without residual use of antibiotics is a temporary protective strategy used in many communities, as it has been in Buffalo. Selective antibiotic pressure can sustain MRSA in any environment; therefore, moving patients out of the hospital and sending them home with cephalosporins will sustain MRSA in outpatient populations. This practice must be discouraged.

The full time course of the selective pressure process is described in figure 3. Cefazolin is the likely source of the initial population heterogeneity, but antibiotic selective pressure continues in those subsets of patients who remain in the hospital for a longer time. As shown in figure 3, the constitution of this heterogeneous MSSA/BSSA (“borderline” susceptible *S. aureus*)/MRSA organism is further altered with exposure to third-generation cephalosporins. Eventually only MRSA, with its high-level resistance to cephalosporins, survives the continual selective pressure. These strains primarily colonize patients who have been in the hospital for 1–2 weeks. Many of these patients are subsequently transferred back to intensive care units as MRSA carriers [26]. The final steps in the continuum are vancomycin use and the selection of vancomycin-resistant *Enterococcus faecium* in a proportion of patients, as shown in figure 3.

The MRSA pool of a hospital further expands when MRSA carriers are admitted from the community or from nursing homes. In such situations, lapses in infection control procedures play an increasingly important role.

Figure 3. A representation of serial nasal cultures and colony counts beginning before admission and continuing for the next 21 days, assuming all clinical events take place as described in the text. For 90% of admitted patients, discharge occurs in 2 days, and the remainder have complicated courses and remain hospitalized for 21 days. The typical antibiotic use patterns among the inpatients are the administration of ceftazidime on day 5 and vancomycin on day 8, after cultures on day 7 yield methicillin-resistant *Staphylococcus aureus* (MRSA). This is a temporal study of selective pressure on staphylococci, resulting from cephalosporin use, and then on *Enterococcus faecium*, resulting from vancomycin use. BSSA = “borderline” susceptible *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; VREF = vancomycin-resistant *E. faecium*.

The Controversy over Cefazolin Prophylaxis for Surgery

Resistance will occur more readily during the course of antibiotic therapy in patients infected with *S. aureus* for which the baseline antibiotic MIC approaches the laboratory breakpoint for resistance. Many investigators have noted that the MICs of the penicillinase-resistant penicillins, such as oxacillin, do not change during therapy as readily as the MICs of cephalosporins [34–36, 52]. This phenomenon, which is typical of MSSA for which the cefazolin MIC breakpoint is 4.0–8.0 μg/mL [24, 25], is easily recognized and remarkably predictive. On the other hand, there are also animal models [72–74] and studies of antibiotic prophylaxis in surgery [75–77] that have shown clinical differences among the cephalosporins in the same rank order that would be predicted only on the basis of in vitro tests [34, 35, 78, 79].

Strongly documented arguments have been made against using cefazolin and in favor of using more stable cephalosporins such as cefamandole, cephalothin, and perhaps, cefuroxime [24, 34, 73–77]. The use of cefazolin has been defended in studies of animal models [72] and of antibiotic prophylaxis in...
surgical patients [80]. The authors of the favorable cefazolin studies have been criticized for using doses of the competing newer cephalosporins that were too low [81]. There actually is considerable evidence [82] of the importance of dosing regimens and timing for all the cephalosporins with a short half-life.

Routine prophylactic use of the most labile of the cephalosporins, cefazolin, is further compromised by lowering its dosage to 1.0 g every 8 hours. The impact of the resulting underexposure is readily appreciated by comparing the drug’s pharmacokinetics [33] with its MIC. Figure 3 shows the serum cefazolin concentrations during a typical prophylactic regimen of 1 g every 8 hours. The calculated AUIC for cefazolin at this dosage does not comfortably exceed 125 when the MIC for the MSSA present at baseline is 4–8 µg/mL. Furthermore, these AUICs are based on the total concentration of cefazolin (free and protein bound). The free concentrations of cefazolin are <10% of the values shown in figure 3.

How often does this occur? Even in the early-to-mid 1980s, it appeared to occur quite frequently in hospitals with MSSA and perhaps a few BSSA isolates [24]. Furthermore, the heterotypic nature of MRSA guarantees that there are selectable sub-populations in most colonized, cefazolin-treated patients. What, then, were the consequences? After cardiothoracic surgery, cefazolin-treated patients had more infections than did cefamandole-treated patients [24, 75–78].

At that time, there was good reason to link resistance development to the BSSA variant of MSSA. Now that many apparent MSSA strains carry the mecA gene and synthesize β-lactamase [83], it is even more important to consider borderline susceptibility of MSSA. For patients infected with these strains, the poor outcomes of prophylaxis are predictable from the relationship between cefazolin serum concentrations and the MICs for the S. aureus populations (figure 3).

Thus the studies done >10 years ago by Sabath et al. [34, 52], Fong et al. [84], Regamey et al. [79], and Kernodle et al. [35] are now being viewed as prophetic. Unfortunately, because of cefazolin’s longer half-life [31, 33] and other desirable characteristics such as its lower price, it became the predominant antibiotic used as prophylaxis before surgery. Cefazolin has remained the drug of choice over the past 15 years. However, this long run of monopolistic use might be nearing an end. Cefazolin achieved its status because of its pharmacokinetic characteristics. Unfortunately, it has poor stability in the presence of the current version of S. aureus, now a mutated organism that both produces β-lactamase and possesses mecA to facilitate its survival. Furthermore, it doesn’t help when the cefazolin dose is continually lowered in an effort to save money.

If first-generation cephalosporins can be linked to selective pressure—mediated resistance, part of the solution could be better antibiotic management strategies. Prophylactic use is a logical topic with which to begin a new focus on antibiotic management, for several reasons:

1. Prophylaxis accounts for the largest volume of cefazolin use in most hospitals, and it appears that prophylaxis is the usual situation in which cefazolin AUIC values are routinely below 125 for MSSA.
2. Prophylactic use affords the first opportunity for many patients entering the hospital to be treated with an antibiotic regimen that may result in selective pressure—mediated resistance, potentially expressing the inherent MRSA in a majority of MSSA carriers.
3. Even if cefazolin is not the selecting agent for all MRSA, it is generally easier to alter regimens containing this antibiotic because prophylaxis guidelines are under better control in most hospitals than are empirical regimens.
4. Strictly on the basis of volume of use, which approaches 80% of all cephalosporin use, cefazolin use is an attractive target for interventions designed to target resistance. Targeting monopolistic use first makes sense in a world in which hospitals are understaffed and the staffs are over-worked.

Why Is the Emergence of Vancomycin-Resistant Enterococcus faecium the Next Step in the Chain of Events?

Clearly, selective antibiotic pressure due to the use of cephalosporins is a plausible explanation for the transformation of MSSA to MRSA and the associated endemic status of this organism in United States hospitals. Perhaps less apparent are the links between the use of cephalosporins and MRSA and the use of vancomycin and vancomycin-resistant Enterococcus faecium (VREF), the process diagramed in figure 3. If all of these links stand the test of time, then the VREF epidemic might also be directly linked to use of cephalosporins, as suggested by Noskin et al. [85]. These investigators observed a clear decline in the incidence of VREF in relation to reductions in the use of third-generation cephalosporins and the associated replacements by the combination of a penicillin with a β-lactamase inhibitor. If the use of cephalosporins selects for MRSA, then the solution to the current VREF epidemic could be closely tied to the solution to the MRSA problem. After all, MRSA drives the use of vancomycin.

Restriction of vancomycin use at the Millard Fillmore Hospital might be considered a direct attack on the specific problem. We already had effective infection control measures, as indicated by the fact that VREF was not transmitted from patient to patient. In our institution, the emergence of VREF was associated with the use of oral vancomycin, so restriction of oral vancomycin use alone was an effective countermeasure. The absence of a transplant population, which represents a second epidemiologic pattern (a patient population less responsive to the strategy of restricting the use of oral vancomycin), allowed this simple strategy to
break the chain of events depicted in figure 2, has not yet been specifically implemented as a strategy for eradicating VREF in a major medical center. However, its partial implementation could explain the observed reduction in VREF in one study, when the use of cephalosporins was restricted and penicillins were substituted in their place [85].

Figure 4. Serum cefazolin concentrations resulting from three doses of 1 g, given 8 hours apart. Data on healthy volunteers were used to construct the serum time course, assuming a one-compartment model. These pharmacokinetic data were superimposed on cefazolin MIC values of 8 µg/mL, 4 µg/mL, and 2 µg/mL. In each case, the 24-hour area under the curve–to-MIC (AUIC) value was calculated. Target AUIC values are above 125 for efficacy, with values below 125 predictive of resistance as well as therapeutic failure. Organisms for which cefazolin MICs were 8.0 µg/mL are unlikely to be eradicated.

Cycling, Switching Classes, Surveillance, and Changing Formulary Agents: Can We Catch Up with These Organisms, and Perhaps Get Ahead Again?

Each institution is different, as are the strategies that might need to be applied to its own resistance problems. For some institutions, but perhaps a minority in this modern era, the solutions to endemic resistance lie in better infection control. In addition to our experiences, the results of Wright et al. [86], who conducted a study in a university hospital, support the association between the emergence of VREF and vancomycin use patterns. In that study, VREF was related more to the use of iv drug than to the use of oral drug. Use of oral vancomycin was restricted hospitalwide, but the associated strategy was to restrict the use of iv vancomycin in one of the two intensive care units. It is not surprising that a decline in the incidence of VREF was observed in the intensive care unit where the use of iv vancomycin was restricted, while there was no change in the unit where the use of iv vancomycin was not restricted. If the incidence of VREF had declined in both units, then a link between VREF and hospitalwide restriction of the use of oral vancomycin might be the explanation. Wright et al. clearly identified the VREF that was linked to the use of iv vancomycin, typical of an endemic pattern in intensive care units. Whether an institution in this position needs to restrict the use of oral vancomycin is debatable, but it seems prudent to do so on the basis of the Centers for Disease Control and Prevention guidelines [87].

Thus a strategy to eradicate MRSA, such as replacement of cefazolin with cephalothin or another more stable antibiotic for prophylactic use, could lower the frequency with which MSSA becomes MRSA. In turn, the lower frequency of MRSA will result in less use of vancomycin; with less vancomycin-related selective pressure, the incidence of VREF will decline in the transplant population. This combined strategy, designed to work better at our hospital than it might at hospitals with both epidemiologic patterns.

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of the ones we have. That strategy could be to quickly reverse what we did to cause our current problems.

First, to reverse the rapidly accelerating resistance pandemic, formularies need once again to be opened up to include various agents in order to lessen the selective advantages afforded certain bacteria. Second, the empirical use of antibiotics should be alternated among classes rather than within classes (e.g., from cephalosporins to quinolones rather than from cephalosporin to cephalosporin) [91, 92]. Alternating the pattern of use should be applied more randomly and should be less driven by the rigidity of a closely controlled formulary. Third, in some units with specific patterns of endemic resistance, the cycling of antibiotic use, at intervals of several months between cycles, should be considered. This cycling should be done between classes, not within members of the same class. The cycling strategy should also be applied to surgical antibiotic prophylaxis, which would be a way of attacking the source of the MRSA problem.

One of the more effective ways to cycle among antibiotic classes in a hospital is to institute a day-3-driven switch and streamlining program [28, 92–94]. Day-3-oriented cycling programs are logically accompanied by opening up formularies to allow the use of many different types of antibiotics and combinations on day 1. This practice maximizes the initial diversity of exposure, and is then followed by the implementation of the switch programs on day 3 of treatment (after cultures have revealed the specific pathogen), which furthers diversity. Considerable amounts of money will be saved after day 3 by the switch to oral antibiotics. In fact, in hospitals where this oral switch strategy is implemented, both incidence of resistance and the total antibiotic expenditures should decline [28, 44, 90–94].

Implementing a strategy that includes dosing to AUIC targets, antibiotic switch and streamlining at day 3, and selective cycling is admittedly more complex than the current approach of monitoring the number of nosocomial infections in a hospital and changing the formulary agents every few years as prices change. Some attention still needs to be devoted to the detection of clonal cross-transmission, which indicates a breakdown in infection control. Most of the attention will shift to day 3 for patients treated with empirical antibiotics and away from formulary enforcement on day 1. Actually, much of the formulary enforcement effort is sufficiently labor-intensive that pharmacy personnel can be diverted to a new focus on day 3. Computerized systems can help in the identification of patients and in dosage calculations [28, 94].

No doubt, increasing attention should be devoted to the synthesis of new antibiotics, particularly those of different classes, in case we are not able to continue using our currently available antibiotics.

In this symposium, several new agents have been discussed as alternatives for resistance problems such as penicillin-resistant Staphylococcus aureus, MRSA, and VREF. Use of these new agents promises treatment alternatives, but these agents must also be used as part of a coordinated antiresistance strategy. We will not succeed either with monopolistic use or with nonuse of these new agents. They must be used to solve some of our resistance problems, meaning that they might have roles in cycling regimens, switch programs, and the treatment of infections due to specific pathogens. The lessons of history need to be applied if we are to integrate the new agents into the overall antibiotic armamentarium.

References


20. Edmond MB, Wenzel RB, Pasuelle AW. Vancomycin resistant Staphylo-


24. Kernodle DS. Surgical prophylaxis: How far have we really come? Pharmacotherapy 1988; 8 (suppl):11S–3S.


36. Kernodle DS, McGraw PA, Stratton CW, Kaiser AB. Use of extracts versus whole cell bacterial suspensions in the identification of Staphylo-


40. Varaldo PE. The “borderline susceptible Staphylococcus aureus.” J Anti-


53. Fleming TF, Rudiger S, Hoffmann U, Schmidt H. Identification of Actino-


