Infection Control or Formulary Control: What Is the Best Tool to Reduce Nosocomial Infections due to Methicillin-Resistant Staphylococcus aureus?

Bala Hota
Rush University Medical Center and Stroger Hospital of Cook County, Chicago, Illinois

(See the article by Charbonneau et al. on pages 778–84)

The burden of infectious disease due to methicillin-resistant Staphylococcus aureus (MRSA) has increased since MRSA was first implicated as a nosocomial pathogen 4 decades ago [1, 2]. Data from the SENTRY Antimicrobial Surveillance Program estimate that ~40% of S. aureus isolates recovered in intensive care units (ICUs) have been resistant to methicillin [2]. Risk factors for nosocomial infection with MRSA include exposure to antimicrobials and cross-colonization by health care workers from colonized or infected patients or from the contaminated inanimate environment (e.g., in ICUs or burn units) [3, 4]. Control of MRSA within hospitals generally relies on proper infection-control practice, as reflected by the statement that “the rate of MRSA transmission in a hospital reflects the effectiveness of infection control practices in that facility” [3, p. 11S].

In this issue of Clinical Infectious Diseases, Charbonneau et al. [5] examine an alternative approach to control of MRSA rates: a reduction in fluoroquinolone use. With use of the incidence density of MRSA (defined as the number of nonduplicate cases of MRSA/1000 patient-days) and the prevalence of MRSA (defined as the number of nonduplicate clinical MRSA isolates/total number of clinical S. aureus isolates), the authors found that a 10-fold reduction in fluoroquinolone use was associated with a statistically significant reduction in rates of MRSA. These reductions, although modest (a reduction of prevalence from 36.0% to 32.3%), were not present in the control hospitals. The postintervention incidence density of MRSA was less than the lower limit of the 95% CI for incidence, as predicted by a forecasting model, suggesting that fluoroquinolone use had an impact on MRSA rates among clinical isolates at this center.

Prior studies have revealed an association between nosocomial infection with MRSA and fluoroquinolone use [6–12], and the article by Charbonneau et al. [5] provides additional evidence to support such a relationship. However, the methodological quality of studies of the impact of antimicrobial use on antimicrobial resistance must be considered when assessing the impact of interventions. Because multiple infection-control interventions are often simultaneously implemented, investigators should measure and analyze the impact of infection-control variables (e.g., hand hygiene, environmental cleaning, and colonization pressure) as covariates in statistical analyses when feasible.

A second methodological issue is the unit of observation of studies: investigators must make clear whether the unit of observation is the patient or whether an ecologic or population-based unit is being assessed (i.e., a comparison of units within a hospital or hospitals within a region; risk estimates calculated by the study will pertain to this unit of observation). Readers will be interested in both levels of observation (i.e., whether the risk that an individual will be infected with MRSA increases if the individual is given a fluoroquinolone, and whether patients who are hospitalized in an ICU that uses excess fluoroquinolones are at higher risk of acquiring MRSA infection). Finally, studies examining antimicrobial use interventions should consider whether autocorrelation in longitudinal data is present and should adjust appropriately with use of time-series analytic methods.

Charbonneau et al. [5] examine both the ecologic impact and the impact over time of diminished fluoroquinolone use. To address the correlation between observations that occurs by comparing large groups subject to interventions (i.e., clus-
ter-randomization [13]), generalized estimating equations were used. Time series analysis was used to assess the impact of fluoroquinolone restriction over time. It is notable that, during the intervention, significant reductions in the incidence density of MRSA occurred, and after cessation of the intervention, the incidence density of MRSA increased to preintervention levels.

Infection-control interventions were implemented in both the intervention and control hospitals before or during the study period. In control hospitals A and B, hand hygiene procedures changed during the study period: in hospital A, increases in use of alcohol gel were noted, whereas in hospital B, alcohol gel was introduced in May 2001. At Caen Hospital (Caen, France), the site where fluoroquinolone use was restricted, alcohol rubs were introduced before 2001. The use of control groups in which similar infection control processes were used mitigates confounding associated with infection-control practice; however, direct comparison of the use of alcohol gel may have provided more evidence to support the effectiveness of the antimicrobial use intervention, given the modest decrease in the prevalence of MRSA. If hand hygiene quality was better in the intervention hospital because of the earlier institution of alcohol gel, this might partially explain differences between the hospitals.

Among the prior studies that have used ecologic data, 1 study showed a positive association between ciprofloxacin use and numbers of MRSA isolates among 50 Belgian hospitals [6]; a second study demonstrated that the incidence of MRSA varied in specific units of a French hospital on the basis of use of fluoroquinolones and other antimicrobials [7]; and a third study showed that the prevalence of MRSA in 17 US hospitals and their surrounding communities correlated highly with total rates of fluoroquinolone use ($r = 0.77; P = .0003$) [8]. Patient level data supporting a relationship include 3 case-control studies [9–11]. The least biased of these studies used a case-case-control study design to compare the risk of fluoroquinolone use between MRSA-affected patients and methicillin-susceptible S. aureus (MSSA)–affected patients; a random sample of unaffected patients served as control subjects [11]. On multivariate analysis, use of ciprofloxacin or levofloxacin increased the odds of development of MRSA infection and did not impact the odds of development of MSSA infection. Time series data examining the relationship of antimicrobial use and MRSA showed highly correlated changes in the prevalence of MRSA following changes in use of fluoroquinolones, third-generation cephalosporins, and macrolides [12].

Why would changes in use of fluoroquinolones lead to changes in MRSA rates? Possible explanations include enhanced likelihood of colonization of individuals with MRSA because of the greater virulence of colonizing strains, higher density of colonization or likelihood of dissemination, or suppression of competing flora. Fluoroquinolone use may enhance the adhesiveness of MRSA and select more fit isolates [11], and use of fluoroquinolones has been noted to be a risk factor for persistent colonization with MRSA [14]. Finally, antimicrobial use may enhance dissemination of S. aureus: tetracycline use was shown to enhance dissemination of tetracycline-resistant S. aureus from carriers [15], and the same phenomenon theoretically might occur in MRSA exposed to fluoroquinolones.

The general applicability of the results reported by Charbonneau et al. [5] may be limited. Study hospitals performed active surveillance for MRSA using nasal swab specimens obtained from patients admitted to ICUs, and carriers of MRSA were isolated. This level of surveillance is unlikely to be isolated in many hospitals because of resource constraints. Because prevalence of colonization is not reported, it is also unknown whether reductions in fluoroquinolone use led to reductions in the need for isolation of carriers of MRSA in ICUs.

It remains unclear whether improvements in infection-control practices or reductions in fluoroquinolone use are paramount in hospitals. Given that increases in the number of infections with extended-spectrum β-lactamase–producing Enterobacteriaceae were noted in the study (attributed to increased cephalosporin use), improved hand hygiene and enhanced compliance with isolation precautions seem to be more benign practices. With the emergence of community-onset infection with fluoroquinolone-susceptible MRSA [16], the impact of fluoroquinolone use on MRSA control becomes even more complex. Therefore, as high-quality evidence accumulates suggesting a role for antimicrobial use in control of MRSA, multifaceted interventions may evolve that can complement the basics of hand washing, contact isolation, and cohorting. The additional tools in the infection-control toolbox would be welcome.

Acknowledgments

Potential conflicts of interest. B.H.: no conflicts.

References