Editorial

More Evidence of the Benefits of Rational Antimicrobial Use in Clinical Practice

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Many of us work in overcrowded hospitals with overworked nursing staff and overstressed physicians. It is easy to dream about moving to a brand-new hospital with wonderfully clean wards and wonderfully inspired staff (with perfect hand hygiene). Surely then all of our infection control problems would be over forever, or would they?

Unless physicians within the hospital modified their patterns of antibiotic use, it is doubtful that our problems with antibiotic-resistant bacteria would be over. Selection of antibiotic-resistant organisms would almost certainly occur. The extent of the subsequent problem with antibiotic resistance would be determined in part by the level of misuse of antimicrobial agents. Antibiotic management or, as it is sometimes termed, antibiotic stewardship clearly has an integral role in infection control. It has long been appreciated that the use of narrower spectrum, more targeted antimicrobials for as short a time as possible is associated with a lower likelihood of the development of resistance. It can be difficult to promote the importance of this message to prescribers. They often consider the immediate interests of their patients as being of paramount importance and do not appreciate or observe the subsequent resistance problems that may arise.

Four articles in this issue of *Infection Control and Hospital Epidemiology* provide us with further data that will help us to promote rational antimicrobial prescribing.[1-4]

The article by Lodise et al. examines risk factors for bacteremia with methicillin-resistant versus methicillin-susceptible *Staphylococcus aureus* (MRSA vs MSSA).[3] Importantly, these authors take the local perspective in their assessment of risk factors for MRSA. Undoubtedly, they have read the numerous previous articles examining risk factors for MRSA infection. However, they realize that if they are going to reduce vancomycin use by promoting empiric use of antistaphylococcal beta-lactam antibiotics in preference to vancomycin in selected patients in their hospital, they are going to need local data to have confidence in their recommendations. Risk factors for methicillin resistance in Detroit may be different from risk factors for methicillin resistance in Des Moines, Dublin, or Darwin.

Their case–control study involved 494 patients with *S. aureus* bacteremia during 2½ years. Almost half of the infections (45.5%) were caused by MRSA. Onset of bacteremia while in the hospital, a history of hospitalization, and the presence of decubitus ulcers were associated with an increased likelihood of MRSA versus MSSA infection. However, the most significant predictive factor, with an odds ratio of 9.2, was prior antibiotic use. This study reinforces an association that has been established for many other organisms. Importantly, it also allows those advising antibiotic choice prior to susceptibilities becoming available to make recommendations with close to 90% certainty as to the likelihood of an organism being MRSA or MSSA. The next step is for these authors to show that with the use of the information from this study, vancomycin use can be decreased while maintaining favorable outcomes from staphylococcal bacteremias.

The long-term use of intravenous glycopeptides is sometimes clinically indicated and essential. There has been much concern over the long-term use of vancomycin leading to the development of colonization and infection with vancomycin-intermediate *S. aureus* (VISA). The article by Bernard et al. in this issue is encouraging in this regard.[2] For 34 patients with MRSA osteomyelitis, intravenous vancomycin was given in a standard dose (20 mg/kg/d) for a mean of 34 days or a high dose (40 mg/kg/d) for a mean of 37 days. Trough vancomycin levels of 10 to 15 mg/L were targeted in the patients given the standard dose and 20 to 25 mg/L in the patients given the high dose. Swabs from wounds, the anterior nares, and the groin were surveyed during therapy and 2 months after the

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cessation of therapy. No VISA or heterogeneous VISA isolates were detected.

There was also a significant and sustained reduction in MRSA colonization at these sites; the sustained effect was more apparent with the high dose than with the standard dose. Patients received intranasal mupirocin and applications of 4% chlorhexidine soap during the first week of vancomycin therapy. The suggestion that higher doses of vancomycin contributed to a sustained reduction in MRSA colonization is intriguing. A body of literature is also emerging describing mutant prevention concentrations (ie, it is possible that a concentration range of antibiotics exists in which antibiotic-resistant mutants are selected most frequently).[5] Maintenance of antibiotic levels above this concentration may reduce the opportunity for selection of antibiotic-resistant mutants. Clearly, much more needs to be learned about the relationship between antibiotic dosing and antibiotic concentrations and reduction in colonization with resistant organisms and selection of antibiotic-resistant mutants.

Donskey et al. have previously demonstrated that the use of certain antibiotics may be linked to an increased density of vancomycin-resistant enterococci (VRE) in the gastrointestinal tract, and subsequently an increased risk of environmental contamination with VRE.[6] This study underscored an important link between antibiotic use and the potential for horizontal transmission of antibiotic-resistant organisms.

Bhalla et al. have now found that antianaerobic antibiotic therapy promotes increased density of antibiotic-resistant gram-negative bacilli in the gastrointestinal tract.[1] In their 8-month prospective study of 140 stool samples from 37 VRE-colonized patients published in this issue, those who received drugs with antianaerobic activity had a significantly higher incidence and density of stool colonization with gram-negative bacilli resistant to ceftazidime, ciprofloxacin, or piperacillin/tazobactam. Although their study was restricted, for practical reasons, to patients with VRE colonization, there is no obvious reason to think that their results could not be extrapolated to those without VRE colonization. The same group recently showed that there was significant overuse of antibiotics with antianaerobic activity.[7] Studies are now needed in which it is shown that restriction of the use of antibiotics with antianaerobic activity is associated with a reduction in colonization with VRE and antibiotic-resistant gram-negative bacilli.

Finally, the article by Cordero and Ayers in this issue describes a retrospective study of 790 consecutive extremely low birth weight infants in 30 academic centers.[4] Ninety-four percent of these infants had blood cultures performed and empiric antibiotics prescribed for suspected early-onset sepsis. The clinical outcome was the same when those whose blood cultures were negative received short-term (3 days or less) or long-term (7 days or more) antimicrobial therapy. The authors concluded that, at least in this group of patients, discontinuation of empiric antimicrobials at approximately 48 hours was feasible and safe. This situation is somewhat analogous to that observed in adult intensive care practice whereby antimicrobial therapy is commenced for suspected ventilator-associated pneumonia. It is clear that some of these patients will turn out to have had pulmonary infiltrates due to pulmonary edema, pulmonary hemorrhage, or a host of other noninfectious etiologies. Singh et al. used a clinical scoring system that allowed safe, early discontinuation of antibiotic therapy for patients in whom infection was unlikely to be present.[8] Antibiotic management programs are likely to be quickly discredited by restricting the availability of antibiotics for the critically ill. It behooves us to develop mechanisms, like those of Singh et al., by which antibiotics are discontinued rapidly for critically ill patients shown not to have active infection.

The four studies mentioned above published in this issue of *Infection Control and Hospital Epidemiology* assist us in spreading some of the core messages of rational antimicrobial prescribing. (1) Prior antimicrobial use is the most significant factor in the development of resistance; this applies particularly to broad-spectrum agents and to a wide range of organisms. (2) The use of appropriately dosed, narrow-spectrum, targeted antimicrobials is associated with a lower risk of development of resistance than is the use of broad-spectrum agents and can also reduce colonization rates with resistant organisms. (3) Whereas the initiation of empiric antimicrobial therapy is often indicated when sepsis is suspected, such therapy can often be discontinued early without compromise to clinical outcome.

We need all the data we can get from studies such as these to encourage and enforce the rational use of antimicrobial agents. Antibiotic management and measures for preventing spread from patient to patient[9] will almost certainly be needed to reduce the harm emanating from antibiotic resistance in the years ahead.

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