Editorial

More Is More

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First, do no harm.—Hippocrates, 5th century BC

During the past two decades, antibiotic resistance among nosocomial pathogens has gone from bad to worse. According to intensive care unit (ICU) data from U.S. hospitals participating in the National Nosocomial Infections Surveillance System of the Centers for Disease Control and Prevention during the year 2000, 55% of nosocomial *Staphylococcus aureus* isolates were resistant to methicillin, 26% of nosocomial enterococcal isolates were resistant to vancomycin, and 35% of nosocomial *Enterobacter* species isolates were resistant to third-generation cephalosporins.[1] There is also substantial evidence that these organisms are not just confined to the acute care hospital but that they are also being spread and becoming highly prevalent among residents of long-term–care facilities (LTCFs).[2-16] Despite these disturbing data, there has been no concerted or consistently applied, evidence-based effort within the U.S. healthcare system to prevent the spread of these pathogens among the millions of patients entrusting us with their health and safety as they enter hospitals and LTCFs each year.

In this issue of *Infection Control and Hospital Epidemiology*, multiple studies provide important new insights into the epidemiology of colonization and infection with several important nosocomial pathogens, including vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and antibiotic-resistant gram-negative bacilli. Antimicrobial-resistant pathogens are often considered individually, with the relative importance assigned to each organism varying from institution to institution. It has been noted, however, that these pathogens often travel together due to similar modes of transmission, similar risk factors for acquisition,[17] and sharing of resistance determinants between pathogens. A particularly notable and worrisome example of the sharing of resistance mechanisms between pathogens was the recent identification of the *vanA* vancomycin resistance gene from VRE in clinical isolates of vancomycin-resistant *S. aureus*.[18,19]

Important new data in this area are presented by Donskey et al., who suggest that the benefit of identifying and isolating patients colonized with VRE may extend beyond that of preventing the spread of VRE.[20] A point-prevalence survey in a Veterans Affairs acute care facility and its associated nursing facility found that 19% of the study population had stool colonization with VRE. VRE-colonized patients were significantly more likely to be colonized with ceftazidime-resistant gram-negative bacilli than were patients who were not colonized with VRE (17% vs 4%; $P = .026$). During a 6-month follow-up period, VRE-colonized patients were also significantly more likely to have *Clostridium difficile*–associated diarrhea (26% vs 2%) and to have antibiotic-resistant gram-negative bacilli isolated from a clinical specimen (39% vs 11%). In addition, 4 (17%) of the 23 VRE-colonized patients were treated for MRSA infection during the follow-up period. Two (9%) of the VRE-colonized patients were colonized or infected with all three of the other pathogens included in the evaluation (ie, *C. difficile*, a resistant gram-negative bacillus, and MRSA). Diarrhea due to *C. difficile* in patients colonized with VRE has important implications for the spread of both pathogens.

On a similar note, Pacio et al. examined the relative frequency of colonization and infection and the rate of clearance of colonization with several antibiotic-resistant organisms (VRE, MRSA, and a select group of antibiotic-resistant gram-negative bacilli) among residents of an LTCF in New York.[21] During the 3-month enrollment period, the investigators identified 65 episodes of colo-

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nization among 49 residents. Colonization with MRSA (30 residents), VRE (27 residents), or both was more common than was colonization with resistant gram-negative bacilli (8 residents) in this setting. Thirteen residents, or 26% of the colonized residents, were colonized with more than one antibiotic-resistant organism. The findings of these two studies suggest a relatively high prevalence of simultaneous colonization with multiple antibiotic-resistant nosocomial pathogens among both hospital patients and LTCF residents.

Another important topic addressed in this issue is that of the clinical significance of colonization with antibiotic-resistant organisms. In addition to a relatively high prevalence of colonization with antibiotic-resistant organisms among LTCF residents, Pacio et al. found a high rate of infection due to these colonizing organisms.[21] Although the median duration of follow-up was only 65 to 77 days, infection was identified in 22%, 25%, and 50% of residents colonized with VRE, resistant gram-negative bacilli, and MRSA, respectively. In yet another article in this issue, Song et al. provide more evidence of both the clinical significance and the economic burden of infections caused by VRE.[22] In their large study, hospitalized patients with nosocomial VRE bacteremia had significantly greater mortality (22.6% attributable mortality), longer hospital (median, 25 days) and ICU (median, 17 days) stays, and greater hospital charges ($81,208 in excess charges per patient) than did non-bacteremic patients matched for severity of illness and other clinical factors. In regression analyses, VRE bacteremia was an independent risk factor for harm to patients: death, excess length of hospital stay, and excess charges. Data from studies in this issue confirm that infection is common among patients colonized with resistant organisms and that VRE is a pathogen of consequence, not merely a marker for severity of illness.

A final theme that emerges from several of the articles in this issue is related to methods of identification of individuals colonized with antibiotic-resistant organisms and how failure to detect and address the entire reservoir for spread can prevent successful control of these organisms. The inability of routine clinical cultures to identify most VRE-colonized patients is well illustrated by the studies of Warren et al.[23] and Donskey et al.[20] VRE was isolated from clinical specimens in only 10% and 17% of VRE-colonized patients participating in these two studies, respectively. In other words, in the absence of active surveillance cultures, 83% to 90% of colonized patients would have gone unidentified. Moreover, in the study of LTCF residents described by Pacio et al.,[21] only 43% of individuals colonized with antibiotic-resistant organisms had positive cultures at the time of admission to the LTCF, indicating that acquisition of the organism, or at least the onset of detectable colonization, occurred during residence in the LTCF for most participants. This may be explained in part by the relatively high prevalence of colonization in the study facility and the long duration of colonization that was documented, particularly for MRSA and VRE, resulting in a risk for spread to other residents, family members, and healthcare workers that persists for months.

The study reported by Warren et al. also illustrates some of the difficulties that arise when programs intended to control the spread of antibiotic-resistant organisms are not designed to identify and address the entire reservoir of ongoing spread in a facility.[23] During a period of 10 months, all patients admitted to the medical ICU at a large university hospital were screened for VRE colonization at the time of admission and weekly thereafter if previous cultures had been negative. The prevalence of VRE colonization at the time of admission was 25% and an additional 21% of those who were initially culture negative became VRE positive during their stay in the ICU. The incidence of subsequent VRE colonization among patients with negative cultures admitted to the ICU was 27 episodes of colonization per 1,000 patient-ICU days. Most patients colonized with VRE had had one or more previous admissions to the study facility and had been hospitalized for 3 or more days prior to transfer to the ICU. These findings seem to suggest that there likely was epidemiologically important "colonization pressure" and transmission of VRE among patients on other hospital units in the study facility.

The high rate of detection of VRE colonization among ICU patients who had negative cultures on admission might lead some to think that active surveillance cultures for VRE and contact precautions for colonized patients do not reduce the incidence of VRE colonization. However, as the authors noted, a more likely interpretation is that failure to control VRE in the study unit was due to implementation of the active surveillance program in a single hospital unit that accounted for only 1.3% of all hospital beds while unrecognized colonization and transmission were allowed to continue on all other hospital units from which many patients were subsequently transferred to the ICU. Detection of VRE in most of the hospital depended on culture of VRE from stool submitted for *C. difficile* testing, but studies have shown that this approach fails to detect most VRE-positive patients in high-risk wards.[24] Patients became culture positive a median of 6 days after transfer to the ICU, perhaps reflecting the accumulation of additional antibiotic-days in the ICU, which may have allowed previously colonized patients who were culture negative due to low colonic concentrations to become positive. The screening and isolation protocol also would have allowed for transmission within the study unit during the 1 to 2 days between admission and the availability of screening culture results for the 25% who were culture positive on arrival. This is similar to previously published studies that have documented only modest control of VRE when control efforts have focused on only a single high-risk unit or two rather than the entire population at risk for spread.[25-29]

Numerous institutions in which surveillance and isolation strategies have been more widely applied have reported more successful outcomes.[11,30-36] For example, during the initial VRE outbreak at the University of

Virginia Hospital, one ICU was found to have a 100% prevalence of VRE.[35] This was reduced to 0% and kept there for the next year using active surveillance cultures and contact precautions, but these measures were being applied throughout the hospital to control spread wherever colonized patients could be detected, not just in a single unit.

In the context of the consistently increasing prevalence of antibiotic-resistant nosocomial pathogens within the U.S. healthcare system, the observations reported in the study by Warren et al.[23] may represent a microcosm of what is occurring on a nationwide basis. In other words, even the most comprehensive control efforts will not be effective in controlling the overall burden of antibiotic-resistant nosocomial pathogens in this country if they are implemented in only a few healthcare facilities. Although recommendations for the prevention and control of vancomycin resistance have been available since 1995,[37] most U.S. hospitals and LTCFs have not performed active surveillance to detect patients colonized with these organisms[38,39] and therefore currently identify only a small fraction of the colonized population,[40,41] resulting in uncontrolled transmission of these organisms within these facilities. Based on a growing amount of evidence, comprehensive control efforts that incorporate active surveillance cultures for patients at risk for colonization, contact precautions for all colonized patients, appropriate use of antimicrobial agents, and compliance with hand hygiene recommendations appear to have the greatest likelihood of success. Unless and until adequate interventions are made nationwide, the numbers of individuals seeking care each year in the U.S. healthcare system who become colonized and infected with antibiotic-resistant nosocomial pathogens will continue to increase unnecessarily.

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