What Infection Control Interventions Should Be Undertaken to Control Multidrug-Resistant Gram-Negative Bacteria?

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Multidrug-resistant gram-negative bacteria are an emerging problem that infection control practitioners, hospital epidemiologists, clinicians, and hospital administrators are struggling to control. The National Nosocomial Infections Surveillance System has reported that the prevalence of multidrug-resistant gram-negative bacteria is increasing. The prevalences of imipenem-resistant Pseudomonas aeruginosa, quinolone-resistant P. aeruginosa, third-generation cephalosporin-resistant P. aeruginosa, third-generation cephalosporin-resistant Enterobacter species, and third-generation cephalosporin–resistant Klebsiella pneumoniae among clinical isolates collected from patients in intensive care units (ICUs) have all increased by >20% in 2003, compared with prevalences in 1998–2002 [1]. Similar increases in multidrug-resistant gram-negative bacteria prevalence are being seen worldwide [2–4].

The potential considerable morbidity and mortality from infections with multidrug-resistant gram-negative organisms are exacerbated by 2 factors. First, there are few if any antibiotics in development to treat these infections, resulting in the use of older antibiotics whose use was previously discontinued because of toxicity [5–7]. Second, much of the research on the effectiveness of infection control measures in preventing transmission has focused on antibiotic-resistant gram-positive bacteria.

Here, we address the following questions: (1) should active surveillance be performed to identify patients colonized with multidrug-resistant gram-negative bacteria, and (2) should contact isolation precautions be taken with patients colonized or infected with multidrug-resistant gram-negative bacteria? These questions cannot be answered in an evidenced-based manner to the extent we would desire. Thus, there is a tremendous need for future research to provide better evidence to address these important questions. As well, considerably less information regarding these questions exists for antibiotic-resistant gram-negative bacteria than for methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, yet there is still tremendous controversy about the role of active surveillance and, to a lesser extent, contact precautions for these antibiotic-resistant gram-positive bacteria [8–10].

In the present article, we first outline the data and variables that are needed to scientifically answer these questions. We then review the existing data on P. aeruginosa, Enterobacteriaceae (Escherichia coli and Klebsiella species in particular), and Acinetobacter baumannii.
Factors that influence the acquisition of a nosocomial antibiotic-resistant bacterial infection

**Siella species in particular**, and *Acinetobacter baumannii*, and, finally, we reach conclusions and make suggestions for the future.

**KEY VARIABLES IN DECIDING WHETHER ACTIVE SURVEILLANCE OR CONTACT ISOLATION IS NEEDED**

The 2 most important parameters for deciding whether active surveillance and contact isolation precautions should be implemented for each multidrug-resistant gram-negative bacterium are the organism-specific proportion of antibiotic resistance attributable to antibiotic use (i.e., the attributable fraction due to antibiotic use) and the organism-specific attributable fraction due to patient-to-patient transmission. With these parameters, relatively simple cost-effectiveness studies could be performed and could yield the answers for hospital epidemiologists and, potentially, for society as a whole. However, at present, no accurate estimates of these parameters exist for any multidrug-resistant gram-negative bacteria in the non-outbreak setting.

Many factors have contributed to this current lack of knowledge. These include a lack of studies measuring these parameters in the nonoutbreak setting, the limited sample sizes in existing studies, the variable and sometimes poor molecular epidemiological techniques used to quantify patient-to-patient transmission, a lack of basic scientific information on the impact of antibiotic resistance on virulence and gut ecology, and the poor epidemiological and statistical methods used to assess the causality of antibiotics in resistance. However, even with the best epidemiological intentions, the complicated interplay of causal factors makes ascertaining and quantifying the attributable fraction due to antibiotics versus patient-to-patient transmission difficult (figure 1).

However, with a limited infection control budget, cost-effective decisions still need to be made. We propose that assessment of the variables listed below is needed to address whether active surveillance should be performed to identify patients colonized with multidrug-resistant gram-negative bacteria and, thus, to control the increasing emergence of multidrug-resistant gram-negative bacteria, as well as whether contact precautions should be implemented for patients colonized or infected with multidrug-resistant gram-negative bacteria.

**Undetected ratio.** The undetected ratio is the proportion of patients undetected by clinical cultures among all patients colonized or infected with a specific antibiotic-resistant organism. The higher the ratio, the more effective active surveillance culturing will be at detecting patients not known to be colonized with antibiotic-resistant gram-negative bacteria who are at risk of transmitting the antibiotic-resistant bacteria to other patients.

Exact measurement of the undetected ratio is likely unattainable, given the limited sensitivity and specificity of culture of swab samples in identifying colonized persons [11]. However, estimates from previous studies are available and are calculated as the proportion of patients detected using surveillance cultures among patients detected using both surveillance and clinical cultures. Thus, in previous studies, it has been estimated that the undetected ratio of vancomycin-resistant enterococci is ∼90% [12–15]. For methicillin-resistant *S. aureus*, the undetected ratio varies between 30% and 90% [16–18]. It is hypothesized that the undetected ratio for antibiotic-resistant gram-negative bacteria is likely to be lower than that for van-

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**Figure 1.** Factors that influence the acquisition of a nosocomial antibiotic-resistant bacterial infection
comycin-resistant enterococci and methicillin-resistant \textit{S. aureus} because of the increased virulence of gram-negative bacteria. We previously found that, among patients admitted to the medical or surgical ICU, the undetected ratio for extended-spectrum \(\beta\)-lactamase–producing \textit{E. coli} and \textit{Klebsiella} species was 69\% \[19\]. Bertrand et al. \[20\] reported the undetected ratio for non–antibiotic-resistant \textit{P. aeruginosa} in the ICU setting to be 55\%.

\textbf{Duration of colonization.} The duration of colonization represents the amount of time that patients remain colonized with antibiotic-resistant bacteria. This variable is important because it determines the impact of patient isolation on patient-to-patient transmission during the period of hospitalization during which patients are identified as being colonized with antibiotic-resistant gram-negative bacteria and also during future hospitalizations. Some argue that the dictum “once colonized, always colonized” is true: The appearance of having cleared colonization is likely a result of errors in culturing, poor sensitivity of the surveillance culturing methods, and removal of the antibiotic selective pressure. However, the official guideline of the Hospital Infection Control Practices Advisory Committee for vancomycin-resistant enterococci is that, after 3 negative culture results (\(\geq 1\) week apart), patients may be removed from isolation precautions \[21\]. Some have interpreted this rule of 3 negative culture results as applying to all antibiotic-resistant organisms.

The duration of colonization for most antibiotic-resistant bacteria is unknown. However, studies have attempted to estimate this parameter for methicillin-resistant \textit{S. aureus} \[22–24\], vancomycin-resistant enterococci \[25\], multidrug-resistant \textit{K. pneumoniae} \[26\], and multiple antibiotic-resistant pathogens \[27\]. A recent study of residents of long-term-care facilities found that those colonized with resistant \textit{A. baumannii} and \textit{P. aeruginosa} were significantly more likely to clear their colonization than were residents colonized with methicillin-resistant \textit{S. aureus} or vancomycin-resistant enterococci \[27\]. For vancomycin-resistant enterococci, the literature estimates the duration of colonization to be \(\geq 60\) days \[25, 27, 28\]. A retrospective cohort study of 116 patients colonized with vancomycin-resistant enterococci found that 64\% had a negative result of perirectal culture for vancomycin-resistant enterococci after a mean follow-up period of 125 days \[25\]. Two studies have demonstrated that patients may have prolonged colonization with methicillin-resistant \textit{S. aureus}, in excess of 1 year, despite active decolonization efforts or hospital discharge and resulting absence of antibiotic selective pressure \[22, 23\]. Last, a small study of patients discharged to nursing homes reported that the mean duration of colonization with multidrug-resistant \textit{K. pneumoniae} was 160 days (range, 7–548 days) \[26\].

\textbf{Colonization pressure.} The importance of colonization pressure was first described by Bonten et al. \[29\] in a study of transmission of vancomycin-resistant enterococci in a medical ICU. Colonization pressure represents the prevalence of resistance in the surrounding environment—that is, in the environment that can lead to patient-to-patient transmission. The following example illustrates the importance of colonization pressure. A patient admitted to a 10-bed ICU in which 5 patients are colonized or infected with vancomycin-resistant enterococci is at greater risk of acquiring vancomycin-resistant enterococci than is the same patient admitted to an identical 10-bed ICU (under the assumption that the severity of illness of patients, antibiotic use, and all important causal and confounding variables are the same) in which only 1 patient is colonized or infected with vancomycin-resistant enterococci. This difference is a result of higher colonization pressure, most likely leading to higher environmental contamination rates, and of higher transient rates of hand carriage by health care workers, leading to higher rates of patient-to-patient transmission. Other studies have estimated the importance of colonization pressure and environmental contamination for transmission of methicillin-resistant \textit{S. aureus} \[30, 31\]. However, to our knowledge, the importance of colonization pressure in transmission of multidrug-resistant gram-negative bacteria has not been estimated.

\section*{EXISTING DATA FOR ANTIBIOTIC-RESISTANT GRAM-NEGATIVE BACTERIA}

\textbf{Pseudomonas.} To our knowledge, limited data exist on the attributable fraction due to patient-to-patient transmission that accounts for colonization or infection with antibiotic-resistant \textit{P. aeruginosa} in the nonoutbreak setting. Existing estimates of the percentage of antibiotic-resistant \textit{P. aeruginosa} attributable to patient-to-patient transmission have ranged from 18\% in a hospital-wide setting with existing isolation procedures to 29\%–64\% in ICU settings to 79\% in a long-term-care facility \[32–35\]. The majority of published studies have attempted to quantify the amount of patient-to-patient transmission of \textit{P. aeruginosa} independent of antibiotic susceptibility. In this area, tremendous controversy exists, with reported rates ranging from 0\% to 50\% \[20, 36–40\]. Unlike the case with other organisms, the importance of water colonization with \textit{P. aeruginosa} is another controversial area \[41, 42\].

\textbf{Enterobacteriaceae.} Published studies have not been in agreement on the attributable fraction due to patient-to-patient transmission for extended-spectrum \(\beta\)-lactamase–producing \textit{E. coli} and \textit{Klebsiella} species \[43, 44\]. Two studies used molecular methods based on the hypothesis that patient populations in which isolates are genetically similar are most likely acquiring the organism via patient-to-patient transmission. One study of an 18-month cohort of patients undergoing organ transplantation used pulsed-field gel electrophoresis to demonstrate that 66 of 69 isolates were unique \[43\]. However,
another study conducted in France reported that, of the 55 hospital-acquired cases of colonization, >85% were due to the same genotype [44]. A study of nursing home and residential home residents in Scotland reported that, despite some environmental contamination, there was no evidence of transmission from patients known to be colonized or infected with multidrug-resistant *K. pneumoniae* who were discharged from the hospital [26].

**Acinetobacter.** Antibiotic-resistant *A. baumannii* is an emerging problem that seems to have acutely worsened in the past 10 years [6, 45, 46]. Incidences of carbapenem-resistant *A. baumannii* are increasing worldwide [47, 48]. The present antibiotic-resistant *A. baumannii* appears to be different from the earlier strains of *A. baumannii* in terms of its increasing incidence among both susceptible and antibiotic-resistant bacterial strains and its increase in interhospital transfer [49–51]. Reasons for these increases are still unclear. Thus, data are even more limited, in that the earlier literature on *Acinetobacter* species that often linked increases in the number of organisms to contaminated respiratory equipment may no longer be applicable. To our knowledge, no studies have quantified the attributable fraction due to patient-to-patient transmission versus antibiotic selective pressure for acquisition of *A. baumannii.*

**CONCLUSION AND RECOMMENDATIONS**

The present literature does not provide sufficient data to determine infection control measures that would be effective in controlling the spread of multidrug-resistant gram-negative bacteria. At our institution, University of Maryland Medical System, even with the limited data available, we are presently isolating patients who have clinical culture results that are positive for gram-negative bacteria susceptible to only 1 antibiotic. We have chosen to use active surveillance culturing for antibiotic-resistant gram-negative bacteria only in the outbreak setting. We recommend that future research aim to quantify the attributable fraction due to patient-to-patient transmission for antibiotic-resistant gram-negative bacteria, using large cohort studies. Other studies should measure key variables, including duration of colonization, the undetected ratio, and colonization pressure. Although the duration of colonization and undetected ratio represent universal or relatively constant values, colonization pressure varies both between locations and over time and therefore needs to be measured in the individual institution where the decision is being made. Future studies with larger sample sizes combining clinical research and molecular epidemiological techniques need to be done with adequate statistical power to separate the numerous causal risk factors and identify the attributable fraction due to antibiotics as a whole and individually and the attributable fraction due to patient-to-patient transmission while controlling for important confounding variables such as comorbidity and severity of illness.

At present, modeling studies may help us in making decisions that need to be made immediately [52]. We hope that future research will help us make more-educated infection control decisions that will help curb the increasing emergence of antibiotic-resistant gram-negative bacteria.

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