The Role of the Intestinal Tract as a Reservoir and Source for Transmission of Nosocomial Pathogens

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The intestinal tract provides an important reservoir for many nosocomial pathogens, including *Enterococcus* species, Enterobacteriaciae, *Clostridium difficile,* and *Candida* species. These organisms share several common risk factors and often coexist in the intestinal tract. Disruption of normal barriers, such as gastric acidity and the indigenous microflora of the colon, facilitates overgrowth of pathogens. Factors such as fecal incontinence and diarrhea contribute to the subsequent dissemination of pathogens into the health care environment. Selective pressure exerted by antibiotics plays a particularly important role in pathogen colonization, and adverse effects associated with these agents often persist beyond the period of treatment. Infection-control measures that are implemented to control individual pathogens may have a positive or negative impact on efforts to control other pathogens that colonize the intestinal tract.

The large intestine provides an important reservoir for many nosocomial pathogens. These include *Enterococcus* species, Enterobacteriaciae and other gram-negative bacilli, *Clostridium difficile* , and *Candida* species [1–6]. Recent data suggest that the intestinal tracts of hospitalized patients may also be an important reservoir of *Staphylococcus aureus* [7]. Although the clinical manifestations of these pathogens are diverse, a common pathogenesis is involved in their colonization of and dissemination from the intestinal tract [1–7]. These pathogens also share many common risk factors and often coexist in the intestinal tract [6–9]. This review will examine common factors that facilitate intestinal colonization and subsequent transmission of nosocomial pathogens. The role of potentially modifiable factors, such as antibiotic therapy, will be emphasized, and implications for infection control will be discussed.

INDIGENOUS MICROFLORA OF THE COLON AS A DEFENSE AGAINST COLONIZATION BY NOSOCOMIAL PATHOGENS

The human colon contains as many as 10^{12} bacteria per gram of contents and >100 bacterial species [1]. These indigenous bacteria are important for host defense because they inhibit the growth of potentially pathogenic microorganisms. This defense mechanism, termed "colonization resistance," can be applied to prevention of colonization by exogenously introduced organisms and to prevention of overgrowth by potential pathogens, such as *Escherichia coli* [1]. Multiple mechanisms may contribute to inhibition of pathogens, including depletion of nutrients, prevention of access to adherence sites or niches associated with the mucosa, and production of inhibitory substances or conditions (e.g., volatile fatty acids and anaerobic conditions) [1, 10]. On the basis of studies of mice and humans treated with antibiotics and with use of in vitro models, it has been suggested that obligate anaerobes play a crucial role in colonization resistance; however, the specific members of the microflora that inhibit colonization by pathogens are not known [1–3, 10].

The efficacy of colonization resistance is illustrated by the situation of health care workers, whose hands and clothing frequently become contaminated with nosocomial pathogens capable of colonizing the intestinal tract, including *C. difficile,* vancomycin-resistant enterococci (VRE), antibiotic-resistant gram-negative bacilli, and *Candida* species. It is likely that small numbers of these pathogens are intermittently ingested, particularly given the low levels of compliance of health care workers with recommended hand hygiene practices. However, intestinal colonization with detectable levels of antimicrobial-resistant pathogens and *C. difficile* diarrhea remain uncommon among health care workers because the indigenous

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microflora inhibit growth of these organisms [2, 11]. Health care workers should be aware, however, that disturbance of their colonic microflora may place them at risk. For example, a colleague and I [11] reported the case of a patient transporter who developed *C. difficile* diarrhea and VRE colonization after receiving clindamycin.

FACTORS THAT FACILITATE INTESTINAL OVERGROWTH AND TRANSMISSION OF NOSOCOMIAL PATHOGENS

Among patients in health care settings, a variety of factors facilitate intestinal overgrowth and subsequent transmission of nosocomial pathogens (figure 1). Some of these factors are intrinsic to the patient populations involved, whereas others are iatrogenic factors that may be amenable to intervention. Although most interest has been focused on *C. difficile* and antimicrobial-resistant pathogens, the same pathogenesis contributes to overgrowth and transmission of organisms that are more susceptible to antimicrobials. Nosocomial pathogens may be acquired exogenously or may be present among the indigenous microflora at admission (figure 1). VRE and *C. difficile* are usually acquired in health care settings, whereas *Enterobacter* species and *Candida albicans* often emerge from the indigenous microflora [4, 12].

Exposure to nosocomial pathogens. The hands of health care workers are considered to be the major source of transmission of pathogens from patient to patient. Contaminated medical devices or environmental surfaces may also contribute to transmission, particularly for organisms that survive for prolonged periods on surfaces (e.g., *C. difficile* and VRE)

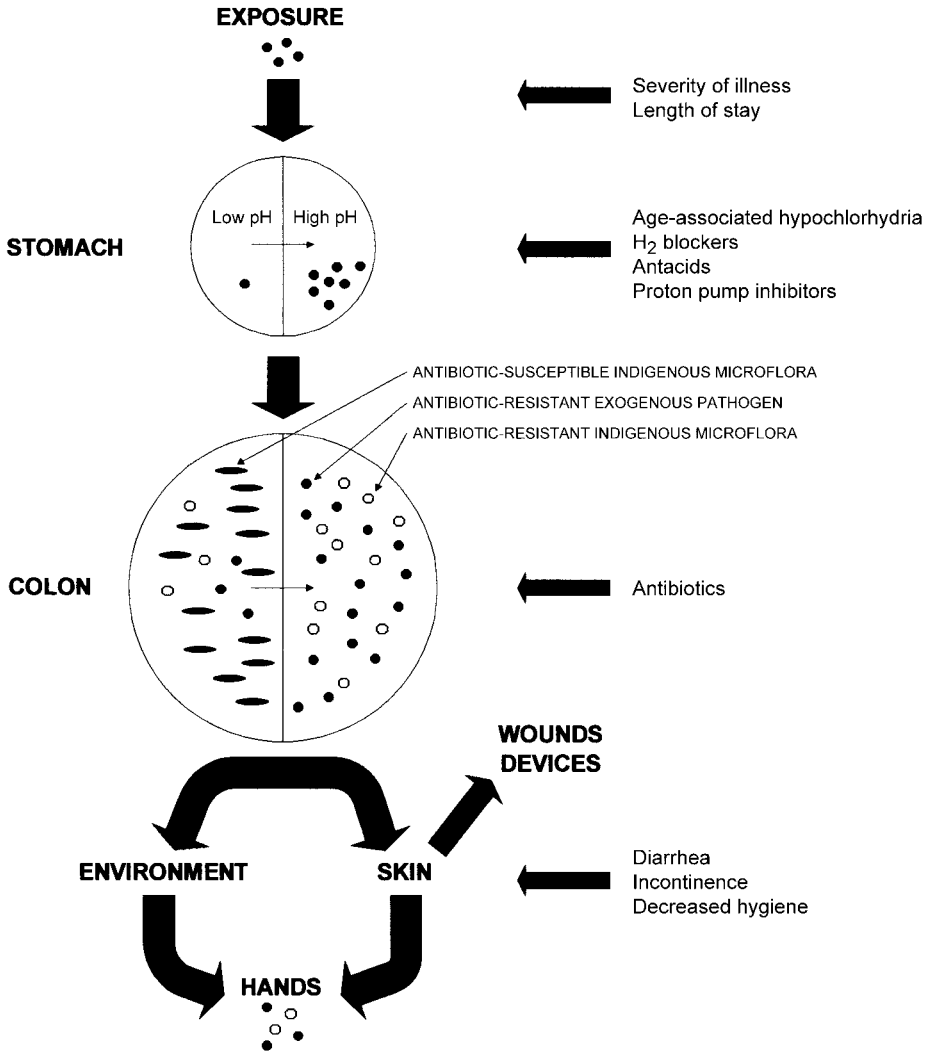

Figure 1. Factors that facilitate intestinal overgrowth and transmission of nosocomial pathogens. The left halves of the circles illustrate the presence of normal acidity in the stomach and intact indigenous microflora in the colon; the right halves illustrate the effects of increased stomach pH and antibiotic selective pressure in the colon.

[2, 3]. Increased severity of illness and prolonged duration of hospitalization place patients at increased risk for acquisition of pathogens, in part because these factors result in increased opportunities for interaction with health care workers and contaminated surfaces or devices.

Reduction in gastric acidity. The acidic pH of the stomach reduces the number of ingested microorganisms that enter the intestinal tract [13]. More than 99.9% of ingested coliform bacteria are killed within 30 min by normal gastric acidity [13]. Although *C. difficile* spores pass into the intestinal tract, 99% of vegetative cells are killed in the stomach [2]. Medications that inhibit production of stomach acid (e.g., proton pump inhibitors and H_2 blockers) have been associated with several pathogens, including *C. difficile, S. aureus* , VRE, and gram-negative bacilli [7, 13, 14]. The association between nasogastric tubes and/or enteral feeding and pathogens may be attributable, in part, to the fact that these interventions bypass or buffer the gastric acid barrier [8]. Nasogastric tubes may also facilitate colonization of the oropharynx by gram-negative pathogens, such as *Pseudomonas aeruginosa;* the ability of these pathogens to adhere to plastic surfaces and form biofilm may contribute to colonization of this site [15].

Alteration of the colonic microflora. Antibiotics that are excreted into the intestinal tract exert selective pressure on the microflora. The magnitude of the effect of antibiotics is determined by the concentrations achieved, the degree of inactivation that occurs, and the activity of agents under the in vivo conditions in the colon [1, 16]. Studies of the in vivo effect of antibiotics on the microflora provide a useful reference when considering the potential impact that agents may have on pathogen colonization [16]. Selective pressure results in inhibition of susceptible members of the indigenous microflora and facilitates overgrowth of antibiotic-resistant members of the indigenous microflora, as well as overgrowth of ingested antibiotic-resistant pathogens (figure 1). Such overgrowth may have important infection-control implications. For example, increased density of VRE colonization has been associated with increased frequency of environmental contamination [3]. Overgrowth of pathogens may also facilitate antibiotic-resistance gene transfer and translocation across the intestinal lining.

Fecal contamination. Dissemination of pathogens from the intestinal tract to environmental surfaces and patients' skin creates what has aptly been termed a "fecal veneer" in health care settings. Health care workers' hands frequently become contaminated after contact with this veneer (figure 2) [17, 18]. Contamination of patients' skin with VRE may result in false-positive blood culture results. Fecal incontinence and diarrhea contribute to fecal contamination; however, continent VRE-colonized patients also frequently contaminate surfaces in their rooms [17]. Factors that reduce standards of hygiene (e.g., alteration of mental status and debilitation) also contribute to the likelihood of fecal contamination.

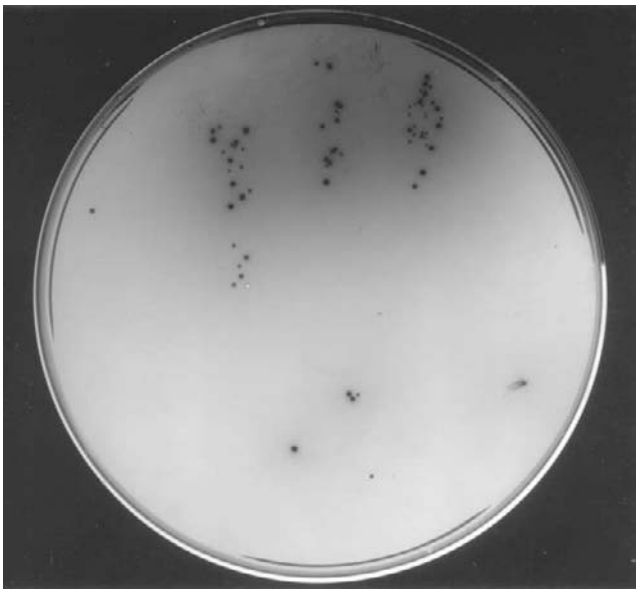

Figure 2. Gloved-hand imprint culture demonstrating vancomycin-resistant *Enterococcus faecium* contamination after brief examination of a colonized patient's abdomen (from [18]).

Immunosuppression. The immune system plays an important role in the pathogenesis of *C. difficile* infection [19]. The development of a systemic antibody response to *C. difficile* toxin A protects against development of acute diarrhea and against recurrence [19]. Although colonization is not prevented, an antibody response might reduce transmission of infection by preventing diarrhea. The immune system plays a role in preventing clinical disease due to other pathogens, but it is not known whether host immunity has an impact on colonization with these organisms.

COEXISTENCE OF MULTIPLE NOSOCOMIAL PATHOGENS IN THE INTESTINAL TRACT

Nosocomial pathogens often coexist in the intestinal tract [6–9]. Figure 3 illustrates concurrent overgrowth of multiple pathogens in the stool of a patient. One implication of such coexistence of pathogens is that control measures implemented for one pathogen may have an impact (positive or negative) on coexisting pathogens. Coexistence of multiple pathogens also has implications for efforts to cohort patients who carry particular antibiotic-resistant pathogens. For example, a VRE-colonized patient sharing a room with the patient shown in figure 3 could be exposed to methicillin-resistant *S. aureus* and antibiotic-resistant gram-negative bacilli. The coexistence of pathogens also provides an opportunity for transfer of antibiotic-resistance genes. For example, VRE-colonized patients often have coexisting intestinal colonization with *S. aureus,*

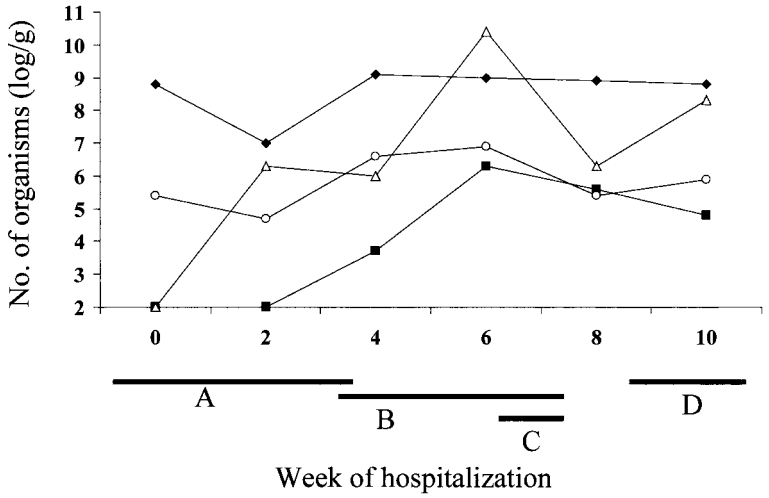

Figure 3. Coexisting overgrowth of vancomycin-resistant enterococci (VRE) *(solid diamonds)*; *Escherichia coli* that is resistant to ciprofloxacin, ceftazidime, and piperacillin-tazobactam *(open triangles)*; *Candida albicans (open circles)*; and methicillin-resistant *Staphylococcus aureus* (MRSA) *(solid squares)* in stool samples from a 54-year-old man who developed multiple complications after undergoing vascular surgery. The patient also had overgrowth of multidrug-resistant *Enterobacter cloacae* in stool (not shown) and developed *Clostridium difficile* diarrhea after week 10 of hospitalization. Antibiotic therapy included the following: vancomycin, rifampin, and linezolid (regimen A); clindamycin and ciprofloxacin (regimen B); metronidazole and cefepime (regimen C); and meropenem (regimen D). Clinical cultures during the study yielded *E. coli* and *E. cloacae* from pus samples obtained from a perirectal abscess, MRSA and VRE from blood samples, and *C. albicans* from sputum samples.

providing a potential reservoir for emergence of vancomycin-resistant *S. aureus* [7].

ANTIBIOTICS AND PATHOGEN COLONIZATION

Assessing the clinical literature. Clinical studies provide invaluable information regarding the association of particular antibiotics with pathogens, but some limitations should be acknowledged. Patients often receive multiple antibiotics simultaneously or sequentially, making it difficult to determine the effect of individual agents. Classes of antibiotics are sometimes grouped together despite the fact that individual agents within the class differ significantly. For example, cephalosporins include agents with potent antianaerobic activity that are excreted in high concentrations in bile (e.g., cefoxitin) and agents with relatively little antianaerobic activity that are minimally excreted in bile (e.g., cefepime) [3, 16]. Studies that evaluate the effect of formulary changes on rates of colonization or infection with nosocomial pathogens are subject to bias due to difficulties in controlling for nonantimicrobial-related confounding factors, and group-level effect estimates may not reflect the biological effect at the individual-patient level.

Given the limitations of clinical studies, it is helpful to apply 3 criteria when navigating the maze of conflicting data and opinions regarding antibiotics and nosocomial pathogens. First, do multiple studies consistently associate use of an antibiotic with a pathogen? Second, is an association microbiologically plausible? Third, what potential impact could an antibiotic have on pathogens that are not the focus of a study? On the basis of these criteria, it is believable that third-generation cephalosporins are an important risk for VRE because multiple studies have demonstrated this association and because these agents disrupt the anaerobic microflora but have minimal activity against enterococci [3]. Third-generation cephalosporins also promote intestinal colonization with *Candida* species, cephalosporin-resistant gram-negative bacilli, and *C. difficile*, suggesting that restriction of these agents might have a broad impact [9]. In contrast, recent studies that have strongly associated fluoroquinolones (such as ciprofloxacin and levofloxacin) with *C. difficile* infection require further confirmation [20]. Other studies suggest that these fluoroquinolones, which cause relatively little disruption of the anaerobic microflora, are a relatively infrequent cause of *C. difficile* diarrhea, particularly when administered as monotherapy [16, 21].

Animal models. Figure 4*A* provides a general framework for considering the effects of antibiotics on pathogen colonization. During therapy, antibiotics that are excreted into the intestinal tract may inhibit both pathogens and competing members of the indigenous microflora. After completion of therapy, the indigenous microflora recover over a period of days to weeks. Susceptibility to overgrowth of pathogens may persist during the period of recovery of the indigenous microflora. For example, risk of *C. difficile* infection may persist for $\geqslant$1 month after antibiotic treatment is discontinued.

Figures 4*B* and 4*C* summarize our findings from several mouse model studies of VRE colonization [5, 22], which illustrate the tenuous balance that may exist between inhibition

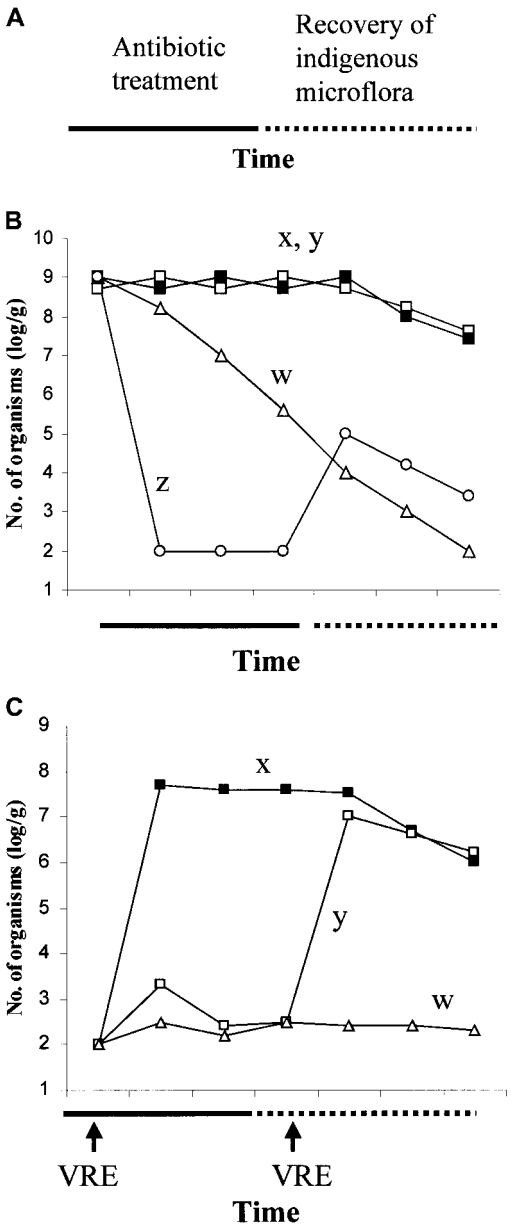

Figure 4. Effect of antibiotic treatment on vancomycin-resistant *Enterococcus* intestinal colonization in mice. *A,* General framework for considering the effect of antibiotics on pathogen colonization. *B,* Effect of antibiotic treatment on vancomycin-resistant enterococci (VRE) colonization that was previously established (the persistence model). *C,* Effect of antibiotic treatment on establishment of colonization of VRE that was administered orally (10,000 colony-forming units), both during and after completion of antibiotic treatment (the establishment model). Four potential effects of antibiotic treatment are shown: w, antibiotics that do not disrupt the anaerobic microflora (e.g., cefepime or aztreonam); x, antibiotics that disrupt the anaerobic microflora and possess minimal antienterococcal activity (e.g., clindamycin or cefoxitin); y, antibiotics that disrupt the anaerobic microflora and possess moderate antienterococcal activity (e.g., piperacillin-tazobactam); and z, antibiotics that disrupt the anaerobic microflora and possess potent activity against VRE (e.g., bacitracin).

of pathogens and inhibition of competing microflora [4, 5, 22]. In figure 4*B*, VRE colonization was established before antibiotic treatment was started (the persistence model); in figure 4*C*, VRE was administered orally during and/or after completion of subcutaneous antibiotic treatment (the establishment model). Antibiotics that did not disrupt the anaerobic microflora (e.g., cefepime or aztreonam) did not promote VRE colonization. Cefepime and aztreonam have minimal antianaerobic activity, and cefepime is minimally excreted in bile [16]. Antibiotics that disrupted the anaerobic microflora and possessed minimal antienterococcal activity (e.g., clindamycin or cefoxitin, with MICs of >10,000 μg/mL for the VRE test strain) promoted colonization (figure 4*B* and 4*C*). An antianaerobic antibiotic that possessed moderate antienterococcal activity and is excreted in high concentrations in bile (i.e., piperacillin-tazobactam, with an MIC of 625 μg/mL for the test strain) inhibited establishment of VRE colonization during treatment but promoted overgrowth when exposure to VRE occurred during the period of recovery of the indigenous microflora (figure 4*C*). When VRE colonization was established before treatment was commenced (figure 4*B*), piperacillin-tazobactam promoted persistent overgrowth. Finally, antibiotics with potent activity against VRE (e.g., bacitracin) inhibited colonization, but relapses after discontinuation of treatment were common (figure 4*B*).

How well do findings in mice correlate with data from patients? Among patients with established VRE or antibiotic-resistant gram-negative bacillus colonization, antibiotic regimens with potent antianaerobic activity, including piperacillin-tazobactam, promoted persistent overgrowth [3, 6]. Antibiotics with minimal antianaerobic activity did not promote overgrowth of VRE [3], but limited data are available regarding the effects of such agents on VRE and other pathogens. We found that intensive care unit patients who received piperacillin-tazobactam frequently acquired VRE colonization; however, these patients often received concurrent or sequential treatment with other antibiotics that have been shown to promote VRE [23]. Piperacillin-tazobactam has not been associated with VRE in case-control studies, and substitution of this agent for third-generation cephalosporins has been associated with reductions in the incidence of VRE [22, 23]. Additional data are therefore needed to clarify the effect of piperacillin-tazobactam on VRE colonization.

IMPLICATIONS FOR INFECTION CONTROL

Because nosocomial pathogens that colonize the intestinal tract share similar risk factors and pathogenesis (figure 1), the opportunity exists to implement control measures that may limit transmission of multiple pathogens. Conversely, some strategies that target individual pathogens may have unintended adverse effects on other organisms. This review will focus on a few

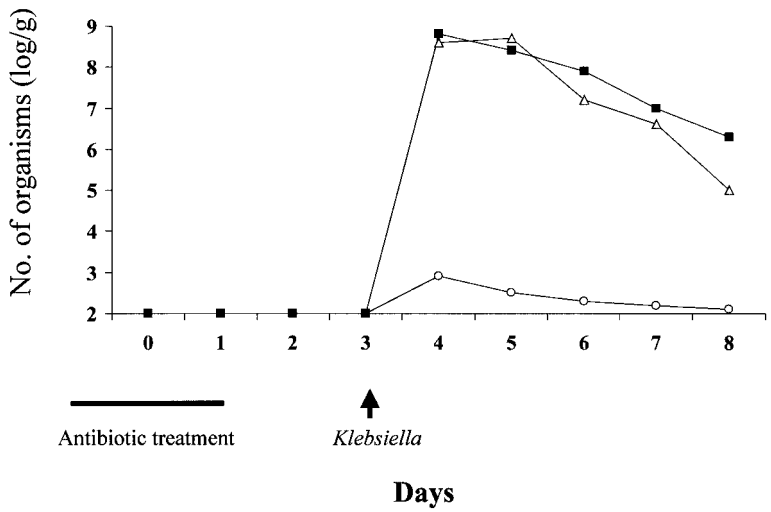

Figure 5. Effect of subcutaneous antibiotic treatment on establishment of colonization by extended-spectrum β-lactamase–producing *Klebsiella pneumoniae* in mice. Subcutaneous antibiotic regimens included ciprofloxacin *(circles),* ciprofloxacin in combination with clindamycin *(squares),* or cefotetan *(triangles)* once daily for 3 days. Ten thousand colony-forming units of the *K. pneumoniae* test strain were administered.

promising or controversial areas in which additional research is needed.

"Selective" decontamination of the intestinal tract. The goal of selective decontamination is to selectively inhibit pathogens in the gastrointestinal tract without disturbing the anaerobic microflora [1]. Nonabsorbed oral antibiotics are administered, with or without concurrent intravenous antibiotics. In theory, selective decontamination has tremendous potential, because it addresses a major source of pathogen dissemination. However, selective decontamination may be associated with overgrowth and infections due to pathogens that are resistant to the agents being administered [24]. In part, this reflects the fact that selective decontamination regimens are seldom truly selective. For example, oral ramoplanin and bacitracin inhibit VRE and gram-positive anaerobes in the colon and, therefore, may facilitate overgrowth of gram-negative pathogens in mice (author's unpublished data).

Antibiotic use strategies. Numerous studies have demonstrated that antimicrobials are often used unnecessarily in hospitals and nursing homes [25]. For example, we found that 30% of all antimicrobial-days of therapy in a teaching hospital were unnecessary [25]. Antianaerobic agents that promote overgrowth of VRE and antibiotic-resistant gram-negative bacilli accounted for 35% of these unnecessary days of therapy [3, 6]. Antimicrobials were frequently administered for longer-than-recommended durations or to treat noninfectious or nonbacterial syndromes [25]. Efforts to minimize such overuse of antibiotics are clearly needed. Unfortunately, antibiotic management programs face a number of theoretical and practical obstacles.

One obstacle facing antibiotic-control programs is that even a few doses of some antibiotics may cause prolonged disruption of the colonic microflora [1, 3, 16]. For example, 1 or 2 days of antianaerobic therapy promoted overgrowth of VRE among colonized patients that persisted for weeks [3]. Therefore, control programs should ideally strive to prevent initiation of unnecessary therapy. In practice, it is often easier to streamline or discontinue empirical therapy if culture results are available or if infection seems unlikely. If total antibiotic exposure is reduced, however, such interventions may have an effect. Singh et al. [26] found that patients with suspected ventilator-associated pneumonia who received 3 days of ciprofloxacin followed by discontinuation of therapy (if infection was unlikely) had lower rates of superinfection and antimicrobial resistance than did patients who were given standard therapy consisting of a variety of antibiotics (mean duration of antibiotic therapy, 9.8 days). Interpretation of these results is confounded, however, by the choice of ciprofloxacin as the short-course agent, because ciprofloxacin causes relatively little disruption of intestinal anaerobes [16]. In mice, 3 days of ciprofloxacin therapy does not facilitate overgrowth of extended-spectrum β-lactamase–producing *K. pneumoniae* or VRE, whereas 3 days of antianaerobic treatment does (figure 5) (author's unpublished data). These data illustrate that, with respect to antibiotics and intestinal colonization, initial choices matter.

Another obstacle confronting antibiotic-control programs is the fact that many different antibiotics may promote intestinal colonization with nosocomial pathogens. For example, efforts to control VRE by restricting use of third-generation cephalosporins might produce relatively little benefit unless concurrent efforts are made to restrict other agents that promote VRE (e.g., clindamycin and vancomycin). Agents such as piperacil-

lin-tazobactam and ampicillin-sulbactam that are potential replacements for third-generation cephalosporins may also promote VRE, although, with hope, to a lesser degree (see the subsection "Animal models," above) [3, 22, 23]. In theory, substitution of antibiotics that cause relatively little disruption of the anaerobic microflora (e.g., cefepime and aztreonam) for third-generation cephalosporins might be effective in reducing intestinal overgrowth of multiple pathogens; in practice, these agents are often given in combination with agents that disrupt the intestinal microflora [6, 23]. In an intensive care unit, patients treated with regimens containing cefepime frequently acquired colonization with nosocomial pathogens [23]. These patients often received multiple concurrent and sequential antibiotics with the potential to promote pathogens.

Maintenance of stomach acidity. Further studies are needed to examine the clinical significance of the stomach acid barrier with regard to pathogen colonization of the large intestine. Medications that inhibit production of stomach acid are widely used among hospitalized patients, often without a clear indication (author's unpublished data).

Preservation or restoration of the indigenous colonic microflora. Because antibiotic activity within the lumen of the intestine is not needed for treatment of most infections, elimination of the portion of antibiotic that is excreted into bile could potentially preserve colonization resistance [27]. In mice, we found that oral administration of a class A β-lactamase reduced piperacillin-associated alteration of the indigenous microflora and prevented overgrowth of nosocomial pathogens [27]. After antibiotic therapy, administration of members of the indigenous microflora could facilitate restoration of colonization resistance. Administration of feces through nasogastric tubes or by enemas has been effective as a means to prevent recurrences of *C. difficile* infection [2]. Administration of probiotics, such as lactobacilli or bifidobacteria, has shown promise in animal model and in vitro studies, but further research involving humans is needed [28, 29].

Decontamination of environmental surfaces or patients' skin. Reducing the burden of pathogens present on patients' skin and on environmental surfaces might potentially reduce transmission by decreasing the number of organisms acquired on health care workers' hands and by decreasing transmission from environmental surfaces to patients. Environmental decontamination has shown promise as a control measure for *C. difficile* [2]. Vernon et al. [30] recently reported that use of a chlorhexidene gluconate body cleanser reduced patient skin, environmental, and health care worker hand contamination with multiple pathogens.

CONCLUSION

Despite infection-control efforts, many nosocomial pathogens that colonize the intestinal tract are increasing in prevalence and clinical importance. Antimicrobial selective pressure has contributed to steadily increasing rates of antimicrobial resistance among these pathogens. It is hoped that a better understanding of the pathogenesis of intestinal colonization and of the subsequent dissemination of pathogens will contribute to improved infection-control strategies. Because the nosocomial pathogens that colonize the intestinal tract often coexist, efforts are needed to evaluate the impact of infection-control measures on a broad range of pathogens.

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