

Antibiotic Resistance in the Intensive Care Unit

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Antimicrobial resistance has emerged as an important determinant of outcome for patients in the intensive care unit (ICU). This is largely due to the administration of inadequate antimicrobial treatment, which is most often related to bacterial antibiotic resistance. In addition, the escalating problem of antimicrobial resistance has substantially increased overall health care costs. This increase is a result of prolonged hospitalizations and convalescence associated with antibiotic treatment failures, the need to develop new antimicrobial agents, and the implementation of broader infection control and public health interventions aimed at curbing the spread of antibiotic-resistant pathogens. Intensive care units are unique because they house seriously ill patients in confined environments where antibiotic use is extremely common.

They have been focal points for the emergence and spread of antibiotic-resistant pathogens. Effective strategies for the prevention of antimicrobial resistance in ICUs have focused on limiting the unnecessary use of antibiotics and increasing compliance with infection control practices. Clinicians caring for critically ill patients should consider antimicrobial resistance as part of their routine treatment plans. Careful, focused attention to this problem at the local ICU level, using a multidisciplinary approach, will have the greatest likelihood of limiting the development and dissemination of antibiotic-resistant infections.

Ann Intern Med. 2001;134:298-314.

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There is a general consensus that antimicrobial resistance has emerged as an important variable related to patient outcomes and overall resource use in the intensive care unit (ICU) (1–3). Worldwide, ICUs are faced with increasingly rapid emergence and spread of antibiotic-resistant bacteria. Both antibiotic-resistant gram-negative bacilli and gram-positive bacteria are reported as important causes of hospital-acquired infections (4–8). In many circumstances—particularly with vancomycin-resistant *Enterococcus faecium* and gram-negative bacteria producing extended-spectrum β -lactamases that are resistant to many other antibiotics—few antimicrobial agents remain effective. Therefore, there have been many recent calls to intensify current infection control efforts aimed at reducing the emergence and dissemination of infections caused by antibiotic-resistant bacteria (1, 9, 10).

Many clinical studies of antibiotic resistance have been performed in specialized areas of the hospital, such as ICUs (4, 5, 11, 12). These clinical settings are particularly appropriate because a wide variety of pressures play a role in escalating the emergence of antibiotic-resistant infections. Such pressures include frequent use of broad-spectrum antibiotics; crowding of patients with high levels of disease acuity in relatively small, specialized areas of the hospital; reductions in nursing staff and other support staff because of economic pressures (which increases the likelihood of person-to-person transmission of microorganisms); and the presence of more chronically and acutely ill patients who require

prolonged hospitalization and often harbor antibiotic-resistant bacteria (13, 14). In this review, we discuss the risk factors associated with the acquisition of antibiotic-resistant bacterial infections and potential strategies for the prevention of antibiotic resistance in the ICU. We recognize that many of these strategies are based on limited available scientific data that do not always focus on ICUs. Nevertheless, we hope that this review will assist ICU clinicians in focusing their efforts on the problem of antimicrobial resistance.

METHODS

Articles were identified by searching MEDLINE and Current Contents. The search was limited to English-language articles published from 1970 to 1 February 2000. We used the search terms *resistance*, *antibiotics*, *nosocomial*, *infection*, and *intensive care*. The bibliographies of the identified publications were also checked for potentially eligible studies. Finally, the abstract books for the 1999 American Thoracic Society and the 1999 Interscience Conference on Antimicrobial Agents and Chemotherapy meetings were reviewed. Eligible articles presented at these meetings were included if they were available for review and had been accepted for publication in a peer-reviewed medical journal.

The strength of documentation regarding the efficacy of our recommendations is based on the following grading scheme. Level I recommendations are supported by randomized, controlled investigations; level II recom-

recommendations are supported by nonrandomized concurrent-cohort investigations and historical-cohort investigations; and level III recommendations are supported by case series. A major limitation of our review is the small number of randomized, controlled studies examining the issue of antibiotic use and the emergence of resistance both in and outside the ICU. Therefore, clinicians should consider these recommendations along with their local experience, input from regional and national experts in antimicrobial resistance, and published recommendations (1, 10).

RISK FACTORS FOR ANTIMICROBIAL-RESISTANT INFECTIONS

The use of antimicrobial agents has been identified as an important factor in the emergence of antibiotic-resistant bacterial infections in the ICU. Several investigators have demonstrated a close association between previous use of antibiotics and the emergence of subsequent antibiotic resistance in both gram-negative and gram-positive bacteria (15–22). The recent experience with scheduled antibiotic class changes also demonstrates how rapidly antibiotic-resistant bacteria can emerge in the ICU and in hospitals as patterns of antibiotic use change (23–25). Trouillet and coworkers (26) examined 135 consecutive episodes of ventilator-associated pneumonia, of which 77 (57%) were caused by potentially antibiotic-resistant bacteria (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*). At least 7 days of mechanical ventilation, previous antibiotic use, and previous use of broad-spectrum antibiotics (third-generation cephalosporin, fluoroquinolone, carbapenem, or a combination) were the most important risk factors associated with the development of ventilator-associated pneumonia caused by antibiotic-resistant pathogens.

Other risk factors, such as prolonged length of hospital stay, also seem to predispose patients to infection with antibiotic-resistant bacteria (26, 27). This may be due, in part, to the greater likelihood over time of becoming colonized with such bacteria from either horizontal nosocomial transmission or endogenous emergence of resistance. Similarly, the presence of invasive devices, such as endotracheal tubes, intravascular catheters, and urinary catheters, also seems to encourage such

infection (28, 29). The increasing prevalence of antibiotic-resistant infections among patients in long-term treatment facilities can also be an important source for the entry of resistant bacteria into the ICU (30, 31). Finally, outbreaks of antibiotic-resistant bacterial infection due to inadequate infection control practices, failure to recognize the presence of antibiotic resistance, or use of contaminated equipment are also important factors promoting the spread of resistance (23, 32, 33).

IMPLICATIONS OF INCREASING BACTERIAL ANTIBIOTIC RESISTANCE

In general, infections caused by antibiotic-resistant bacteria are associated with higher in-hospital mortality rates and longer lengths of hospital stay (1). Colonization and infection with antibiotic-resistant bacteria also increase the likelihood that patients will receive inadequate antimicrobial treatment. Inadequate antimicrobial treatment is defined as the use of antibiotics with poor or no in vitro activity against the identified organisms causing infection. Examples of inadequate treatment include the failure to use antimicrobial agents directed at a specific class of microorganisms (for example, no therapy for fungemia due to *Candida* species) and the administration of antimicrobial agents to which the infecting microorganisms are resistant (for example, empirical nafcillin treatment for pneumonia subsequently attributed to methicillin-resistant *S. aureus*). Several investigations have demonstrated a strong association between inadequate antibiotic treatment and in-hospital mortality rates for patients with ventilator-associated pneumonia (34–37). More important, it seems that for patients who initially receive inadequate antibiotic treatment, changing antimicrobial therapy on the basis of subsequent culture results may not reduce the excess risk for in-hospital death (35).

Most inadequate antimicrobial treatment of nosocomial infections in the ICU seems to be related to bacteria that are resistant to the prescribed antimicrobial agents (38, 39). Although inadequate antibiotic treatment may explain, in part, the higher mortality rates associated with antibiotic-resistant bacterial infections, other factors may contribute. Antibiotic-resistant gram-positive bacteria, such as methicillin-resistant *S. aureus*, can express several virulence factors that may contribute to higher associated mortality rates (40–42). However,

Table 1. Antimicrobial Strategies for Reducing the Emergence of Antibiotic Resistance in the Intensive Care Unit*

Recommendation	Level of Evidence†	References
Limit unnecessary antibiotic administration		
Develop hospital-based guidelines for antibiotic use	II	68–78
Create an antibiotic use quality improvement team	II	79
Provide education and professional detailing on antibiotic use for physicians	II	80–82
Create a national intervention policy restricting antimicrobial use	II	74, 83
Develop guidelines with a multidisciplinary approach, involving local and national peer leaders	II	75, 84
Restrict the hospital formulary	II	23, 76–78, 85, 86
Use narrow-spectrum or older antibiotics	I and II	87–90
Use quantitative cultures and quantitative assessments for nosocomial pneumonia	I and II	91–93
Optimize antimicrobial effectiveness		
Avoid inadequate treatment by using automated guidelines	II	69, 71
Use combination antimicrobial treatment	I and II	26, 94–96
Consult with an infectious disease specialist	II	97–99
Use antibiotic cycling and scheduled antibiotic changes	II	100–104
Use area-specific empirical antimicrobial therapy‡	III	105
Limit short-course antibiotic prophylaxis to clinically validated indications	I and II	106, 107
Avoid routine antimicrobial decontamination of the aerodigestive tract in the intensive care unit	I and II	108–110

* Level I = supported by randomized, controlled investigations; level II = supported by nonrandomized concurrent-cohort investigations and historical-cohort investigations; level III = supported by case series.

† Includes practices and strategies used in the intensive care unit as well as outside of it to optimize antibiotic use.

‡ Based on area-specific information regarding likely pathogens and their antimicrobial susceptibilities.

not all studies have shown higher mortality rates as a result of infections due to methicillin-resistant *S. aureus* compared with methicillin-sensitive *S. aureus* (43). Similarly, some antibiotic-resistant gram-negative bacteria are associated with more virulence factors than antibiotic-susceptible pathogens, which may also explain some of the excess attributable mortality rates observed in patients infected with these pathogens (20, 44–47).

Nosocomial bloodstream infections are among the most serious infections acquired by ICU patients. Antibiotic resistance seems to have been responsible, at least in part, for inadequate antimicrobial therapy for such infections. This, in turn, is associated with higher in-hospital mortality rates, although possibly not for all pathogens (48–56). Nevertheless, the problem of antibiotic-resistant bacteremia is increasing both in the hospital setting as well as in the community (57). Because infections due to antibiotic-resistant bacterial strains tend to be more severe in critically ill patients, greater morbidity and mortality can be expected, particularly when inadequate empirical antimicrobial therapy is administered (39). In addition to higher patient mortality rates, antibiotic-resistant bacterial infections are associated with prolonged hospitalization and increased health care costs compared with antibiotic-sensitive bacterial infections (58–62). The overall annual national cost of control and treatment of infections caused by antibiotic-resistant bacteria has been estimated to be between \$100

million and \$30 billion, including the cost of development of new antibiotics (60, 63–67).

STRATEGIES FOR PREVENTING ANTIMICROBIAL RESISTANCE

Various strategies have been proposed to improve use of antibiotics and prevent the emergence of antibiotic resistance. Table 1 describes several of these strategies, which are aimed at limiting the unnecessary use of antibiotics or at optimizing their effectiveness in hospitalized patients. In addition to these strategies, clinicians must ensure that antibiotic administration follows certain minimal requirements, such as proper dosing, interval administration, optimal duration of treatment, monitoring of drug levels when appropriate, and avoidance of unwanted drug interactions. Lack of adherence to these minimal requirements can result in inadvertently low or excessive tissue concentrations of the antibiotic, which increases the likelihood for antibiotic resistance, patient toxicity, and lack of effectiveness despite a qualitatively correct regimen (111–114).

Protocols and Guidelines

Antibiotic practice guidelines or protocols have emerged as a potentially effective means of both avoiding unnecessary antibiotic administration and increasing the effectiveness of prescribed antibiotics. One recent

study showed that implementation of such guidelines can dramatically affect the extent of their use. Infection management guidelines developed with the active participation of practicing clinicians are more likely to be followed than predeveloped guidelines that are imposed with little or no clinician input (115). Optimal practice guidelines require the integration of medical knowledge and experience, patient preferences, and a well-organized system for implementation (116). However, individual physicians often form barriers to the successful implementation of protocols and guidelines because of fears about loss of clinical autonomy as well as lack of local data on effectiveness (117). Therefore, locally developed guidelines often have the best chance of being successfully implemented with the cooperation and acceptance of local health care providers (118, 119).

Automated guidelines for antimicrobial use have successfully improved identification and minimized the occurrence of adverse drug effects and have improved antibiotic selection (68, 69, 120). Guideline use has also been associated with stable antibiotic susceptibility patterns for both gram-positive and gram-negative bacteria, possibly as a result of promoting antimicrobial heterogeneity (70, 121). Automated and nonautomated antimicrobial guidelines have also been used to reduce the overall use of antibiotics and to limit the use of inadequate antimicrobial treatment, both of which could affect the development of resistance (70–73, 79). Finally, antibiotic- or disease-specific interventions—combining guidelines on antibiotic use with physician education and professional detailing—have been successfully used in the outpatient setting to reduce unnecessary use of antibiotics and to improve bacterial resistance profiles (74, 80–84). Similar interventions could be developed for the ICU setting to reduce antibiotic misuse and overuse, decrease inadequate or ineffective antimicrobial treatment, and help curtail the problem of antimicrobial resistance (75).

Hospital Formulary Restrictions

Restricting specific antibiotics or antibiotic classes from the hospital formulary has been adopted as a strategy to reduce the occurrence of antibiotic resistance and antimicrobial costs. Such an approach has been shown to reduce pharmacy expenses and adverse drug reactions from the restricted drugs (122). However, not all expe-

riences have been uniformly successful, and some have been associated with increased overall antibiotic costs (123). In general, hospitals have restricted antibiotics with a broad spectrum of action (such as carbapenems), rapid emergence of antibiotic resistance (such as cephalosporins), and readily identified toxicity (such as aminoglycosides). To date, it has been difficult to demonstrate that restricted hospital formularies are effective in curbing the overall emergence of antibiotic resistance among bacterial species. This may be due in large part to methodologic problems. However, such restrictions have been successful in specific outbreaks of antibiotic-resistant infection, particularly in conjunction with infection control practices and educational activities. Table 2 summarizes the experiences of several hospitals that used antibiotic restriction programs to curb the outbreak of nosocomial infections caused by antibiotic-resistant bacteria (23, 76–78, 85, 86). However, it is important to note that this type of intervention can be successfully implemented only if such outbreaks are recognized. This requires systematic patient surveillance for antibiotic-resistant bacteria and a microbiology laboratory that can detect the presence of resistance. Such detection is not always simple, especially for gram-negative bacteria possessing extended-spectrum β -lactamases. An outbreak of infection with these pathogens can go unrecognized for a prolonged period by many of the currently available detection methods (23, 24).

Use of a Narrow Spectrum and Older Antibiotics

Another proposed strategy to curtail the development of antimicrobial resistance, in addition to the judicious overall use of antibiotics, is to use drugs with a narrow antimicrobial spectrum or “older” antibiotics. Several investigations suggest that some infections, such as community-acquired pneumonia and urinary tract infections, can usually be successfully treated with narrow-spectrum antibiotic agents, especially if the infections are not life-threatening (87–89). Similarly, the avoidance of broad-spectrum antibiotics (for example, cephalosporins) and the reintroduction of narrow-spectrum agents (penicillin, trimethoprim, gentamicin), when combined with infection control practices, have been successful in reducing the occurrence of *Clostridium difficile* infections (90). Country-wide programs aimed at combining judicious overall use of antibiotics with use

Table 2. Examples of Programs for Restricted Antimicrobial Use Aimed at Reducing Bacterial Resistance*

Study (Reference)	Country	Target Pathogen	Intervention	Outcome
Rahal et al. (23)	United States	ESBL-producing <i>Klebsiella</i> species	Hospital-wide restriction of cephalosporin antibiotics	Reduction in occurrence of infection due to ESBL-producing <i>Klebsiella</i> species Increased use of imipenem Increased occurrence of infection due to imipenem-resistant <i>Pseudomonas aeruginosa</i> Overall reduction in multidrug-resistant gram-negative bacteria
Giamarellou and Antoniadou (76)	Greece	Gram-negative bacteria	Specific rules for hospital hygiene Educational programs directed to small groups of health care workers Antibiotic policy aimed at restricting the use of broad-spectrum drugs, especially cephalosporins and quinolones	Decreased consumption of restricted antibiotics Lack of increase in consumption of non-restricted antibiotics Associated reductions in antimicrobial resistance
Climo et al. (77)	United States	Clindamycin-resistant <i>Clostridium difficile</i>	Restricted use of clindamycin	Overall reduction in clindamycin use Reduction in cases of <i>C. difficile</i> -associated diarrhea Increased susceptibility of <i>C. difficile</i> to clindamycin
Quale et al. (78, 85)	United States	Vancomycin-resistant enterococci	Restricted use of vancomycin Restricted use of cephalosporins Addition of β -lactamase inhibitors to formulary (ampicillin-sulbactam and piperacillin-tazobactam)	Decreased point prevalence of fecal colonization with vancomycin-resistant enterococci
Rice et al. (86)	United States	ESBL-producing <i>K. pneumoniae</i>	Restricted use of ceftazidime Educational efforts on the importance of ESBLs Addition of piperacillin-tazobactam to formulary Patient surveillance	Decreased use of ceftazidime Decreased occurrence of ESBL-producing <i>K. pneumoniae</i> isolates No substantial increase in the rate of resistance to piperacillin-tazobactam

* ESBL = extended-spectrum β -lactamase.

of narrow-spectrum agents have also been associated with reductions in antibiotic resistance (74, 83). However, patients in the ICU have often already received previous antimicrobial treatment and are therefore more likely to be infected with an antibiotic-resistant pathogen (124). To avoid inadequate treatment, initial empirical treatment with broad-spectrum agents may be necessary until culture results become available (39).

Quantitative Cultures and Assessment of Infection Risk

Pneumonia is the most common hospital-acquired infection among mechanically ventilated patients (28, 39). However, establishing a definite diagnosis is difficult because pneumonia has nonspecific signs and symptoms. This has resulted in largely empirical treatment for nosocomial pneumonia. Several groups of investigators have shown that the use of both quantitative bacterial cultures (obtained with bronchoalveolar lavage) and quantitative assessments of the risk for nosocomial

pneumonia can reduce prolonged antibiotic use in many patients with suspected infection (91–93).

Combination Antibiotic Therapy

Combination antimicrobial therapy has been used successfully for *Mycobacterium tuberculosis* and has been proposed as a strategy to reduce the emergence of bacterial resistance (122). However, no convincing data exist to validate this hypothesis for nosocomial pneumonia (125). Similarly, conclusive data that such therapy for nosocomial bloodstream infections prevents the subsequent emergence of antibiotic resistance are lacking (126, 127). Combination antibiotics also have the potential drawback of increasing overall resistance if not properly controlled, resulting in greater overall use of antibiotics. Nevertheless, some indirect evidence suggests that combination antimicrobial therapy may be useful in limiting resistance.

Ballow and Schentag (128) observed that increased

use of ceftazidime was associated with an increase in cephalosporin resistance among *Enterobacter cloacae* isolates—from 17% to 46%—between 1988 and 1990. Substitution of piperacillin plus an aminoglycoside for ceftazidime was associated with a reversal of the previous trend, reducing ceftazidime resistance to 25% within 2 years. Similar results have been reported by other investigators (94). However, it is not clear from these studies whether the restricted use of specific classes of antibiotics or the introduction of combination antimicrobial therapy contributed to the observed reductions in antimicrobial resistance. In the county of Northern Jutland in Denmark, all bacteremia isolates were analyzed with regard to antibiotic resistance over 10 years (from 1981 to 1995) (95). A total of 8840 isolates were identified from 7938 episodes of bacteremia. Among Enterobacteriaceae, the level of resistance to third-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones was low (<1%). The recommended regimen for empirical antibiotic treatment in this region is a combination of penicillin G or ampicillin and an aminoglycoside, which provided an overall coverage of 94%. This experience can be viewed as a successful program promoting the use of combinations of narrow-spectrum or “old” antibiotics for the treatment of bloodstream infections and avoiding the routine use of broader-spectrum agents, such as cephalosporins and quinolones, that can rapidly induce resistance. Finally, mathematical models also suggest that combination antibiotic therapy will always be superior to single antibiotics in preventing resistance (129).

In addition, combination antimicrobial therapy may be more effective at producing clinical and microbiological responses. This could also help to minimize antibiotic resistance by preventing the horizontal transmission of inadequately treated antibiotic-resistant pathogens. Several groups of investigators have demonstrated that in their ICUs, certain antibiotic combinations are more likely than others to provide higher rates of bacteriologic cure in patients with nosocomial infections (26, 96).

Infectious Disease Specialists

Several studies have shown that infected patients treated by an infectious disease specialist are less likely to receive inadequate antimicrobial treatment (97, 98). Similarly, routine input by infectious disease specialists has also been shown to be associated with less use of

broad-spectrum antibiotics; a more rapid shift to oral antibiotics; and, as part of a multidisciplinary effort, reductions in infection caused by antibiotic-resistant bacteria (97, 99).

Antibiotic Cycling and Scheduled Antibiotic Changes

Antibiotic class cycling has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance (130). In theory, a class of antibiotics or a specific antibiotic drug is withdrawn from use for a defined period and is reintroduced at a later time in an attempt to limit bacterial resistance (131). This offers the potential for use of antibiotic classes that have greater overall activity against the predominant ICU pathogens, resulting in more effective treatment of nosocomial infections (102). In addition, studies have shown that withdrawing an antibiotic or class of antimicrobial agents from use can potentially restore its effectiveness because bacterial resistance to it decreases (23, 77, 83, 85).

Table 3 summarizes the available data on using antibiotic cycling and scheduled antibiotic changes to promote antimicrobial heterogeneity (100–104). Antimicrobial heterogeneity can be viewed as the use of a variety of antibiotics rather than one or limited agents for any specific clinical indication (for example, empirical antimicrobial treatment in the ICU). Strategies promoting antimicrobial heterogeneity are new and are limited to antibiotics directed against gram-negative bacteria. Although the initial studies are promising, this practice cannot be viewed as a replacement for judicious overall antibiotic use and rigorous adherence to infection control practices as a means of controlling resistance.

New Antimicrobial Agents

Two newly approved antibiotics (linezolid and quinupristin–dalfopristin) with activity against hospital-acquired antibiotic-resistant gram-positive bacteria (methicillin-resistant *S. aureus* and vancomycin-resistant enterococci) are now available for clinical use. Before these new antibiotics were developed, antimicrobial therapy for these infections was limited. Linezolid and quinupristin–dalfopristin can be used to promote the heterogeneous treatment of infections because they are used against increasingly important antibiotic-resistant bacteria. In theory, therapy with these agents may

Table 3. Examples of Antibiotic Cycling and Scheduled Antibiotic Class Changes*

Study (Reference)	Country	Stimulus for Intervention	Intervention	Outcome
Gerding et al. (100)	United States	Increasing resistance of gram-negative bacteria to gentamicin	Cycling of gentamicin and amikacin using time cycles of 12 to 51 months over 10 years	Increased susceptibility of gram-negative bacteria to gentamicin
Kollef et al. (101)	United States	Increasing resistance of gram-negative bacteria to ceftazidime	Scheduled ICU-wide change to ciprofloxacin for empirical gram-negative treatment	Reduced occurrence of ventilator-associated pneumonia and bloodstream infections, primarily due to reductions in ceftazidime-resistant gram-negative bacterial infection
Kollef et al. (102)	United States	Increasing resistance of gram-negative bacteria to ceftazidime	Scheduled ICU-wide changes to ciprofloxacin (6 months) followed by cefepime (6 months) for empirical treatment of gram-negative bacterial infections	Reduced administration of inadequate empirical antimicrobial treatment during the two antibiotic change periods
Dominguez et al. (103)	United States	Concerns about infection due to vancomycin-resistant enterococci and multidrug-resistant gram-negative bacteria among neutropenic patients	Cycling of four antibiotic regimens (4 to 6 months) over 19 months among neutropenic oncology patients	No substantial changes in antibiotic susceptibility profiles over time Found to be safe in this patient population Overall increase in enterococcal infections
Gruson et al. (104)	France	Increasing resistance of gram-negative bacteria to ceftazidime and ciprofloxacin	Restricted use of ceftazidime and ciprofloxacin Cycling of empirical antibiotic treatment regimens for suspected gram-negative bacteria on the basis of monthly review of bacterial susceptibility profiles	Reduced occurrence of ventilator-associated pneumonia, primarily due to reductions in infection caused by antibiotic-resistant gram-negative bacteria Reduced administration of inadequate empirical antimicrobial treatment during the cycling intervention

* ICU = intensive care unit.

decrease overall resistance to vancomycin by reducing its use (85, 99). However, vancomycin, linezolid, and quinupristin–dalfopristin should be used only for serious infections due to antibiotic-resistant gram-positive bacteria. Widespread empirical use of these antibiotics in the ICU should be avoided because it may lead to the emergence of bacterial resistance and thus limit their long-term effectiveness.

Area-Specific Antimicrobial Therapy

Consensus-driven recommendations have been developed for the treatment of hospital-acquired and community-acquired infections (132, 133). However, the types of pathogens associated with nosocomial infections in ICUs, along with their antibiotic susceptibility profiles, have been shown to vary (105). This suggests that consensus guidelines for antimicrobial therapy will need to be modified at the local level (for example, according to county, city, hospital, and ICU) to take into account local patterns of antimicrobial resistance. It also suggests that because of intrahospital variations, hospitals may need to develop systems for reporting patterns of antimicrobial susceptibility in individual hospital areas or

units (19, 134). Such information may help clinicians develop more rational prescribing practices that will reduce the unnecessary administration of broad-spectrum drugs and avoid inadequate antimicrobial treatment of critically ill patients.

Strategies for Antimicrobial Decolonization

The prophylactic administration of parenteral antibiotics has been shown to reduce nosocomial infections in specific high-risk patient populations requiring intensive care (106, 107). Topical antibiotic administration (that is, selective digestive decontamination), with or without concomitant parenteral antibiotics, has also been shown to be effective (135, 136). However, the routine use of selective digestive decontamination has been associated with the emergence of antimicrobial resistance (109, 110). Therefore, topical decontamination of the aerodigestive tract can be recommended only for specific high-risk patients or for the containment of outbreaks of multidrug-resistant bacterial infections in conjunction with infection control practices (108).

NONANTIMICROBIAL PREVENTION STRATEGIES

In general, nonantimicrobial strategies for preventing nosocomial infections due to antibiotic-resistant bacteria can be divided into two broad categories: 1) specific interventions aimed at primary prevention of nosocomial infections and 2) use of infection control practices to prevent horizontal transmission of nosocomial bacterial pathogens.

Primary Prevention Programs for Specific Nosocomial Infections

Systematic efforts have been made to improve patient outcomes by preventing nosocomial infections through the use of optimal medical practices (137). Several focused clinical efforts have shown that practice guidelines or protocols promoting sound clinical practices can reduce the rates of ventilator-associated pneumonia (138–141). Similarly, prevention programs have successfully reduced rates of nosocomial bloodstream infections by achieving higher rates of compliance with established medical practices (142, 143).

Reducing Length of Stay

In addition to general strategies focusing on the prevention of nosocomial infection, the application of specific novel changes in practice can achieve the same goal. Duration of mechanical ventilation is an important risk factor for nosocomial pneumonia and antibiotic resistance (26, 144). Therefore, efforts aimed at reducing the duration of mechanical ventilation could also decrease the incidence of ventilator-associated pneumonia. One method of achieving this goal has been to avoid tracheal intubation or to convert patients already intubated to noninvasive mask ventilation. This strategy has been associated with reduced rates of nosocomial pneumonia (145–148). In addition, formalized weaning protocols for patients requiring mechanical ventilation have been shown to reduce the duration of mechanical ventilation and the length of ICU stay (149, 150).

Central Venous Catheters

Central venous catheters have been associated with an increased occurrence of bloodstream infections and increased rates of infection with antibiotic-resistant bacteria (28, 29). Strategies aimed at minimizing the use of central venous catheters for total parenteral nutrition by

more effectively employing enteral nutrition have been associated with lower rates of nosocomial infection (151, 152). However, for patients who cannot be managed without central venous catheters, prevention of catheter-related bloodstream infections should be part of the routine care plan. This includes a strict evaluation of the indications for the continued use of the catheter and strict hygienic precautions during catheter insertion and maintenance (153–155). Several clinical studies have shown that adherence to strict infection control practices—using guidelines, intravenous therapy teams, and clinician education—can reduce infection rates and be cost-effective (142, 156–158).

In addition to infection control practices, the use of antimicrobial-coated intravascular catheters has been associated with reductions in rates of nosocomial infection (159–161). Similar devices have been proposed to reduce the occurrence of nosocomial urinary tract infections (162). However, it is still not clear whether such devices are routinely necessary if optimal infection control practices, including timely removal of all catheters, are strictly followed. Individual institutions must determine whether such devices should be routinely used on the basis of cost, clinical effectiveness, and availability. Widespread, routine use of such antimicrobial-coated catheters may also increase the potential risk for bacterial resistance to the antimicrobial agents (163).

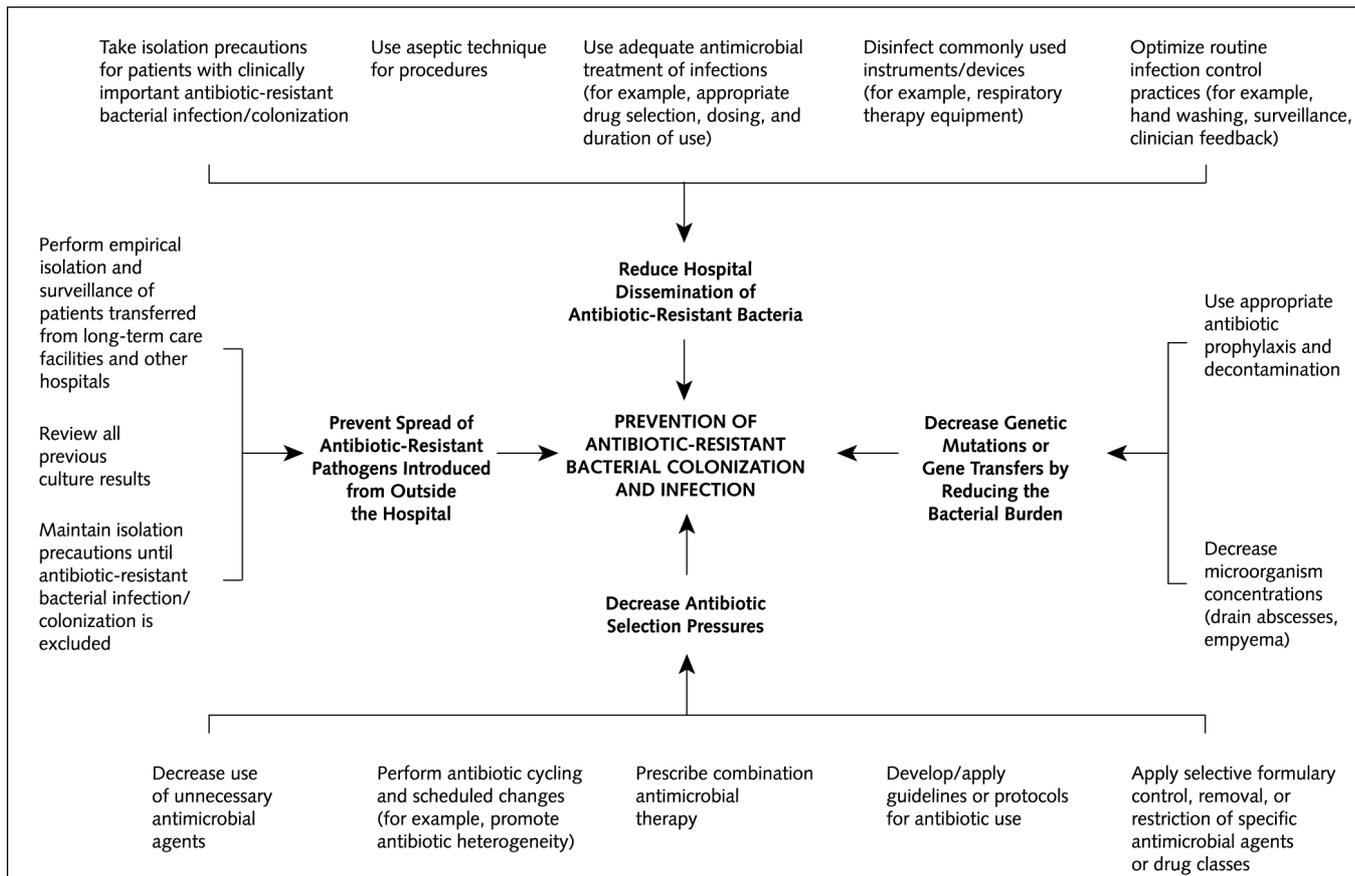
Vaccines

Various community vaccination programs for adults and children have successfully reduced the incidence of respiratory infections caused by specific pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, and the influenza virus (164–166). It would be expected that vaccination against these pathogens may also prevent a small number of nosocomial infections each year. In addition, vaccines directed against *P. aeruginosa* and *Staphylococcus aureus*, common causes of nosocomial infection, hold promise for infection prevention and possibly reduced resistance rates if overall antimicrobial use can be decreased (167, 168).

Prevention of Horizontal Transmission of Bacteria

The prevention of horizontal transmission of bacterial pathogens is an important strategy for the prevention of antibiotic-resistant infections (Figure). Coloniza-

Figure. Potential strategies to control colonization and infection due to antibiotic-resistant bacteria in clinical settings.



tion with pathogenic bacteria is an important precursor to subsequent nosocomial infection with those same pathogens, especially antibiotic-resistant bacteria (such as *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus*) (169–171). Therefore, efforts directed at reducing such colonization could help to reduce the rates of antibiotic-resistant infections.

Handwashing

Handwashing is still considered the most important and effective infection control measure to prevent horizontal transmission of nosocomial pathogens (172, 173). Several investigations have demonstrated the benefits of handwashing as a means to decrease the spread of nosocomial infections (174, 175). However, increased patient workloads and decreased staffing have contributed to poor compliance with handwashing and other routine infection control measures, especially in the

ICU (176–179). In an attempt to reverse this trend, alternative handwashing methods using alcohol solutions have been developed. These methods are effective, do not require sinks, and can be performed more rapidly than traditional handwashing with soap solutions (180, 181). In addition, patient education models, group feedback to and education of health care workers, and incorporation of moisturizers into skin care products for health care professionals can also improve compliance with handwashing (181–184).

Workload in the ICU

Increased workloads for ICU clinicians can adversely influence patient outcomes. The weaning of patients from mechanical ventilation can be prolonged if adequate nurse staffing is not provided; this can potentially increase the risk for nosocomial pneumonia (185). Increased housestaff workloads can increase the use of

umbilical artery catheters and reduce the performance of phlebotomy in neonates, further predisposing patients to nosocomial bacteremia (186). Increased nursing workloads in ICUs have also been associated with increased resource use, while absence of an ICU physician has been associated with a higher rate of septicemia (187). As can occur with poor compliance with handwashing, increasing the workloads of health care professionals can degrade other institutional infection control practices, thereby increasing the rates of infection caused by antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (188).

Gloves and Gowns

In addition to handwashing, the use of gloves and gowns has also been shown to reduce horizontal transmission of specific bacterial pathogens (189–191). However, it has been demonstrated that infection control practices—such as handwashing, contact isolation of patients infected or colonized with vancomycin-resistant enterococci, and appropriate gown and glove use—are more effective in reducing horizontal transmission of vancomycin-resistant enterococci and other nosocomial pathogens when combined with controlled antibiotic use (85, 99, 192). Therefore, ICU clinicians should attempt to develop a program for limiting antimicrobial resistance at their institutions by using a combination of infection control and antibiotic control interventions. This will require a consideration of the institution's patient population, the availability of resources, and some ongoing estimate of local antibiotic resistance.

SUMMARY

Infection control practices, including programs aimed at prevention of antibiotic resistance, are often viewed as an expense item on a hospital's budget (193). However, the costs associated with infection control practices must be balanced against the costs of the nosocomial infections they are aimed at preventing (61, 194). In addition, it is important to note that some infection control practices have been shown to be of no value and needlessly add to the complexity and cost of health care. For example, level I clinical studies have shown that routinely changing ventilator circuits or in-line suction catheters is unnecessary unless these ventilator components are visibly soiled or mechanically

Table 4. Steps in the Development and Implementation of a Program To Control Antibiotic Resistance

1. Identify the prevention of antibiotic-resistant bacterial colonization and infection as a high-priority task
 - To decrease horizontal transmission of antibiotic resistance, provide professional and academic detailing for hospital staff on infection control practices and reducing antibiotic misuse and overuse
 - Educate hospital administration on program benefits
 - Employ local and outside experts and opinion leaders for program development and acceptance
2. Establish microbiological definitions of antimicrobial resistance and clinical definitions of tracking and defining treatment failures
3. Establish systems for tracking and reporting antibiotic-resistant infections
 - Publish and disseminate antimicrobial resistance trends (unit- or ward-specific)
 - Identify administration of inadequate antimicrobial treatment (such as inappropriate antibiotic selection based on culture results)
 - Rapidly report antimicrobial-resistant infection, inadequate antimicrobial treatment, or both to clinicians
 - Develop a mechanism for detecting unit-specific outbreaks of antibiotic-resistant infections
4. Optimize compliance with institutional infection control policies and practices (handwashing, use of barrier precautions, environmental decontamination)
 - Use surveillance to detect antibiotic resistance
 - Use isolation for patients colonized or infected with antibiotic-resistant pathogens
 - Identify optimal patient-to-staff ratios
 - Hold regular educational in-services
 - Give feedback regarding individual or unit-specific infection control performance
 - Establish local or unit-specific ownership and accountability of infection control practices in addition to hospital-based programs
 - Develop interventions to interrupt horizontal transmission of antibiotic resistance
5. Develop or obtain appropriate information systems support
 - Maintain unit or physician profiling of antimicrobial resistance and inadequate or inappropriate antibiotic prescription
 - Develop a decision support system to optimize administration of antimicrobial agents
 - Unburden patient care staffs from administrative duties, data collection, and generation of reports
6. Review and update the program on a regular basis
 - Incorporate new technology
 - Review changing disease patterns
 - Incorporate new information on antibiotic resistance
 - Exchange experiences and data with other institutions
 - Evaluate changes in practices according to their effect on antibiotic resistance

damaged (195, 196). Available medical evidence has been used to develop recommendations for successful implementation of more cost-effective infection control and antibiotic control practices (197, 198). Table 4 outlines several steps for developing and implementing a successful program to reduce the threat of antibiotic-resistant infections.

In addition to implementing currently recognized strategies for the prevention of antimicrobial resistance, continued research is needed to identify and develop

innovative approaches. One traditional approach is the development of new antimicrobial agents with broader spectrums of activity. However, resistance has developed to every new antimicrobial agent introduced into clinical use (65). Some nontraditional approaches that could influence the development of resistance are being investigated. These approaches include the prevention of biofilm formation on the surfaces of invasive medical devices (199); the topical mucosal application of mammalian defensin peptides to augment host defenses against colonization and infection with antibiotic-resistant bacteria (200, 201); and the use of vaccines directed against the pili of gram-negative bacteria, such as *P. aeruginosa*, to prevent host colonization with these pathogens (202, 203). At present, however, the local establishment of a rigorous multidisciplinary approach to the prevention of antibiotic resistance in the ICU should help to curtail the problem and allow future advances to be more readily integrated into the prevention program. Finally, interventions aimed at limiting antibiotic resistance should be carefully evaluated to determine their effectiveness and cost-benefit, allowing scarce resources to be deployed in the most efficient manner.

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Acknowledgments: The authors thank Kim Tinsley for her assistance in preparing this manuscript.

Grant Support: In part by a grant from the Centers for Disease Control and Prevention (UR8/CCU715087).

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