Antimicrobial resistance: Consideration as an adverse drug event

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Antimicrobial resistance has increased dramatically in the past 15 to 20 yrs and presents a patient safety concern unlike any other in the intensive care unit. Antimicrobial resistance in critically ill patients increases morbidity, mortality, length of hospital stay, and healthcare costs. Some organisms may have intrinsically high levels of resistance or may be spread between patients by poor infection control practices. However, a major driver of antimicrobial resistance is antibiotic use. As such, the development of antimicrobial resistance can often be thought of as an adverse drug event. This article explores the link between drug use, drug dosing, other selective pressures and resistance, and describes concepts to minimize the negative impact of antimicrobial therapy. Two broad themes of these concepts are minimizing the use of antibiotics whenever possible and optimizing antibiotic usage when they are needed. Strategies for minimizing the use of antimicrobials include using optimal diagnostic procedures to ensure the need for antimicrobials, streamlining or discontinuing therapy when possible based on culture results, and using the shortest duration of therapy needed for documented infections. Strategies for optimizing antimicrobial use include using optimal dosing based on the manufacturer's instructions and current pharmacodynamic data, guiding better prescribing based on local susceptibility patterns and formulary restriction, and avoiding drugs with more propensity to foster resistance. (Crit Care Med 2010; 38[Suppl.]:S155–S161)

Key Words: antimicrobial resistance; pharmacokinetics; pharmacodynamics; antimicrobial de-escalation; dosing; duration of therapy

Antimicrobial resistance has increased dramatically in the past 15 to 20 yrs and presents a patient safety concern unlike any other in the intensive care unit (ICU). Antimicrobial resistance in critically ill patients increases morbidity, mortality, length of hospital stay, and healthcare costs. There are overwhelming data that these adverse outcomes are largely driven by antimicrobial use. However, drug use alone is not the only consideration; more importantly, the dose used and the duration of exposure play important roles in causing antimicrobial resistance. There are a number of strategies that can be used to minimize the adverse impact that occurs with antimicrobial use. This article explores the link between drug use, drug dosing, other selective pressures and resistance, and concepts to minimize the negative impact of antimicrobial therapy.

An adverse event is an untoward medical experience in a patient who has been administered a medication, and that event does not necessarily have to have a casual relationship with the treatment. In serious events of an adverse drug effect, the administration of a particular drug results in prolonged hospital stay, causes a permanent disability, or causes death. Resistance to antibiotics and other antimicrobial agents clearly fits this definition. Resistance that is generated after antibiotic exposure, either to a single patient or to a cohort of patients, often results in prolonged ICU and hospital stay and can result in morbidity or mortality. There are many examples of drug therapy causing antibiotic resistance.

Linking antibiotic resistance to antibiotic use

Neu (1) recognized in 1984 that extensive use of antimicrobial agents in the hospital caused selection of organisms resistant to many agents through chromosomally mediated mechanisms. He pointed out several examples of drug-driven resistance, including methicillin-resistant *Staphylococcus aureus*; aminoglycoside-, erythromycin-, and tetracycline-induced resistance in enterococci; *Haemophilus influenzae* resistant to penicillins and chloramphenicol; beta-lactamase-mediated resistance in Enterobacteriaceae, *Escherichia coli*, and *Klebsiella pneumoniae*; and *Pseudomonas aeruginosa* and *Serratia marcescens* resistance to aminoglycosides and penicillins. Bacteria adapt to the presence of antibacterial agents in their environment to survive. It is thought that bacteria contain a low level of genetic resistance for protection against exposure of naturally occurring antibiotics produced by other microorganisms in the environment (2). However, the proliferation and diversity of resistance genes in bacteria became more extensive when human-made antibiotics were introduced into widespread use.

Bacteria continuously exchange genetic material, thereby acquiring resistance genes from other microbes. Bacterial chromosomal DNA contains the genes for antibiotic resistance, but many genes that confer antibiotic resistance are found on mobile genetic elements such as plasmids. Resistance also can be acquired by mutation or by acquisition of new DNA. The rate of spontaneous mutation is much lower than the acquisition of resistant plasmids. Plasmid-acquired resistance is largely driven by antimicrobial exposure.

Antibiotic use did not create resistant genes but has led to an increased number of resistant genes and resistant bacteria

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(3). It is common now for clinically important bacteria to have combinations of genes that enable multiple resistance mechanisms against a wide variety of antibiotics. Because antibiotics are also used to treat infectious diseases in animals and plants, and because antimicrobial soaps and other cleansers are commonplace in homes and businesses, there is continual exposure to resistance divers in the environment (4).

Historically, drug-resistant strains initially appeared in hospitals, where use of antibiotics was greatest. Antibiotic use is highest in the ICU, where patients are constantly exposed to antibiotic therapy because of their increased risk of infection. Recent examples in the contemporary ICU point to specific agents that increase risk for antibiotic resistance. Fluoroquinolones have been implicated in resistance among *S. aureus*, *P. aeruginosa*, and other Gram-negative bacilli. In an investigation of 17 U.S. hospitals and surrounding communities, there was a significant association between fluoroquinolone use in hospitals and the incidence of methicillin-resistant *S. aureus* among *S. aureus* infections ($r = .77$; $p = .0003$) (5). A similar strong association was found between total fluoroquinolone use in the communities surrounding the hospitals and fluoroquinolone-resistant *E. coli* in hospitalized patients ($r = .57$; $p = .002$). In a French study of 47 hospitals across the country, the incidence of methicillin-resistant *S. aureus* among *S. aureus* isolates was significantly correlated with ciprofloxacin consumption (Spearman correlation test, $\rho = .31$; $p = .03$) (6). The incidence of ciprofloxacin resistance in *P. aeruginosa* increased with the use of fluoroquinolones and the percentage of a hospital's ICU beds (adjusted $\rho = 0.28$). Madaras-Kelly et al (7) found that decreasing fluoroquinolone use (by approximately 34%; with levofloxacin use decreasing approximately 50%) significantly lowered the methicillin-resistant *S. aureus* infection rate from 1.37 to 0.63 episodes per 1000 patient-days ($p = .02$). Interestingly, coagulase-negative *Staphylococcus* and *Enterococcus* infections rates also decreased.

Increasing fluoroquinolone-resistant *P. aeruginosa* has been positively correlated with fluoroquinolone use. From 1991 to 2000, Gasink et al (8) found fluoroquinolone use the only independent risk factor for fluoroquinolone-resistant *P. aeruginosa* (adjusted odds ratio, 3.43; 95% confidence interval, 2.37–4.96; $p < .001$). Patients with fluoroquinolone-resistant *P. aeruginosa* had significantly higher hospital costs ($62,325 vs. $48,734; $p = .007$) and higher mortality rates (47.5% vs. 35.5%; $p = .004$).

Fluoroquinolones are drivers in fluoroquinolone-resistant *P. aeruginosa*, but other drug therapy may also be associated with this adverse event. Carmeli et al (9) studied the emergence of resistance associated with ciprofloxacin, ceftazidime, imipenem, and piperacillin in hospitalized patients. In 271 patients with infections attributable to *P. aeruginosa*, the hazard ratio for emergence of resistance to each individual agent associated with treatment with that same agent were: ceftazidime, 0.8 ($p = .7$); piperacillin, 5.2 ($p = .01$); ciprofloxacin, 9.2 ($p = .04$); and imipenem, 44 ($p = .001$). In a large U.S. teaching institution, antibiotic restriction to reduce ceftazidime use (decreased by 44%) and imipenem use (decreased by 18%) resulted in reductions in *P. aeruginosa* resistance to ceftazidime (24% to 11.8%; $p < .001$), piperacillin (32.5% to 18.5%; $p < .001$), and imipenem (20.5% to 12.3%; $p < .001$) (10). Interestingly, despite a 57% increase in use of aztreonam, aztreonam resistance among *P. aeruginosa* declined from 29.5% to 16.5% ($p < .001$). Pakyz et al (11) also found reduced carbapenem resistance among *P. aeruginosa* with restricting carbapenem use. From 2002 to 2006 in a consortium of eight academic hospitals that restricted carbapenem use, carbapenem-resistant *P. aeruginosa* significantly declined ($p = .01$) (11).

In a university hospital in Taiwan, cefotaxime-resistant or ciprofloxacin-resistant *E. coli* and meropenem-resistant *P. aeruginosa* were significantly correlated with increasing consumption of extended-spectrum cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, carbapenems, fluoroquinolones, and aminoglycosides (12). Imipenem-resistant *P. aeruginosa* have been positively correlated with fluoroquinolone use (odds ratio, 2.52; confidence interval, 1.61–3.92; $p < .001$) among 879 patients infected with the organism during 1999 to 2000 in a single center study (13). Compared to imipenem-susceptible infections, imipenem-resistance was associated with longer lengths of stay in the hospital (9 vs. 15.5 days; $p = .02$), greater hospital costs ($48,381 vs. $81,330; $p < .001$), and higher mortality (16.7% vs. 31.1%; $p < .001$).

Treatment with third-generation cephalosporins or imipenem have been associated with imipenem-resistant *Acinetobacter baumanii* infections (14). In a case-control analysis of 104 cases (387 controls), risk factors for imipenem-resistant *A. baumanii* infections were a previous ICU stay (odds ratio, 21.54; 95% confidence interval, 10.73–43.23) and previous exposure to imipenem (odds ratio, 9.18; 95% confidence interval, 3.99–21.13) or third-generation cephalosporins (odds ratio, 2.11; 95% confidence interval, 1.13–3.95). In a large teaching hospital in Taiwan, imipenem and meropenem use, along with ceftazidime use, were positively associated with ICU patients with extensive antibiotic-resistant *A. baumanii* infections (15). The odds ratio of the resistant infections developing was increased with increasing exposure to multiples of the drugs.

The data associating antimicrobial use with antimicrobial resistance are overwhelming, with certain agents, such as ciprofloxacin, imipenem, and ceftazidime, seemingly more extensive drivers of resistance than other agents. Nonetheless, virtually any antimicrobial agent can drive resistance with increasing exposure, especially to sublethal concentrations of the drug for extended periods.

The impact of optimizing antibiotic dosing strategies on the development of resistance

Bacteria causing infection demonstrate a range of susceptibilities to each individual antibiotic. In most circumstances, organisms that are more susceptible comprise the dominant population, suppressing the more resistant subset of pathogens. However, on administration of an antibiotic, the more susceptible population of organisms is easily eradicated, leaving the more resistant subpopulation to proliferate. Antibiotic concentrations that are sublethal, especially against more resistant subpopulations, can promote the emergence of resistant pathogens. Optimization of antibiotic regimens on the basis of pharmacokinetic and pharmacodynamic principles could play a role in the reduction of antibiotic resistance.

The duration of time the serum drug concentration remains above the minimum inhibitory concentration (MIC) of the antibiotic (time > MIC) enhances bacterial eradication with beta-lactams and may reduce the development of re-

sistance. Maximal killing with beta-lactams generally occurs when the antibiotic concentration is maintained greater than or equal to four times MIC (16). Frequent dosing, prolonged infusion times, or continuous infusions appear to be the methods most likely to consistently achieve these concentrations as opposed intermittent, bolus infusions administered over 30 to 60 mins (17–19) The concept of extended duration infusion (e.g., administered over 3–4 hrs) or continuous infusion of antibiotic is founded on the results of Monte Carlo simulations, which utilize pharmacokinetic parameters from healthy and sick volunteers and MIC distributions from local or national microbiological surveillance programs. In general, as the MIC of a pathogen increases (e.g., resistant subpopulations), it becomes more likely that achieving target concentrations becomes idealized with higher antibiotic doses over prolonged infusions. This is likely to be of benefit only in patients with normal renal function. As renal function becomes impaired, traditional bolus infusions adequately achieve target concentrations (20).

Carbapenems, as a member of the beta-lactam family, exhibit time-dependent kill characteristics, although they require a reduced percentage of time > MIC for optimal activity (40% of time > MIC compared with penicillins [50% time > MIC] and cephalosporins [60% to 70% time > MIC]). Nonetheless, similar to other beta-lactams, *in vitro* models have demonstrated trough concentrations (C_{min}:MIC) that are in excess of six times the MIC are likely necessary to prevent the emergence of resistance (21). To achieve and sustain these concentrations throughout the dosing interval, high doses infused over extended periods are being evaluated. The concept of an extended infusion has been evaluated in a randomized, controlled trial comparing doripenem as a 4-hr administration with imipenem-cilastatin administered over 30 to 60 mins for the treatment of ventilator-associated pneumonia (VAP). The development of resistance in the subset of patients infected with *P. aeruginosa* as delineated by an increase in MIC of four or more times the baseline MIC occurred in 35.7% (10 of 28) of patients in the extended infusion doripenem group compared with 53% (10 of 19) who received intermittent bolus infusions of imipenem (22). It should be noted that despite efforts designed to maintain drug concentrations that are above the MIC, resistance may develop, as observed in this trial. This is likely because of drug concentrations that are higher than the MIC but lower than the mutant prevention concentration, the so-called mutant selection window, in which not enough drug is administered to kill all bacteria and thus prevent selection of mutants or resistant organisms (23).

Fluoroquinolones display a combination of concentration-dependent and time-dependent kill characteristics. As such, the area under the concentration–time curve during a 24-hr period divided by the MIC (AUC_{0-24}/MIC) appears to be most reflective of clinical success or failure for the class of fluoroquinolones. Consider the case of ciprofloxacin, an antibiotic with a poor susceptibility profile against Gram-negative pathogens in most hospitals. It has been observed that achieving an AUC_{0-24}/MIC >125 is associated with a significantly increased clinical and microbiological cure rate in severely ill patients (24). This target value is likely true for any antibiotic with a half-life of 3 to 4 hrs or less. To achieve this target value, a dose of 400 mg every 8 hrs must be administered, as evidenced by a study including patients with severe sepsis (25). Whereas this dose is recommended in the package labeling, it has been common practice to dose ciprofloxacin at 400 mg every 12 hrs. In doing so, it is unlikely an AUC_{0-24}/MIC value of >125 will be achieved, which, in turn, not only increases the chance of therapeutic failure but also significantly promotes the development of resistance (26).

To maximize the bactericidal effects of aminoglycosides, clinicians must optimize the maximum drug concentration (C_{max}) to MIC ratio. A C_{max}:MIC ratio of ≥10:1 using once-daily aminoglycoside dosing (5–7 mg/kg) has been associated with preventing the emergence of resistant organisms (27, 28). The pharmacodynamic profile of vancomycin is less clear. There are data to support time-dependent, concentration-dependent, and AUC_{0-24}/MIC-dependent activity (23). However, the current consensus is that optimizing AUC_{0-24}/MIC is the most important approach to preventing resistance with vancomycin (23).

A method often posed as a means to prevent the emergence of resistance is via combination therapy, such that the addition of a second drug will result in an additive or synergistic pharmacodynamic interaction. The answer as to whether this strategy is effective clinically likely lies in the MIC of the pathogen. In the case of ciprofloxacin, if an infection caused by *P. aeruginosa* with an elevated MIC occurs, for example 0.5 μg/mL, the administration of ciprofloxacin as monotherapy at a dose of 400 mg every 8 hrs would not achieve the desired pharmacokinetic and pharmacodynamic end point (29). However, in combination with piperacillin, that end point of an AUC_{0-24}/MIC >125 is achieved, which should, in turn, lead to improved outcome and a decreased chance of resistance development. Several studies have investigated whether or not combination therapy reduces the risk of resistance development compared with monotherapy. One such study classified patients according to whether they had received previous monotherapy or previous combination therapy in the past 30 days and evaluated the risk of resistance in subsequent episodes of *P. aeruginosa* bacteremia (30). In a multivariate analysis that controlled for each antipseudomonal antibiotic, previous monotherapy was independently associated with resistance on subsequent infection, a risk not apparent in those who received antipseudomonal agents in combination. However, when comparing the two treatment strategies, there was not a significant difference with respect to subsequent resistance. Similarly, a meta-analysis concluded that the development of resistance does not differ when comparing monotherapy and combination therapy (31).

General strategies to minimize antibiotic resistance

The Centers for Disease Control has a program titled "Campaign to Prevent Antimicrobial Resistance in Healthcare Settings" that critical care clinicians should review (32). In addition, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology have guidelines for antimicrobial stewardship teams in hospitals (33). One of the goals of these guidelines is to minimize antimicrobial resistance. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology guidelines recommend that all hospitals form antimicrobial stewardship teams. This was in response to data showing that previous guidelines for preventing antimicrobial resistance were inadequate at changing clinical practice. Subsequently, studies have shown that antimicrobial steward-

Table 1. Recommendations to avoid antimicrobial resistance as an adverse drug event

Implement an Antimicrobial Stewardship Team
Effectively diagnose infections using high-quality cultures
In patients with documented infections: Streamline therapy when possible Decrease the duration of therapy when possible
Discontinue antibiotics in patients with negative cultures who are not infected Use appropriately aggressive antimicrobial dosing based on the type and severity of infection and body weight when applicable Use local antibiograms and pathways to improve antibiotic selection and usage Consider avoiding agents that are highly associated with resistance or *Clostridium difficile*- associated diarrhea
Not routinely recommended at this time to avoid resistance (may be used in selected situations): Continuous/extended infusions of beta-lactams Gram-negative combination therapy Scheduled antibiotic cycling

ship programs improve patient care and provide cost savings. Thus, it appears that formalized services are required to effectively implement antimicrobial stewardship concepts.

Some issues, such as optimizing infection control, are outside the scope of this paper. However, several Centers for Disease Control and Prevention and Infectious Diseases Society of America and the Society for Healthcare Epidemiology recommendations deal with minimizing/optimizing antimicrobial therapy and thus constitute a framework for the recommendations of this article. Recommended practices to minimize antimicrobial resistance as an adverse drug event are listed in Table 1.

Effectively diagnosing infection

Perhaps the most powerful tool for decreasing antimicrobial use is to obtain appropriate cultures and then use the results to streamline therapy to a narrower spectrum agent or discontinue antimicrobials in patients without infection. It is widely recommended that clinicians obtain high-quality cultures to definitively diagnose infections in the ICU (32, 34–36). Whereas the diagnosis of some infections is relatively straightforward (e.g., Gram-negative bacteremia), the diagnosis of other infections is less clear because of a lack of consensus on the optimal technique.

A common example is suspected hospital-acquired pneumonia (HAP)/VAP, which accounts for approximately 50% of antibiotic use in the hospital (35). Clinical signs and symptoms alone are ineffective at diagnosing HAP/VAP. As such, current guidelines recommend using quantitative cultures from deep in the respiratory tract. This is because only approximately 40% of patients with signs and symptoms of VAP actually have VAP based on culture results (37). Thus, it is clear that these patients require a high-quality culture to avoid a massive misuse of antibiotics in patients who do not have an infection (38).

Discontinuing therapy in patients with negative cultures

The Centers for Disease Control and Prevention and Surviving Sepsis Guidelines recommend discontinuing antibiotics if cultures are negative and infection is unlikely. Again, HAP/VAP is a nice model for this concept because a lack of a clear consensus on diagnosis makes interpretation of culture results unclear. However, several recent studies suggest that empirical antibiotics for HAP/VAP can be safely discontinued in patients with negative pulmonary cultures who have infection clinically ruled out (39–43). Similarly, the guidelines for catheter-related bloodstream infection generally advise against a course of systemic antibiotics in patients with only an infected catheter but negative blood cultures. Exceptions include a catheter positive for *S. aureus* or if the patient is frankly septic (36). Nonetheless, the overall trend is clear that there is a large number of patients with negative cultures who can have antibiotics discontinued.

Streamlining therapy in patients with documented infections

A number of sources recommend streamlining antibiotics to narrower-spectrum agents based on culture results (32–34). This practice is intuitive; however, recent data suggest that it is safe (44) and even has been associated with improved outcomes (45).

Shorter duration of therapy in patients with documented infections

There are surprisingly few data on the optimal duration of definitive therapy for most infections in critically ill patients. However, recent research has started to answer this question for some infections. At least three studies in HAP/VAP have compared short- (7–8 days) and long-duration therapy (14–15 days) (46–48). Short-duration therapy was shown to be as effective as long-duration therapy in all three trials. In addition, patients with short-duration therapy had fewer relapses with resistant organisms (46–47). Current HAP/VAP guidelines recommend shortening definitive therapy to 7 to 8 days in patients who are clinically improving (35). Similarly, the Surviving Sepsis guidelines recommend 7 to 10 days of therapy for patients who are responding well (34). The catheter-related bloodstream infection guidelines recommend as few as 7 days of therapy for some pathogens (36). However, there are exceptions to shorter definitive therapy, including *Pseudomonas aeruginosa* HAP/VAP and *Staphylococcus aureus* bacteremia, both of which do not respond as well to short-term therapy (47, 49).

Aggressive dosing

The rationale for aggressive antimicrobial dosing has been discussed. Suboptimal dosing in critically ill patients may occur because of a lack of awareness about dosing recommendations, infections in spaces that have poor drug penetration (e.g., meningitis, pneumonia), and pharmacokinetic changes in some patients. Higher doses may be recommended for certain types of infections or for severe/life-threatening infections (Table 2). For other drugs, the Food and Drug Administration-indicated dose may not reflect the current knowledge of how to best dose the agent in a critically ill patient based on pharmacokinetic and pharmacodynamic data (Table 2). Vancomycin dosing has received particular attention lately. Current guidelines recommend keeping trough concentrations >10 mg/dL to avoid resistance. A trough concentration range of 15 to 20 mg/dL is recommended for severe infections (50). This will necessitate a dosing interval <12 hrs in many patients. It is unknown if therapeutic drug monitoring of vancomycin (or aminoglycoside) concentra-

Table 2. Examples of aggressive antimicrobial dosing needed for some intensive care unit patients

Drug	Typical Dose	Aggressive Dose	Reason
Cefepime	1–2 g every 12 hrs	2 g every 8 hrs	Provide optimal PK/PD against moderately susceptible organism (62)
Imipenem	500 mg every 6 hrs	1 g every 8 hrs or every 6 hrs	For moderately susceptible organisms in severe/life-threatening infections[a]
Meropenem	500 mg every 6–8 hrs	1–2 g every 8 hrs	Provide optimal PK/PD to avoid resistance (21)
Piperacillin/tazobactam	3.375 g every 6 hrs	4.5 g every 6 hrs	Nosocomial pneumonia[a]
Ciprofloxacin	400 mg every 12 hrs	400 mg every 8 hrs	Nosocomial pneumonia, severe/complicated bone/joint, skin/soft tissue infection[a]
Vancomycin	1 g every 12 hrs	15–20 mg/kg every 8–12 hrs	Provide optimal PK/PD in severe infections, avoid resistance (50)
Fluconazole	400 mg daily	6 mg/kg/d	Improve outcomes (63, 64)

PK/PD, pharmacokinetic and pharmacodynamic principles.
[a]Manufacturer's prescribing information.

tions affects resistance, but it is associated with improved patient outcomes and less nephrotoxicity (51).

Aggressive dosing is also warranted because some critically ill patients have increased volume of distribution and/or increased clearance of antimicrobials. ICU patients with burns are the most likely to have increased volume of distribution and clearance, but the phenomenon also can be seen in trauma and medical/surgical ICU patients (52).

Drug selection based on local patterns

It is recommended that empirical antibiotic selection should be based on local organism patterns (34, 35). This may allow the use of narrower-spectrum agents in patients who are not at high risk for infection with pathogens such as *P. aeruginosa* and methicillin-resistant *S. aureus*. The Clinical and Laboratory Standards Institute recommends that antibiograms be updated every 6 mos to 1 yr (53). However, because antibiograms traditionally only report the susceptibility patterns for organisms, the pattern of organisms actually causing infections also must be tracked to make the best empirical antibiotic decisions.

Drug selection/formulary restriction

Formulary restriction of certain drugs or drug classes has had mixed results in minimizing resistance (10, 33, 54). It appears that the best role for formulary restriction is as part of an overall program in controlling well-defined outbreaks of resistant organisms (54). Similarly, formal pathways have been used to affect antibiotic selection with some success in improving initial antibiotic selection, minimizing adverse drug events, promoting streamlining when culture results are known, and giving guidance on discontinuation (54). It is unclear if clinicians should avoid agents that may be associated with more resistance (as described). However, it may be reasonable to consider resistance potential as one of many factors in choosing agents.

Antibiotic cycling

Scheduled antibiotic cycling has been shown to decrease resistance in some single-center studies; however, not all studies have been successful. The study designs have been very heterogeneous, which limits applicability and comparisons (54, 55). Also, resistance modeling suggests that cycling may not be as effective as using a more routine, heterogeneous mix of antibiotic classes (55). Strict cycling also has the potential to "force" the clinician into rotating to an empirical regimen with less activity against expected pathogens in a given unit. Cycling is not routinely recommended by current guidelines (34, 35).

Antibiotic selection and the risk of Clostridium difficile-associated diarrhea

The development of *C. difficile*-associated diarrhea (CDAD) is essentially an adverse event of antimicrobial therapy that can turn into an outbreak and/or a chronic problem in an institution because of poor infection control. This is of utmost importance because the incidence of hospitalizations caused by or complicated by CDAD has increased from 5.5 cases per 10,000 in 2000 to 11.2 in 2005. In addition, the age-adjusted, CDAD-related mortality rate has increased from 1.2% to 2.2% over the same time period (56). Almost every antibiotic has been associated with CDAD (57). The Society for Healthcare Epidemiology of America/Infectious Diseases Society of America guidelines for preventing CDAD recommend implementing good antimicrobial stewardship to minimize antimicrobial therapy. More specifically, it is recommended that the use of antimicrobials that are "strongly associated" with CDAD be restricted (57). This recommendation seems to be aimed at fluoroquinolones because most of the recent data implicate this drug class (57). However, the data are not clear. Some studies have shown fluoroquinolones to be more strongly associated with CDAD than beta-lactams, macrolides, or clindamycin. Other studies have not shown a higher risk of CDAD with fluoroquinolones compared to beta-lactams. Other data suggest that antibiotics with anti-anaerobic activity are more strongly associated with CDAD (58). One possible explanation for the greater emphasis placed on fluoroquinolone restriction stems from the recent study of the virulent NAP-1/027 strain of *C. difficile* that was associated with the Quebec outbreak in the early 2000s. In addition to mutations of the regulatory *tcd*C protein, which results in hyperproduction of toxin A and B, as well as the production of binary toxin, the NAP-1/027 strain demonstrates high-level resistance to gatifloxacin and moxifloxacin and, thus, may have a competitive advantage in institutions with liberal fluoroquinolone use (59). Hospital formulary restriction and the corresponding reduction in antibiotic use appear to be an effective way to reduce the number of infections due to *C. difficile* (60–62).

Summary

Adverse events that occur as a result of antimicrobial resistance impact humanistic, clinical, and economic outcomes in the critically ill. Although not all antimicrobial agents have the same propensity to foster resistance, there are sufficient data that several agents, including the fluoroquinolones, carbapenems, and some cephalosporins, increase the risk of resistance. Effective diagnostic procedures to ensure the need for antimicrobial drug use are important. Empirical therapy should be based on local susceptibility patterns, and prescribing can be directed through formulary restriction, antibiotic cycling, or other means to limit inappropriate choices. In addition to judicious use of all antibiotics, appropriate and aggressive dosing to maximize the pharmacodynamic capabilities of each agent should be followed. Drug therapy should be discontinued in patients with negative cultures and should be streamlined when culture and sensitivity data are available. Shorter durations of therapy for documented infections may produce equivalent results and potentially lead to decreased resistance patterns.

Antimicrobial therapy will eventually be needed in the care of the critically ill. Resistance can be minimized by recognizing the resistance phenomenon as a preventable adverse drug event and by implementing processes as outlined in this article to minimize poor patient outcomes.

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