Routine Cycling of Antimicrobial Agents as an Infection-Control Measure

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Antimicrobial cycling is the deliberate, scheduled removal and substitution of specific antimicrobials or classes of antimicrobials within an institutional environment (either hospital-wide or confined to specific units) to avoid or reverse the development of antimicrobial resistance. True antimicrobial cycling requires a return to the antimicrobial(s) that were first used. Testing of the hypothesis that cycling will result in a lower prevalence of resistance is ongoing, mostly occurs within intensive care units, and largely involves cycling regimens targeted for treatment of suspected gram-negative bacterial infections. Unfortunately, there has been insufficient study to determine whether any meaningful impact on resistance has occurred as a result of a cycling program. Mathematical models question the usefulness of cycling as an infection-control method. Published studies demonstrate that cycling may be one way to change prescribing practices by clinicians without sacrificing patient safety. However, optimizing antimicrobial use through traditional and novel methods (e.g., computer decision support) should not be abandoned.

Health care delivery in the intensive care unit (ICU) continues to face new and difficult challenges. Patients who receive care in ICUs are at increased risk for hospital-acquired infections, especially pneumonia, urinary tract infection, and bloodstream infection [1]. Also, the emergence of antimicrobial-resistant pathogens in ICUs has made treating these infections very difficult or, in some cases, impossible [2]. The unique nature of the ICU environment makes this part of the hospital a focus for the emergence and spread of many antimicrobial-resistant pathogens. Rates of resistance have increased for most pathogens associated with hospital-acquired infections among patients in the ICU (figure 1) [3], and rates are almost universally higher among patients in the ICU than among patients who are not in the ICU [2].

However, there are many opportunities to prevent the emergence and spread of these antimicrobial-resistant pathogens through improved use of established infection-control measures (e.g., patient isolation, hand hygiene, glove use, and appropriate gown use) and implementation of a system to optimize appropriate use of antimicrobials in efforts to diminish environmental factors conducive to the emergence of antimicrobial-resistant bacteria [1]. One method to exert control over antimicrobial use among patients in the ICU is the systematic rotation of available antimicrobial agents for use in empirical and directed therapy in the ICU setting—that is, cycling of antibiotics.

PATHOGENS OF CONCERN

In general, the gram-positive organisms (e.g., Staphylococcus aureus and enterococci) are commonly associated with central line–associated bloodstream infections and surgical site infections [1]. The prevalence of methicillin-resistant S. aureus (MRSA) has increased steadily during the past decade. In 2000, more than 55% of the S. aureus isolates associated with hospital-acquired infection in patients in the ICU were resistant to nafcillin or oxacillin. Similar increases have been seen for enterococci resistant to vancomycin (figure 1).

Gram-negative bacilli frequently cause ventilator-associated pneumonia and catheter-associated urinary tract infection [1, 4]. Common antimicrobial-resistant pathogens encountered among patients in the ICU include Pseudomonas aeruginosa resistant to imipenem, quinolones, or cefazidime and Entero-
bacteriaceae resistant to third-generation cephalosporins, such as cefotaxime, ceftriaxone, and ceftazidime. Data from National Nosocomial Infections Surveillance (NNIS) system hospitals show that rates of resistance among these pathogens have increased to varying degrees during the past 5 years (figure 1). Furthermore, when pneumonia occurs later during the ICU stay, the likelihood that these pathogens are resistant to the antimicrobial of choice more than doubles (figure 2). This provides a window of opportunity for altering the selective pressure during the ICU stay and thereby altering the microflora of the oropharynx and reducing the risk of acquisition of antimicrobial-resistant pathogens.

### Changing Aggregate Antimicrobial Exposure

There are 2 major approaches to reducing excessive or inappropriate use of antimicrobials: those that attempt to optimize...

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**Table 1.** Proportion of isolates tested for resistance to select antimicrobial agents among pathogens associated with ventilator-associated pneumonia, by early (<7 days) versus late (≥7 days) onset category, National Nosocomial Infections Surveillance system, intensive care unit component, 1989–1999. Caz, ceftazidime; Cip, ciprofloxacin or ofloxacin; Imi, imipenem; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; Tobra, tobramycin.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Early (%)</th>
<th>Late (%)</th>
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<tbody>
<tr>
<td>Meth</td>
<td>40</td>
<td>60</td>
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<tr>
<td>Caz</td>
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<td>Caz</td>
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<td>Tobra</td>
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<td>Imi</td>
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**Figure 1.** Proportion of isolates of select pathogens associated with hospital-acquired infections that are resistant to the specified antimicrobial agent (percentage of resistant isolates) among patients in the intensive care unit, National Nosocomial Infections Surveillance system [3]. For each antimicrobial/pathogen pair, the pooled mean percentage of isolates resistant is determined for January through December 2000 (●). Next to or overlapping this point is the average percentage of resistant isolates (± 1 SD) during the previous 5 years (bars). Finally, the increase in the resistance rate in 2000 compared with the previous 5 years is shown in the column to the right of the graphed point (difference in the percentage of resistant isolates between 2000 and the historical mean, divided by historical mean) [3]. CNS, coagulase-negative staphylococci; E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; 3rd Ceph, third-generation cephalosporins.
use, and those that tend to optimize the availability of specific agents. Attempts to change clinician prescribing behavior may be extremely difficult, but these changes are likely to improve patient care and patient safety by providing the best anti-infective care available to patients. One promising method will be through improvement in information systems integrated into patient care activities, such as computer-assisted order entry and computer decision support. Studies of and demonstration projects for developing, testing, and implementing these systems are just beginning.

A second method—changing the availability of specific agents—is very attractive to hospital staff for its simplicity in implementation. One of the measures most commonly implemented is requiring prior authorization for administration of selected antimicrobials. Prior authorization may be required before all empirical use of antimicrobials, directed therapy, or prolonged therapy (i.e., for >3 days) or any combination of these. Three recent studies have demonstrated the impact of prior authorization on the incidence of antimicrobial-resistant infections [5–7]. In these studies, the goals of the prior authorization requirements were to reduce the current antimicrobial resistance problems and excessive costs of antimicrobials used. Within a year, each study demonstrated significant changes in the aggregate susceptibilities of relevant organisms, along with a 15%–22% decrease in the cost of caring for patients studied. However, these programs may not be able to sustain themselves.

The need for staff to support these programs to maintain their function has reduced their popularity, despite some apparent effectiveness. Many hospitals are embracing an absolute restriction of 1 or more specific agents to impact a specific antimicrobial resistance problem. This type of antimicrobial prescribing change is often referred to as a “single switch” and can change physician prescribing through a single switch from a specific agent or class of agents to other agents. Kollef et al. [8] switched the antimicrobial agent of choice for empirical therapy for suspected gram-negative bacterial infection in the cardiothoracic ICU. After a single switch from use of empirical ceftazidime to ciprofloxacin, the percentage of patients exposed to ceftazidime decreased significantly, from 20% to 7%, and there was a relative 25% decrease in the percentage of patients who were infected with ceftazidime-resistant, gram-negative bacteria. This study also demonstrated a decrease in the incidence of ventilator-associated pneumonia. Although the explanation of this finding is not clear, it may relate to the greater efficacy of fluoroquinolone versus β-lactam antimicrobials for suppression of nasopharyngeal flora. In a separate study of patients in the medical ICU, Kollef et al. [9] demonstrated an actual change in outcome (i.e., mortality) among the sickest patients in the ICU during the period in which scheduled single switches occurred. However, there is a major concern about the single-switch approach to reducing a targeted antimicrobial resistance problem: creation of a new resistance problem.

This concern is illustrated by the report by Rahal et al. [10] of a single switch from third-generation cephalosporin use in efforts to impact a recent increase in ICU-acquired infections with extended-spectrum β-lactamase–producing Klebsiella pneumoniae. After limiting the availability of third-generation cephalosporins, there was a relative 66% decrease in the amount of cephalosporins used and a 44% decrease in the incidence of ICU-acquired infection with β-lactamase–producing K. pneumoniae. Unfortunately, during this time, the incidence of infections due to imipenem-resistant P. aeruginosa increased by >60%. The authors attribute this increase to a 140% increase in imipenem use in 1996, compared with 1995. This unintended consequence of the single-switch approach was termed “squeezing the balloon of resistance” by John Burke. In his 1998 editorial, Burke [11] noted that addressing antibiotic resistance by limiting the use of one class of compounds may be countered by corresponding changes in prescribing and drug resistance that are even more ominous. These concerns have led several clinical researchers to explore methods of changing the availability of antimicrobials by routinely cycling available classes of agents to avoid “squeezing the balloon.”

**METHODOLOGIES OF CYCLING**

Scheduled changing of antimicrobials, or “cycling of antimicrobials,” is the premeditated cyclic introduction or removal of specific classes of agents from routine use in a patient population. The duration of these cycles may be determined on the basis of the local microbiologic flora (i.e., local cumulative susceptibility patterns) or a preset time period. The goal of cycling is not just to reduce a current antimicrobial resistance problem, but also to prevent the emergence of new resistance. However, the efficacy and harmful effects associated with cycling programs are unknown.

Many of the methodological issues involved in the cycling of antimicrobials were reviewed by Gerding [12]. For a successful study, it was considered critical to monitor several ongoing factors: the differentiation of clinical isolates representing infection from colonizing isolates, the quality of care delivered and the stability in infection-control measures during the cycling program, a system to track antimicrobial use, and support from clinical staff to participate in the cycling program. In addition, Gerding [12] suggests that either prospective or retrospective monitoring of the changing genetics of the resistant organisms will aid in interpretation of the observed effect of the cycling program.

Such monitoring helps explain the observations of Gerding et al. [13] from their experience with antimicrobial cycling in the 1970s. Gerding and colleagues [13] reported that changes
in the formulary resulted in parallel increases in the rate of gentamicin use and the prevalence of gentamicin-resistant, gram-negative organisms when gentamicin replaced amikacin as the agent available. During the next 10 years, amikacin alternated with gentamicin as the agent of choice in a cycling fashion, and the prevalence of gentamicin resistance dipped and peaked in alternation with amikacin resistance. After several cycles, the resistance problem stabilized at a low level. They later determined that the plasmid that mediated most gentamicin resistance earlier was now absent.

**CHANGING AGGREGATE ANTIMICROBIAL USE THROUGH CYCLING**

The regimens studied in published reports of cycling vary in terms of antimicrobial classes cycled, duration of cycling, flexibility of therapy choices by clinicians, and adjunct controls on or restriction of use of agents [8, 14–19]. Although antimicrobial cycling is attractive in theory for its relative feasibility and ease of implementation, several recent publications indicate that as many as 10%–50% of patients get exposed to antimicrobials that are “off-cycle” due to the clinician’s concerns over allergies, side effects, or consistency with national guidelines.

Gruson et al. [15] demonstrated that antimicrobial cycling in medical ICUs by implementation of a combined antibiotic use restriction (for ciprofloxacin and ceftazidime) and rotation policy significantly reduced specific antimicrobial resistance problems in their ICU. Results demonstrated dramatic decreases in use of both ciprofloxacin and ceftazidime, along with increases in the use of cefepime and piperacillin/tazobactam, during the overall cycling period. However, the generalizability of these findings is not clear. The empirical and therapeutic antimicrobial use guidelines created for this study were implemented through direct supervision by clinicians in the medical ICU under study. The treatment algorithms were cycled monthly, which is much more rapid than the treatment algorithms used in other published studies, which tended to cycle every 3–6 months. Furthermore, therapy was changed to de-escalate or narrow the spectrum of coverage, regardless of the cycling regimen, after diagnostic culture results were available. This approach allowed switching to off-cycle agents, which is inconsistent with the principle of cycling. However, it is consistent with attempts to avoid excessive use of broad-spectrum agents. In fact, this study demonstrated a 50% reduction in overall antimicrobial use, which may actually overshadow any impact the cycling program may have had on the measured outcomes.

A more generalizable result may be the lack of impact on changing prescriber habits of a cycling program reported by Bochorishvili et al. [19]. After reviewing the records of patients who received quinolones when quinolones were off-cycle, they found that clinicians were reluctant to treat community-acquired pneumonia without quinolones in the context of national consensus guidelines that recommended use of these agents as first-line therapy.

Raymond et al. [16] at the University of Virginia studied the impact of rotating empirical antimicrobial regimens among postoperative patients during a 2-year period. In this study, a separate empirical regimen was in place for each of the 2 most frequent syndromes in this population, peritonitis/sepsis and nosocomial pneumonia. Although there were 4 cycles, only 2 regimens were cycled: carbapenems (for peritonitis), and ciprofloxacin and clindamycin (for pneumonia), were alternated with cefepime and metronidazole (for peritonitis), and piperacillin/tazobactam (for pneumonia). Compared with the rate of use during the baseline period, the use of the classes of agents in the cycled regimen doubled during each cycling period. Furthermore, the use fluctuated by quarter of the calendar year, as in a true cycling algorithm (figure 3). Also, review of antimicrobial use revealed that 62%–83% of all use was within the proposed guidelines. This was likely because flexibility was provided to clinicians by allowing syndrome-based choices of antimicrobial agents. This study illustrates that cycling can be accomplished in a surgical ICU; however, no single class of antimicrobial agent accounted for >80% of antimicrobials used during any particular cycle. The result was really due more to the controlled mixing program than to the cycling program.

**REDUCING ANTIMICROBIAL RESISTANCE THROUGH CYCLING**

In general, to date, cycling studies have been limited to single ICUs, introducing many limitations on the ability to interpret and generalize the findings. Also, these studies have evaluated outcomes relying on infecting isolates, which represent only the tip of the iceberg when studying the ecology of antimicrobial resistance among ICU patients. Few of the antimicrobial-resistant organisms circulating and accumulating in an ICU are detected from clinical cultures, and, on average, only 1 in 4 clinical isolates represent ICU-acquired infections [20]. This forces researchers to lump different outcomes together (e.g., total number of antimicrobial-resistant, gram-negative bacteria). This may be misleading, because the resistance mechanisms for the different pathogens can differ, and the expected impact of altered antimicrobial agent pressure likely differs among these pathogens. Finally, analyses of these data tend to be lumped into a before-after design. This type of study design lacks a contemporaneous control group and usually does not account for the natural variation in resistance rates between months. Using time-series analysis would be ideal, but this requires multiple sites of study or long periods of study [21].

None of the studies show improvements in the antimicrobial
susceptibilities of the specific pathogen targeted by the cycling program [8, 14–18]. However, several results are of interest. A cycling program from a medical ICU reported by Gruson et al. [15] appears to have been successful, but the results may not be generalizable for several of the reasons outlined above. The pathogen of greatest interest in this study was \textit{P. aeruginosa}. Although there were slight improvements in susceptibility to ciprofloxacin (an increase from 61% to 78%) and ceftazidime (an increase from 63% to 74%), these changes were not statistically significant. Approximately 50 isolates were recovered from enrolled patients with infections; this was an insufficient number to measure statistical differences unless the resistance problem was essentially eliminated. Although the basic profile of pathogens remained unchanged (e.g., Enterobacteriaceae, \textit{S. aureus}, and \textit{P. aeruginosa}), there was a significant decrease in the number of cases of ventilator-associated pneumonia associated with “potentially antimicrobial-resistant gram-negative bacteria.” This decrease was actually attributed a lower incidence of \textit{Burkholderia cepacia}, \textit{Stenotrophomonas maltophilia}, and \textit{Acinetobacter} species and not to a lower incidence of antimicrobial-resistant \textit{P. aeruginosa}. However, further data on the longer-term impact of this program may yield different results.

Likewise, despite the apparent “success” of a cycling program in the surgical ICU reported by Raymond et al. [16], the impact of that program is not clear. The authors did report decreases in infections due to antimicrobial-resistant, gram-negative and gram-positive organisms. However, the population of patients who had these infections during the intervention period differed from that of the baseline period; the typical infection in the baseline period occurred later in the ICU stay and tended to occur more frequently in patients who had received transplants, who were undergoing hemodialysis, or who had severe liver disease. These host factors need to be considered when we evaluate any change in antimicrobial resistance observed in the cycling period. Second, use of a waterless hand hygiene agent was introduced during the cycling period. Infection-control improvements such as this may have significantly reduced cross-transmission of resistant organisms in this ICU and may explain the decrease in methicillin-resistant \textit{S. aureus} as a cause of ventilator-associated pneumonia.

Moss et al. [17] reported a study from a 16-bed, pediatric medical-surgical ICU in which 3 antibiotic classes were systematically cycled at 3-month intervals for 18 months. Antibiotic regimens were used for all empirical therapy and continued to be used if the bacterial isolate was susceptible (i.e., there was no de-escalation), to minimize use of off-cycle agents. Using surveillance cultures to determine colonization with antibiotic-resistant bacteria, they concluded that cycling of broad-spectrum, empirical antibiotics appeared to be safe. However, a larger study would be needed to measure significant changes in organism susceptibility.

THEORETICAL MODELS TO PREDICT THE IMPACT OF CYCLING

Because the ideal studies may not be achievable, several researchers have been working with theoretical constructs to identify the potential impact of antimicrobial cycling [22]. Mathematical models are a useful tool to determine the con-
ditions under which cycling could be effective and to compare expected benefits of cycling and of “mixed” antimicrobial use (in which a fixed proportion of patients are treated with each of 2 antibiotics). Lo et al. [23] used a stochastic mathematical model (in which one accounting for expected random variation) of the transmission of drug-susceptible and -resistant colonizing bacteria to compare various antimicrobial cycling policies against each other and against “mixed” regimens in an ICU. Simulations compared cycling periods of 7–240 days against variable mixed regimens of 2 drugs (0%–100% mixing) for 204 different parameter combinations corresponding to different kinds of ICUs. In 77% of the theoretical ICUs, the total burden of colonization with drug-resistant strains was lowest with use of a mixing regimen. Cycling substantially outperformed mixing in only 8 ICUs (4%); these ICUs were characterized by the infrequent admission of patients colonized with resistant strains. On the basis of these models, simultaneous mixed use of different antimicrobial classes for different patients in a unit appears to be more effective than cycling. However, there are several reasons why these models may not be applicable to the real world. For example, these models did not consider the impact of multiple-drug resistance conferred by multidrug efflux pumps or plasmids encoding multiple antimicrobial-resistance elements.

SUMMARY AND CONCLUSIONS

Several salient points can be summarized from this review. First, changing the availability of classes of agents appears to reduce the prevalence of resistance. However, new resistance may rapidly emerge, even within 6 months. Compliance with the cycling programs reported to date varied, and it may be impossible to “turn off” use of specific agents completely with these programs—it appears that use of a mix of antimicrobial classes is the end result. In most of these studies, the cycling program did not compromise the quality of patient care delivered to the patients. In fact, 3 studies documented decreases in disease incidence or mortality during the period of antimicrobial cycling or switching [8, 9, 15]. The reasons for this are unclear, but they may be related to better initial empirical coverage or the alteration of nasopharyngeal flora with use of study-driven therapy. A second explanation is that the oversight or availability of study personnel may have resulted in improved supervision and antimicrobial use stewardship. Cycling may be one way to force prescribing changes among clinicians. However, optimizing antimicrobial use through more-difficult methods, such as physician education, computer-assisted decision support, drug use evaluations, and performance feedback, should not be ignored. These methods may offer long-term gains in improving antimicrobial stewardship in hospitals. Unfortunately, there has been insufficient study to determine whether any meaningful impact on resistance has occurred as a result of a cycling program. The optimal study may be best accomplished using a randomized cluster design (i.e., ICUs randomized to undergo the cycling intervention), accounting for different rates of colonization pressure among newly admitted patients. In addition, the duration of the study must account for natural variation in the incidence of colonization and infection with antimicrobial-resistant organisms in ICUs. Patients in the ICU are the most complex and fragile patients in the health care delivery system. Use of evidence-based approaches to reduce antimicrobial resistance is paramount to promoting patient safety. Additional study of cycling of antimicrobials to reduce resistance in this population is needed before this intervention is widely implemented.

References