

FIGHTING THE NEVER-ENDING BATTLE AGAINST ANTIMICROBIAL RESISTANCE

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Rapidly increasing antimicrobial resistance is one of the most serious clinical microbiologic problems facing medicine today. With so many patients in the intensive care unit (ICU) at risk for bacterial and fungal infections, strategies to combat antimicrobial resistance and effectively treat infection are of great importance.

Reducing Antimicrobial Resistance in the ICU

"In truth, we really can't prevent antimicrobial resistance. Rather, it's something we need to try to control," stated Marin H. Kollef, MD, from Washington University in St. Louis, Missouri. One key to controlling resistance is to look at antimicrobial treatment in the ICU as a balancing act. "On one hand, we need to think about appropriately treating patients," Kollef said. "On the other hand, we always need to be thinking about avoiding unnecessary antimicrobial use."

Antimicrobial resistance is of great concern because of its associated increase in morbidity, mortality, and healthcare costs—and because fewer effective antimicrobial agents are available today. One example of ineffective agents can be seen in the quinolone class. According to a study reported in 2003, increases in fluoroquinolone use paralleled increases in resistance rates in *Pseudomonas aeruginosa* and gram-negative bacilli infections from 1990 to 2000 (Neuhauser et al. *JAMA*. 2003;289:885). "Part of the reason for this may have been some underdosing of quinolones," noted Kollef, "particularly for infections in the lung, where you might not get adequate penetration."

The link between more frequent use of an antimicrobial agent and increased resistance, and hence, increased mortality, is well known. "We also know that the resistance mechanisms involve beta-lactamases and multiple efflux pumps," he said. "Whether we like it or not, accumulation of extended-spectrum beta-lactamases (ESBLs), AmpC beta-lactamases, and fluoroquinolone resistance is driving more use of carbapenem." The consequence of that is higher rates of resistance.

The incidence of sepsis in the United States has been rising and is expected to continue to climb over the next few decades (Angus et al. *Crit Care Med*. 2001;29:1303). "Thus, we'll see the need for increased antimicrobial use and more problems with resistance," said Kollef. Using the appropriate agent initially is crucial, he noted, citing data that revealed increased mortality when inappropriate initial antimicrobial therapy was administered (Ibrahim et al. *Chest*. 2000;118:146).

Illustrating the importance of appropriate initial therapy, Kollef described a study involving patients who presented to the emergency department (ED) with septic shock (Micek et al. *Crit Care Med*. 2006;34:2707). Computer-based algorithms indicating appropriate antimicrobial treatment for patients with septic shock were developed for ED staff. Most patients received combination therapy consisting of three antibiotic agents. The ED-based sepsis protocol was associated with reductions in mortality, decreasing from 48.3% to 30% ($p=.04$), length of stay, and costs. No new antimicrobial resistance occurred among these patients, and they were more likely to be treated with an appropriate initial regimen compared with patients who were treated before the algorithms were instituted.

The Centers for Disease Control and Prevention (CDC) provides a 12-step approach to preventing antimicrobial resistance among hospitalized adults (see Table 1). One step involves catheters. "Removing catheters as soon as possible is critical because that's where biofilm forms and where resistance can emerge," Kollef said. Prevention programs are effective in educating ICU nurses and physicians on maintenance of catheters, hand-washing, proper attire during catheter placement, sterilization technique, proper barrier precautions, and other procedures that will minimize the rate of catheter-related infections.

The CDC also recommends targeting pathogens and using local data. "De-escalation and local surveillance are the ways to

handle that," Kollef said. "New technologies are being developed to provide rapid microbiologic evaluation, but until they become available we still have to treat infections broadly. De-escalation is one tool we can use to try to minimize resistance." Examples of de-escalation in the treatment of ventilator-acquired pneumonia (VAP) have been reported in the literature (Rello et al. *Crit Care Med*. 2004;32:2183; Leone et al. *Crit Care Med*. 2007;35:379). De-escalation, which involves narrowing the therapy once microbiologic results are obtained, also enables the clinician to use the shortest course of therapy that is clinically adequate for the infection.

Duration of antimicrobial therapy is of concern in terms of efficacy and potential for resistance. Investigators have reported that longer (15 days vs. 8 days) antimicrobial therapy for VAP had no impact on survival (Chastre et al. *JAMA*. 2003;290:2588). Other researchers examined the occurrence of unnecessarily prolonged antibiotic use in the ICU and found that 50% of patients who had no evidence of infection were still receiving antimicrobial therapy one week later (Aarts et al. *Intensive Care Med*. 2007;33:1369).

Correct dosing also is essential to minimizing antimicrobial resistance. "You have to hit the organism hard up front with the right dose," he said. He cited an investigation of four dosing regimens of meropenem, which found that the highest dose (2 g every 8 hours over a 3-hour infusion) gave the greatest likelihood of appropriately treating *P aeruginosa* and minimizing the emergence of resistance (Santos et al. *Clin Microbiol Infect*. 2007;13:579).

The CDC's seventh and eighth steps involve treating the infection, not the contamination or colonization. An example of this is seen in patients who undergo bronchoalveolar lavage (BAL). Ibrahim et al described the results of a protocol for patients who underwent BAL and had suspected VAP (Ibrahim et al. *Crit Care Med*. 2001;29:1109). All were treated with combination antimicrobial therapy, based on the unit-specific antibiogram. "The key part was de-escalation," said Kollef. "Therapy was modified within 48 hours based on the culture results, and was limited to 7 days. Importantly, the protocol reduced the duration of treatment in the majority of cases."

In closing, Kollef contrasted the old and new paradigm of antimicrobial treatment. The old paradigm advocated starting therapy with narrow-spectrum agents, such as penicillin, and using the efficient low dose, which also may be associated with fewer adverse effects. Duration of therapy under the old paradigm was long: at least 2 weeks. "With the new paradigm, you want to get it right the first time and follow an aggressive de-escalation approach," Kollef explained. "That means hitting the organism hard up front. You also want to avoid low doses, which promote resistance. It's important to optimize the dosing; our pharmacy colleagues can guide us. In terms of duration, seldom do we need to push therapy beyond 7 days."

Table 1. 12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults

Prevent Infection

- Step 1: Vaccinate
- Step 2: Remove catheters as soon as possible

Diagnose and Treat Infection Effectively

- Step 3: Target the pathogen
- Step 4: Access the experts

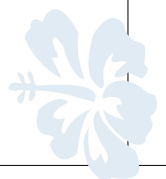
Use Antimicrobials Wisely

- Step 5: Practice antimicrobial control
- Step 6: Use local data
- Step 7: Treat infection, not contamination
- Step 8: Treat infection, not colonization
- Step 9: Know when to say "no" to vancomycin
- Step 10: Stop antimicrobial treatment when cured

Prevent Transmission

- Step 11: Isolate the pathogen
- Step 12: Break the chain of contagion

Centers for Disease Control and Prevention (CDC)



Management of Multiple Drug-Resistance Bacterial Infections

New antimicrobial agents are on the horizon that target multiple-drug resistant infections, which include methicillin-resistance *Staphylococcus aureus* (MRSA), *P aeruginosa*, *Acinetobacter* species, and other gram-negative organisms. In addition, one compound that has been around for a while shows promise in combating multiple-drug resistant infections, according to Steven J. Martin, PharmD, FCCM, from the University of Toledo College of Pharmacy.

Newer agents showing efficacy against MRSA include dalbavancin, oritavancin, telavancin, daptomycin, linezolid, tigecycline, and ceftobiprole. In the treatment of gram-negative organisms, effective newer agents include doripenem, ceftobiprole, and tigecycline, and colistin, which is the oldest of these drugs. Martin focused on a few of these agents.

Doripenem. Doripenem, a new carbapenem, has a similar bactericidal spectrum to that of imipenem and meropenem. It has broad activity against most gram-negative rods, most gram-positive cocci, and most anaerobes. Binding to bacterial membranes, doripenem demonstrates similar or somewhat better potency against *P aeruginosa* compared with imipenem or meropenem. Doripenem also exerts strong activity against *Acinetobacter* species, *Enterobacter aerogenes*, ESBL-producing organisms (*Escherichia coli*, *Klebsiella pneumoniae*), and many other gram-negative rod organisms. In terms of activity against gram-positive cocci, doripenem is not effective in treating MRSA, but it does demonstrate efficacy against pneumococci, particularly penicillin-resistant pneumococcus. Current indications for doripenem include intra-abdominal infection, urinary tract infection, and pyelonephritis.

Doripenem has a relatively short (1 h) half-life, as do other carbapenems, and is administered every 8 hours. "Infusion time and the pharmacodynamic properties of this drug can be put to advantageous use," said Martin. Doripenem undergoes renal elimination.

Recent data from two international multicenter trials show the efficacy of doripenem in the treatment of nosocomial pneumonia (Ortho-McNeil, Inc. Data on file; 2007.) In one study, patients with early onset VAP were randomized to receive doripenem 500 mg every 8 hours or piperacillin/tazobactam 4.5 g every 6 hours. The infusion time for the doripenem dose was short (30 min). When *Pseudomonas* or MRSA infections were suspected, adjuvant therapy consisting of amikacin (80%)/vancomycin (15%) was instituted. "Although the overall clinical cure rates were similar in patients who did not have *P aeruginosa* infection, differences in clinical cure rates were observed for the two therapies among patients with *P aeruginosa*—83% for doripenem versus 71% for piperacillin," he said.

The second study compared doripenem 500 mg every 8 hours over a prolonged (4-hour) infusion with imipenem 500 mg every 6 hours in patients with early/late VAP. "Once again, dramatic differences favoring doripenem were seen in patients who had *P aeruginosa* infection. Clinical cure rates were 65% with doripenem and 35% with imipenem," he reported. "These findings suggest that perhaps a change in the infusion length could have an impact on outcome."

Research indicates that for concentration-independent antimicrobial drugs such as the carbapenems, bactericidal activity is obtained when the time above the minimal inhibitory concentration (MIC) for the dosing interval reaches at least 40%. "Thus, a 4-hour infusion instead of a 30-minute infusion of doripenem may make a great deal of sense," said Martin.

Colistin and Polymyxin B. Although colistin and polymyxin B have been around for decades, their use in the treatment of infections caused by gram-negative organisms is new. Both of these agents are bactericidal and exert their action by binding to the phosphate groups in the lipids of the cytoplasmic membrane of the organism. They are active against nearly all gram-negative bacteria, except *Proteus* species, *Burkholderia cepacia*, *Providencia* species, *Serratia mar-*

escens, *Moraxella catarrhalis*, *Morganella morganii*, *Neisseria gonorrhoeae*, and *N meningitidis*. Colistin and polymyxin B show no activity against the gram-positive bacteria or fungi.

Colistin and polymyxin often are used with other drugs in combination therapy. Limited data suggest a synergistic bactericidal effect in vitro is achieved when colistin is used with rifampin or ceftazidime, particularly against *P aeruginosa* (Sarkar. *Am J Health Syst Pharm.* 2007;64:2462; Zavascki. *J Antimicrob Chemother.* 2007;60:1206).

Clinical data focus on case reports on the use of colistin in the treatment of *P aeruginosa*, *Acinetobacter baumannii*, *E coli*, and *K pneumoniae* (Sarkar. *Am J Health Syst Pharm.* 2007;64:2462). "Although there are limited data in the literature on the microbiologic response observed with this drug in multidrug-resistant infections, empirically colistin therapy appears to be a sound idea," Martin noted.

Use of colistin fell out of favor in the 1960s due to its nephrotoxic properties. In case reports of 199 critically ill patients who were treated with colistin for multidrug-resistant infections, nephrotoxicity was observed in 52 (26%) patients (Sarkar. *Am J Health Syst Pharm.* 2007;64:2462). Colistin also has neurotoxic properties as a neuromuscular blocking agent, but a neurotoxic effect may be difficult to detect in sedated or critically ill patients.

The dosing, pharmacokinetics, and pharmacodynamics of colistin have not been studied well. More work has been reported on the use of colistin in patients with cystic fibrosis than in the critically ill population, leaving the door open to future research in this area.

Dalbavancin. Dalbavancin is a second-generation glycopeptide that received recent Food and Drug Administration (FDA) approval. Like vancomycin, it has broad gram-positive activity, which includes MRSA, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci (VRE). Unlike vancomycin, dalbavancin has a very long half-life (170-210 h). "Thus, dalbavancin allows once-weekly dosing, which is an interesting concept," Martin stated. "Dalbavancin provides a long period of time in which the concentration is above the MIC for most MRSA organisms." Approximately 40% of the intact drug is eliminated renally, and up to 50% is excreted into the feces. Dalbavancin does not appear to produce any significant adverse effects.

Microbiologic data indicate that dalbavancin possesses slightly more potent MICs against methicillin-sensitive *S aureus* (MSSA) than vancomycin and greater potency against MRSA infections than vancomycin, linezolid, or daptomycin (Chen. *Int J Clin Pract.* 2007;61:853). When studied in complicated skin and skin structure infections, dalbavancin and linezolid had similar cure rates (Jauregui. *Clin Infect Dis.* 2005;41:1407). In an open-label multicenter trial comparing dalbavancin and vancomycin in the treatment of catheter-related bacteremia, the success rates were 87% and 50% for dalbavancin and vancomycin, respectively.

Ceftobiprole. Ceftobiprole is an extended spectrum cephalosporin that has activity against MRSA and penicillin-resistant *S pneumoniae* and limited activity against *P aeruginosa* and *Acinetobacter* species. It has a 3- to 4-hour half-life, and is administered as a pro-drug. Ceftobiprole undergoes renal elimination.

Ceftobiprole studies indicate that the agent is effective in inhibiting the growth of 92% of 372 Enterobacteriaceae isolates. This includes ESBL- and AmpC-producing strains (Jones. *Clin Microbiol Infect.* 2007;13[suppl 2]:17). "Ceftobiprole is the only cephalosporin that has effective MRSA activity, as well as other staph infections," Martin said. "It has a similar potency to linezolid or vancomycin against these infections."

In summing up his presentation, Martin noted that more data are needed to learn about these new compounds. He also stressed that the number of new antimicrobials is limited. "With that in mind, good stewardship of antimicrobial use is key to drug preservation," he said.

Managing Invasive Fungal Infections

“Fungal infections are an important problem in the ICU,” said Pamela A. Lipsett, MD, FCCM, from Johns Hopkins University School of Medicine and Nursing in Baltimore, Maryland. “In fact, 10% of bloodstream infections in the ICU are caused by *Candida* species, and these infections—the third most common seen in critical care—have crude mortality rates ranging from 40% to 80%.”

Approximately 72% of all fungal pathogens in the ICU are *C. albicans*. The second most common ICU fungal pathogen is *C. glabrata*. Others include *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. In patients who have undergone solid organ transplantation or who have neutropenia, *Aspergillus* species and other molds are emerging as pathogens of concern. About 50% of respiratory and rectal cultures and a smaller percentage of urinary and wound cultures reveal the presence of fungi, but this does not necessarily signify infection. Rather, it is colonization that usually indicates infection. (Laverdiere et al. *J Crit Care*. 2007;22:245; Pfaller et al. *Clin Microbiol Rev*. 2007;20:133).

“It is important to identify the fungal species, because some are either resistant or partially susceptible to azole agents,” Lipsett stated. For example, amphotericin may not be effective against *C. glabrata*. Fluconazole should not be used against *C. krusei*, which is resistant to the agent. It is also ineffective in *Aspergillus* infections.

Clinicians also must be aware that fungi can have dose-dependent sensitivity to antifungals: the larger the dose, the greater the likelihood of eradication. “Some *C. glabrata* infections, for instance, require a higher than normal dose of fluconazole,” said Lipsett. “Instead of administering a standard dose of 400 mg, you can give an 800-mg dose and it will be effective. This is called *dose-dependent sensitivity*.”

In discussing antifungal use, Lipsett defined some terms. Treatment refers to therapy for proven or probable infections. Empiric treatment refers to therapy given for suspected infection. Preemptive treatment refers to therapy given when the patient has fungal colonization and risk factors for infection. When a patient has risk factors but no known colonization, antifungal therapy is referred to as either general or targeted prophylaxis.

“The problem is there are no consensus definitions about what a fungal infection is and is not in patients who do not have neutropenia,” stated Lipsett. According to the published microbiologic definition, fungal infection consists of the following: detection of fungal elements by cytology or direct microscopy from sterile fluids, detection of *Candida* casts in the urine without a catheter, or detection of *Candida* in the blood (de Paw et al. *Clin Infect Dis*. 2005;41[suppl 6]:S377).

Intensivists need to be knowledgeable in the major risk factors for various ICU fungal infections (see Table 2). Several risk factors also have been identified for disseminated fungal disease: antibiotic therapy for longer than 6 days, treatment with three or more antimicrobial agents, acute renal failure, central venous catheter, age older than 40 years, gastrointestinal surgery, diabetes mellitus, cancer, parenteral nutrition, trauma (multiple), steroids, burns and gram-negative species.

“There is much excitement in antifungal drug development today,” she said. “We now have a wide variety of treatment options for candidemia.” These include amphotericin B deoxycholate, fluconazole (intravenous and oral), amphotericin B lipid complex (ABL-C), amphotericin B colloidal dispersion (ABCD), liposomal amphotericin B, the three echinocandins that became available in 2007 (casposfungin, micafungin, and anidulafungin), and the new tertiary azole agents (voriconazole and posaconazole).

In making a selection among these antifungals, the availability of the agent must be determined. “Then you need to have some idea about the likely pathogen and be familiar with your local pathogens and the sensitivity these pathogens,” stated Lipsett. “You also need to know if the patient has been exposed to any azole agents, which may suggest development of a more resistant pathogen profile.”

According to a meta-analysis of studies comparing the use of flucanazole versus amphotericin in candidemia, no differences in clinical or microbiologic response rates were found, but a greater amount of toxicity was associated with amphotericin (Kontoyiannis et al. *Mycoses*. 2001;44:125). Other data show generally no differences in efficacy outcomes between high-dose (800 mg) fluconazole compared with placebo and with fluconazole plus amphotericin (Rex et al. *Clin Infect Dis*. 2003;36:1221). “Perhaps the only signifi-

cant—and certainly interesting—finding was that the blood did not clear as well with high-dose fluconazole therapy. At present, there is no recommendation to use high-dose fluconazole on a routine basis or to use a combination of amphotericin and fluconazole,” Lipsett said.

In the echinocandin class, half-life differences are seen among the three agents. Anidulafungin, the most recently released of these drugs, has the longest half-life (26.5 h) and the largest volume of distribution. It also is the only echinocandin that is metabolized chemically, with no hepatic involvement.

Clinical trials indicate that casposfungin is similar to amphotericin in treating candidemia in patients with neutropenia (Mora-Duarte. *N Engl J Med*. 2002;347:2020). In addition, no significant differences in efficacy have been observed with casposfungin versus fluconazole (Reboli et al. *N Engl J Med*. 2007;356:2472).

In comparing two echinocandins—casposfungin and micafungin—no differences were found in time to clearance, mortality rates, relapse or adverse events (Pappas et al. *Clin Infect Dis*. 2007;45:883).

In the triazole class, voriconazole was found to be as effective as a regimen of amphotericin followed by fluconazole in the treatment of candidemia in patients without neutropenia (Kullberg et al. *Lancet*. 2005;366:1435). “This would not be true for *Aspergillus* infections, however,” remarked Lipsett. “Voriconazole is actually more effective than fluconazole in treating *Aspergillus* infections.”

Identifying patients at risk for candidemia is important, as they can develop this infection within the first 2 days of entering the ICU. “Many fungal pathogens grow slowly, so if you don’t suspect a fungal infection and you do not begin therapy empirically, there’s a high risk of mortality,” Lipsett said.

New guidelines from the Infectious Diseases Society of America are expected to be released soon. These guidelines will include the new agents that have established their non-inferiority in clinical trials and that might be better in some situations of resistance or toxicity.

Lipsett concluded her discussion of ICU fungal infections by emphasizing the need to consider the possibility of fungal infection in high-risk patients. “Initial therapy needs to be timely and correct. Because of low rates of resistance to azole drugs, I believe fluconazole is the drug of choice. However, if you are in a situation where there are high rates of either azole resistance or *C. glabrata* or *C. krusei* organisms, echinocandins should be considered as first-line therapy.”

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Table 2. Risk Factors of Fungal Infections Seen in the ICU

Risk Factor	Pathogen
Mucosal and cutaneous barrier disruption	<i>Candida</i> , <i>Aspergillus</i>
Neutrophil dysfunction	<i>Candida</i> , <i>Trichosporon</i> , <i>Aspergillus</i> and other molds
Defects in cell-mediated immunity	<i>Cryptococcus</i> , endemic
Metabolic disorders	<i>Zygomycetes</i> , <i>Candida</i>
Exposures	Endemic, <i>Aspergillus</i> and other molds
Age (<1 and >70 y)	<i>Candida</i>

Geerts et al. *Chest*. 2007;119:1325

Continuing Education Self-Assessment

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3. Among patients with ventilator-acquired pneumonia, antimicrobial therapy for 15 days was associated with lower mortality rates compared with 8 days of antimicrobial therapy.
 - a. True
 - b. False
4. Which of the following agents has efficacy against methicillin-resistant *Staphylococcus aureus*?
 - a. Dalbavancin
 - b. Doripenem
 - c. Voriconazole

Complete the post-test at www.sccm.org/CongressReview08.

