A 2-Part Series on

Emerging Modalities to Combat Resistant Gram-Negative Pathogens In Critically Ill Patients:

Part 1: Changes in Gram-Negative Resistance Over Time

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PROGRAM OVERVIEW As confirmed by numerous reports and surveillance studies, multidrug-resistant (MDR) Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are increasing worldwide and pose a considerable public health threat, particularly among hospitalized patients. Data from the National Nosocomial Infections Surveillance (NNIS) System indicate that Gram-negative isolates are the most frequently reported pathogen (65.9%) associated with ICU-acquired pneumonia. Gram-negative pathogens also have been implicated in nosocomially acquired complicated skin and soft-tissue, intra-abdominal, and urinary tract infections, among others. Hospital-acquired Gram-negative infections impose excessive cost burdens, prolonged hospital stays, and increased risks for mortality on affected patients. MDR Gram-negative pathogens enhance virulence, restrict the number of viable therapies, delay the use of effective therapy, and may necessitate the use of more toxic agents. Selective pressures of the use, misuse, and overuse of antimicrobials have resulted in new variants of β-lactamase; thus, resistance to expanded-spectrum β-lactam antimicrobials has rapidly emerged. Reduced access to target, inactivating enzymes, and mutational resistance are just some of the ways that Gram-negative pathogens confer resistance. Collectively, these mechanisms result in resistance to virtually all clinically available antimicrobials, underscoring the urgent need for novel pharmacotherapies.

Clinicians' awareness of emerging Gram-negative pathogens can facilitate more appropriate treatment selection and help prevent the emergence of further resistance. Besides the need for new therapies, comprehensive infection control efforts are appropriate, such as the more prudent use of antimicrobials, active surveillance, and implementation of antimicrobial stewardship programs to prevent emergence and cross-transmission of these pathogens. This special report describes the epidemiology, mechanisms, and predictors of Gram-negative resistance and provides sound strategies and proven institutional programs to prevent and control the emergence of resistance among critically ill patients.

LEARNING OBJECTIVES After reviewing this supplement, participants should be able to:

1. Discuss the emergence of resistant Gram-negative organisms, notably *P. aeruginosa* and *A. baumannii*, in the hospital setting.
2. Identify predictors and costs of multidrug resistance in Gram-negative organisms.
3. Implement effective infection control procedures to contain the spread of resistant Gram-negative pathogens.
4. Choose appropriate treatments for infections due to resistant Gram-negative pathogens in critically ill patients.

TARGET AUDIENCE This activity has been developed for critical care physicians and surgical critical care physicians.

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Epidemiology and Mechanisms Of Resistance in Gram-Negative Pathogens

Recent data provide evidence of growing antibiotic resistance. Multidrug-resistant (MDR) Gram-positive pathogens that have attracted substantial publicity include methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. Likewise, increasing antibiotic resistance among Gram-negative pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase (ESBL)–producing *Klebsiella pneumoniae* has been documented. Trends in Gram-negative pathogen distribution in ICUs reported to the National Nosocomial Infections Surveillance (NNIS) System in 2003 are shown in Figure 1.[1]

P. aeruginosa *Background and Surveillance*

Rarely does *P. aeruginosa*, one of the most prevalent nonfermentative[2] Gram-negative bacteria, cause serious infections in otherwise healthy persons. However, among the critically ill and immunocompromised, this opportunistic pathogen can cause infections ranging from superficial skin infections to fulminant sepsis and is the chief cause of nosocomial respiratory infections. This pathogen has an affinity for moist environments and is therefore problematic in hospital settings, where it contaminates aqueous solutions, sinks, equipment, and other surfaces.[3] *P. aeruginosa* is resistant to a number of antimicrobials of different classes, including ampicillin, amoxicillin-clavulanate, anti-staphylococcal penicillins, narrow- and extended-spectrum cephalosporins (excluding ceftazidime and cefepime), tetracyclines, macrolides, rifampin, chloramphenicol, ampicillin-sulbactam, and trimethoprim-sulfamethoxazole.[4]

Karlowsky and colleagues evaluated trends in *P. aeruginosa* multidrug resistance based on the TRUST (Tracking Resistance in the United States Today) surveillance. From 2001 to 2003, in vitro susceptibilities for all agents tested were less than 87%. The cumulative percentages of susceptible *P. aeruginosa* isolates were as follows: 86% susceptible to piperacillin-tazobactam, 80% to ceftazidime, 68% to ciprofloxacin, and 67% to levofloxacin.[5]

In another study, Obritsch and colleagues evaluated antimicrobial resistance trends in *P. aeruginosa* isolates based on

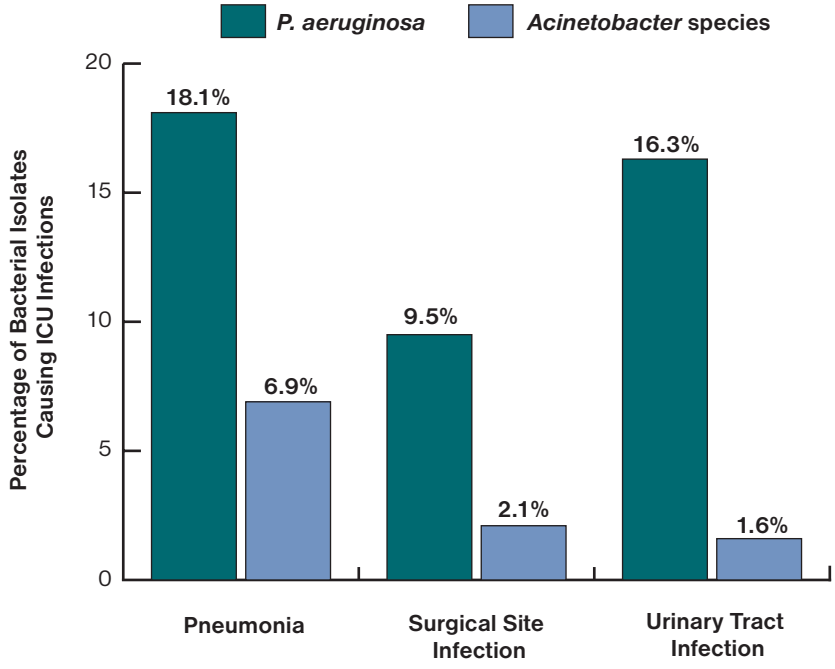

FIGURE 1. PREVALENCE OF GRAM-NEGATIVE PATHOGENS, NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE SYSTEM 2003

Adapted from reference 1.

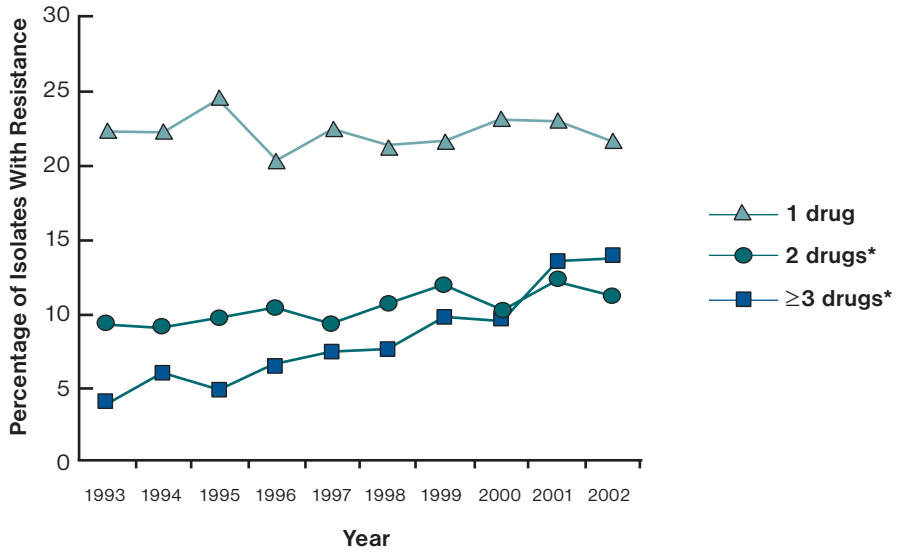

FIGURE 2. NUMBER OF ANTIPSEUDOMONAL AGENTS† TO WHICH *P. AERUGINOSA* WAS RESISTANT, 1993 TO 2002

*P<0.05 for the 10-year interval.
†Imipenem, ceftazidime, ciprofloxacin, and tobramycin.
Adapted from reference 6.

1993 to 2002 data from the Intensive Care Unit Surveillance Study (ISS), which included 45 to 117 ICUs. During this 10-year interval, the susceptibilities of *P. aeruginosa* significantly declined for all drug classes; from 1993 to 2002, statistically significant increases (P<0.0001 for all agents) were seen in antimicrobial resistance to ciprofloxacin (15%-32%), imipenem (15%-23%), tobramycin (9%-16%), and aztreonam (26%-32%). Additionally, from 1998 to 2002, resistance to cefepime increased from 16% to 25% (P<0.0001).[6] As Figure 2 depicts, multidrug resistance increased from 4% in 1993 to 14% in 2002 (P<0.0001).[6]

A. baumannii *Background and Surveillance*

A. baumannii, a nonfermentative Gram-negative bacterium, can survive on both moist and dry surfaces and often contaminates the hospital environment.[3] Similar to *P. aeruginosa*, this species rarely causes serious infections among healthy persons but is a major concern in ICU patients. Those at greatest

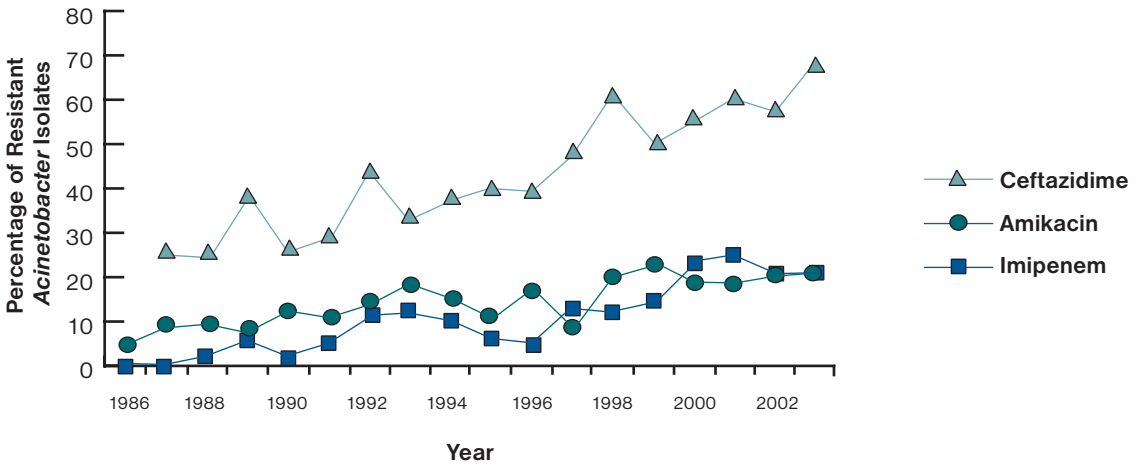

FIGURE 3. NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE SYSTEM 1986-2003 DATA DOCUMENTING INCREASED RESISTANCE OF ICU *ACINETOBACTER ISOLATES TO ANTIMICROBIAL AGENTS**

*In all instances, results of Cochran-Armitage chi-square tests for trend were P<0.001.
ICU, intensive care unit
Adapted from reference 1.

TABLE 1. MECHANISMS AND MEANS OF ANTIMICROBIAL RESISTANCE IN *P. AERUGINOSA* AND *A. BAUMANNII*

Mechanism	Means
Reduced access to target	Slow porin channels Multidrug efflux pumps
Inactivating enzymes	β-lactamases Aminoglycoside-modifying enzymes
Mutational resistance	Point mutations in topoisomerase genes Regulatory mutations increasing expression of intrinsic genes and operons

Adapted from reference 13.

risk include individuals with cystic fibrosis, neutropenia, or iatrogenic immune suppression, and those with disrupted anatomic barriers. Like *P. aeruginosa,* this species is resistant to many different antimicrobial classes; most *A. baumannii* isolates are resistant to ampicillin, amoxicillin-clavulanate, antistaphylococcal penicillins, narrow- and broad-spectrum cephalosporins (excluding ceftazidime and cefepime), tetracyclines, macrolides, rifampin, and chloramphenicol.[4]

Using NNIS System ICU data from 1986 to 2003, Gaynes and Edwards evaluated trends in antimicrobial susceptibilities to *A. baumannii*. Figure 3 illustrates the statistically significant increase ($P<0.001$) in *Acinetobacter* isolates resistant to amikacin, imipenem, and ceftazidime during the study interval.[1]

The increasing resistance of *A. baumannii* was recently documented in a study conducted by Waites and colleagues, who examined the in vitro activities of tigecycline and other antimicrobials against isolates collected in 2004 and 2005 from 76 United States–based TEST (Tigecycline Evaluation and Surveillance Trial) centers. The percentages of antibiotic-resistant *A. baumannii* isolates (n=851) were as follows: piperacillin-tazobactam, 25.3%; ceftazidime, 48.1%; ceftriaxone, 47.5%; cefepime, 38.7%; imipenem, 11.5%; levofloxacin, 47.1%; and amikacin, 8.6%. Notably, the percentage of all *Acinetobacter* isolates resistant to imipenem was higher than the 8.5% and 3.2% reported in 2004 and 2005, respectively, by the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) program.[7-9] Recent reports suggest that MDR strains of *A. baumannii* are also likely to be resistant to tigecycline. Of 82 MDR clinical isolates of *A. baumannii* collected in an Israeli hospital in 2003, 66% were resistant to tigecycline,[10] and a majority of imipenem-resistant *A. baumannii* isolates identified in Chicago in 2005 were not susceptible to tigecycline.[11]

MDR Gram-Negative Strains And Mechanisms of Resistance

The serious infections caused by *P. aeruginosa*, *A. baumannii*, and other nonfermenting Gram-negative bacteria are especially challenging to manage because these organisms are resistant to so many different antimicrobials.[2] Carbapenems and amikacin are active against some isolates of *P. aeruginosa* and *A. baumannii,* and sulbactam (ie, ampicillin-sulbactam) may also offer some activity against *A. baumannii*. The agents most consistently demonstrating activity against both pathogens in vitro are the polymyxins, yet some isolates are resistant to all agents, so that novel combination therapy is required.[12] Clinicians are now confronted with *P. aeruginosa* and *A. baumannii* infections that are resistant to practically all of the most commonly used antimicrobials, with numerous deleterious consequences to patients, clinicians, and public health.[2,3]

Many intrinsic properties of *P. aeruginosa* and *A. baumannii* underlie their resistance to multiple antimicrobials, including reduced access to target, inactivating enzymes, and mutational resistance (Table 1). *P. aeruginosa* possesses more mechanisms of resistance to antimicrobial agents than practically any other microorganism.[13]

Carbapenem resistance in *P. aeruginosa* and *A. baumannii* is attributed to serine and metallo-β-lactamases, OXA-enzymes, and IMP, VIM, SPM, and GIM metallo-β-lactamases, none of which are inhibited by clavulanic acid.[14] Changes in outer-membrane proteins (OMPs) and loss of OprD cause imipenem resistance in *P. aeruginosa.* With regard to efflux pumps, upregulation of the MexAB-OprM system in *P. aeruginosa* reduces susceptibility to meropenem but not imipenem, and upregulation of MexXY-OprN in addition to reduction of OprD can confer resistance to imipenem, meropenem, and several other antimicrobials.[15]

Several β-lactamases have been described in *A. baumannii,* and the chromosomally encoded cephalosporinases (AmpC type) are common to all strains of this pathogen. A problematic and recent occurrence is the emergence of several OXA enzymes in *A. baumannii* that confer β-lactam resistance; use of carbapenems to treat infections caused by this pathogen has resulted in outbreaks of carbapenem-resistant *Acinetobacter* species. Furthermore, in many cases, imipenem resistance in *A. baumannii* is the result of OMP (porin) loss. Reduction of transport into the periplasmic space through changes in OMP

TABLE 2. OUTCOMES RELATED TO BASELINE AND EMERGENT RESISTANCE IN *P. AERUGINOSA* INFECTION

	Patients With Resistance at Baseline		Patients With Emergence of Resistance	
Outcome	**RR (95% CI)**	***P* Value**	**RR (95% CI)**	***P* Value**
Death*	1.3 (0.6-2.8)	0.52	3.0 (1.2-7.8)	0.02
Length of stay†‡	1.0 (0.9-1.2)	0.71	1.7 (1.3-2.3)	<0.001
Daily hospital charges‡§	1.0 (1.0-1.4)	0.41	1.1 (0.9-1.3)	0.43

*The following variables were included in the model: ICU stay, female sex, and Charlson comorbidity score.
†The following variables were included in the model: ICU stay, intensity of culturing, number of days in hospital before baseline culture, and presence of *P. aeruginosa* in urine.
‡RR for this outcome is the multiplicative effect.
§The following variables were included in the model: ICU stay, nosocomial isolate, and major surgery.
CI, confidence interval; **ICU**, intensive care unit; **RR**, relative risk
Adapted from reference 26.

reduces access to penicillin-binding proteins, intensifying the weak enzymatic activity of β-lactamase.[15]

Evidence, Predictors, and Costs of Pan-Resistance

The worldwide emergence of MDR *P. aeruginosa* and *A. baumannii* has been documented in a number of reports. In general, ESBLs are most frequently reported in *Escherichia coli* and *Klebsiella* species but have been found worldwide in *P. aeruginosa* strains.[16] ESBLs originated in western Europe and spread from there to the United States and Asia. Outbreaks reported in Europe include carbapenemase-producing *P. aeruginosa* in Italy[17] and Greece[18] and pan–antibiotic-resistant *P. aeruginosa* in Belgium.[19] Carbapenem-resistant *A. baumannii* has been identified in Brazil.[20]

In the United States, the occurrence rate of ESBL-producing Enterobacteriaceae ranges from 0% to 25% based on the institution, with a national average of approximately 3%.[21] MDR isolates of *P. aeruginosa* were reported in New York hospitals in 2003.[22] In 2005, Lolans and colleagues[23] reported the first US nosocomial outbreak of *P. aeruginosa* producing an integron-borne metallo-β-lactamase and described carbapenemases in *A. baumannii* isolates in Illinois and Indiana.[11] MDR isolates of *A. baumannii* have also been identified in military medical facilities. The introduction of these isolates by returning military personnel could have far-reaching consequences.[24]

Several risk factors for colonization or infection with ESBL organisms have been identified, including prolonged hospital or ICU stay; exposure to third-generation cephalosporins, trimethoprim-sulfamethoxazole, or ciprofloxacin; total antimicrobial use; and indwelling catheter.[16] Gram-negative bacteria have adapted to broad-spectrum β-lactam antimicrobials by modifying the substrate spectrum of common plasmid-mediated β-lactamases and by mobilizing resistance-promoting chromosomal β-lactamase genes into plasmids, allowing spread to new hosts.[14]

A high cost burden is one negative consequence of Gram-negative resistance. In an analysis by Evans and colleagues, patients admitted with resistant Gram-negative rod infections had a higher median hospital cost ($80,500 vs $29,604; $P<0.0001$), higher median antibiotic cost ($2,607 vs $758; $P<0.0001$), longer median hospital stay (29 days vs 13 days; $P<0.0001$), and longer median ICU stay (13 days vs 1 day; $P<0.0001$) than those of patients with sensitive Gram-negative infections.[25]

Carmeli and colleagues published one of the first studies addressing outcomes associated with baseline and emergent antimicrobial resistance in Gram-negative pathogens. At baseline, 144 (29%) of 489 patients with clinical cultures positive for *P. aeruginosa* had an isolate resistant to ceftazidime, ciprofloxacin, imipenem, and/or piperacillin. In addition, resistance developed in 30 patients (6%) during treatment. As shown in Table 2, emergence of resistance during treatment was associated with a higher mortality rate and longer hospital stay.[26]

TABLE 3. CDC CAMPAIGN TO PREVENT ANTIMICROBIAL RESISTANCE IN HEALTHCARE SETTINGS

1. Prevent infection to decrease antimicrobial use.
2. Prevent transmission from patient to patient.
3. Effectively diagnose and treat infections to help save lives.
4. Optimize the use of antimicrobials.

Adapted from reference 33.

Strategies/Policies to Avoid Development of Resistance

Causes of emerging resistance of pathogens include overuse/misuse of broad-spectrum agents, prolonged administration of antibiotics, and increased intestinal colonization arising from use of antibiotics. The expression "collateral damage" captures the adverse ecologic effects of antibiotic therapy, such as selection of drug-resistant organisms and colonization or infection with MDR organisms. A classic example of collateral damage is the worldwide increase in *Clostridium difficile*–associated disease (CDAD), which is related almost exclusively to previous antimicrobial therapy.[27,28] For example, use of imipenem was correlated with β-lactam resistance in *P. aeruginosa* from 1997 to 2000 in a 600-bed community hospital. Monthly rates of resistance of *P. aeruginosa* to imipenem were significantly associated with imipenem prescription rates in the same or preceding month.[29]

A substantial amount of combination antibiotic therapy is redundant, as evidenced in a prospective survey of hospitalized patients. Among 1,189 inpatients receiving 2 or more antibiotics, computer-assisted screening identified 192 (16.1%) receiving potentially redundant combinations; medical chart reviews showed that 137 (71%) of these episodes were inappropriate, and physician errors of excessive prescribing were discovered in 77 (56%). Some of the most common prescribing redundancies included piperacillin-tazobactam and cefazolin, vancomycin and cefazolin, and clindamycin and cefazolin. Of the 77 episodes, 19 (25%) involved redundant coverage for Gram-negative organisms.[30]

The intestinal tract is an important reservoir for antibiotic-resistant Gram-negative bacilli, including *P. aeruginosa* and *A. baumannii,* and a main site for the transfer of genes conferring resistance. Infection can occur with translocation across the intestinal lining or fecal contamination of wounds or devices. Antibiotic therapy may facilitate the colonization and spread of pathogens, although agents with inhibitory activity may offer a protective effect. It is commonly thought that antibiotic therapy does not directly induce mechanisms of resistance, but rather promotes proliferation of antibiotic-resistant Gram-negative bacilli by selective pressure (ie, inhibiting competing microflora but not resistant organisms).[31,32]

Effective Infection Control

Standard measures of infection control are instrumental in limiting the spread of antimicrobial-resistant Gram-negative bacilli. Alcohol-based antiseptics or handwashing products are effective in eliminating Gram-negative bacilli. During outbreaks, or when there is concern about MDR organisms, precautions may include wearing gowns and gloves. Transmission can be minimized by reducing pathogens on skin and environmental surfaces (eg, environmental disinfection). For some patients, isolation may be necessary, particularly those colonized or infected with MDR Gram-negative bacilli if the organisms are susceptible to fewer than 2 classes of antimicrobial agents.[28,32]

Another key intervention to prevent the collateral damage of emerging resistance is to implement adequate surveillance systems, including those for stool carriage, to monitor and identify key pathogens.[28,32] Other strategies include selectively decontaminating the digestive tract, limiting the use of antimicrobials to reduce antimicrobial selective pressure, and limiting the formulary availability of antimicrobials often associated with specific resistant pathogens.[28,32] The Centers for Disease Control and Prevention (CDC) Campaign to Prevent Antimicrobial Resistance in Healthcare Settings outlines key strategies for controlling infection in healthcare settings (Table 3).[33]

Unfortunately, the present literature does not provide ade-

quate data to determine what infection control measures would be most effective in controlling the spread of MDR Gram-negative bacteria.[34] However, a few reports have been published on the efficacy of infection control measures during outbreaks of *A. baumannii*. In one study, after detection of *A. baumannii-calcoaceticus* colonization and infection in an 18-bed ICU in London, a host of infection control measures were introduced over several months. These included use of a closed tracheal suction system for all patients receiving mechanical ventilation, use of nebulized colistin for patients with evidence of mild-to-moderate ventilator-associated pneumonia (VAP), improved availability of alcohol for hand decontamination, and a more concise designation of responsibilities and strategies for cleaning equipment and the environment near patients colonized or infected with this pathogen.[35] The *A. baumannii* outbreak was controlled by emphasizing control of environmental reservoirs, and ICU closure or isolation intervention was not required.[35]

Another study evaluated the effects of cleaning, environmental decontamination, and education in controlling an outbreak of MDR *A. baumannii* in an ICU and a surgical ward. Cleaning, environmental decontamination, and staff education were implemented to prevent immediate spread of the pathogen. Hand hygiene was reinforced, doors to rooms were kept closed, minimal equipment was removed or added to rooms, thorough cleaning measures were enforced, and decontamination of both the surgical ward and the ICU was performed. The net outcome was successful termination of this outbreak at 5-month follow-up.[36]

Maragakis and colleagues investigated an outbreak of MDR *A. baumannii* associated with pulsatile lavage wound treatment in a tertiary care hospital in Maryland. The cultures of 11 patients grew MDR *A. baumannii* during the outbreak period, and among the 10 healthcare-associated cases, 8 patients had received pulsatile lavage treatment. To control this outbreak, pulsatile lavage treatment was terminated in October 2003, and aggressive infection control measures (eg, temporary closure of the wound care treatment room, thorough environmental surface cleaning and disinfection, isolation of infected and colonized patients) were enforced. After these outbreak control measures had been enacted, no further cases of the outbreak strain were identified.[37]

Appropriate Treatment of Resistant Gram-Negative Infections and Antibiotic Stewardship

Inadequate initial antimicrobial therapy is fraught with many problems and is a prominent risk factor for hospital mortality. Once started, antimicrobial therapy should be directed toward the pathogens believed responsible for the clinical infection; the local antimicrobial susceptibility patterns of the responsible pathogens should guide the selection of agents. Failure to treat infections with antimicrobial agents and the delayed administration of adequate antimicrobial treatment increase the risk for hospital mortality.[38]

Kollef and colleagues performed a prospective cohort study to evaluate the relationship between inadequate antimicrobial treatment of infections (both community-acquired and nosocomial) and hospital mortality in patients (n=2,000) requiring ICU admission. Inadequate initial antimicrobial treatment was defined as ineffective therapy for microbiologically documented infection: either absence of pathogen treatment (eg, *Candida albicans* infection had been detected and no antifungal agent was administered) or pathogen resistance to initial treatment. The hospital mortality rate of infected patients receiving inadequate antimicrobial treatment was statistically significantly greater than that of patients without this risk factor (52.1% vs 12.2%; relative risk [RR], 4.26; 95% confidence interval [CI], 3.52-5.15; $P<0.001$). Multivariate analysis demonstrated that inadequate antimicrobial treatment was the most important risk factor for hospital mortality. Among patients with nosocomial infections, absence of adequate treatment for resistant Gram-negative bacteria accounted for most instances of inadequate antimicrobial therapy.[38]

Similarly, Iregui and colleagues showed that initially delayed appropriate treatment was associated with significantly greater mortality attributed to VAP.[39] Inadequate initial therapy was also associated with greater mortality in patients with ESBL *E. coli* and *Klebsiella* infections.[40] Several other analyses further demonstrated increased mortality secondary to inadequate initial therapy in patients with community-acquired pneumonia (CAP) admitted to the ICU with sepsis and in patients with severe VAP.[41-43]

Changes in therapy once culture results are available may not reduce risk for mortality resulting from inadequate initial antimicrobial therapy, as shown in a 1-year prospective multicenter study of 530 patients in whom pneumonia developed in the ICU.[44] A total of 490 (86.7%) patients were treated empirically with antibiotics: most frequently amikacin, tobramycin, ceftazidime, or cefotaxime. Antimicrobial coverage was considered to be adequate in 284 (66%) of 430 cases assessed. Attributable mortality rates were 16.2% in patients with appropriate initial therapy and 24.7% in patients with inappropriate treatment ($P=0.034$).[44]

Similar findings were obtained by Luna and colleagues in a prospective observational study of patients (N=132) with VAP. Findings demonstrated that when therapy was changed after bronchoscopy, more patients (n=42) received adequate therapy, but mortality in this group was comparable with mortality among those who continued to receive inadequate therapy (n=23).[45]

Duration of Therapy

Optimal duration of therapy is an important consideration in the treatment of critically ill patients infected with Gram-negative pathogens. In a prospective, randomized, double-blind trial, Chastre and colleagues[46] found that VAP patients treated for 8 days had neither excess mortality (18.8% vs 17.2%; difference, 1.6%; 90% CI, −3.7% to 6.9%) nor more recurrent infections (28.9% vs 26.0%; difference, 2.9%; 90% CI, −3.2% to 9.1%) when compared with those receiving 15 days of therapy. Of the patients in whom recurrent infections developed, MDR pathogens emerged less frequently in those who had received 8 days of treatment (42.1%) than in those treated for 15 days (62%; $P=0.04$). It is important to note that the optimal duration of therapy for nonlactose fermenters is unknown.[46]

In a prospective observational analysis, Hecker and colleagues reported that of 1,941 days of antimicrobial therapy prescribed to non-ICU adult patients, 576 (30%) were unnecessary. The most common reasons for unnecessary therapy included duration longer than recommended (192 days of therapy), administration for noninfectious or nonbacterial syndromes (187 days), and treatment for colonizing or contaminating microorganisms (94 days).[47] Furthermore, in a retrospective study of infectious episodes in general surgery units, mortality rates were similar for different lengths of antibiotic therapy, and the risk for recurrent infection was higher with longer than with shorter durations of antibiotic therapy.[48]

Institutional Restrictions on the Use Of Selected Antimicrobials

The restricted use of specific antibiotics or classes of antibiotics has been a strategy to reduce resistance in ICU settings. In general, restriction has been applied to treatments with a

broad spectrum of action, associated with rapid emergence of bacterial resistance, and with readily identified toxicity. Restrictions have demonstrated success during specific outbreaks of infection with antimicrobial-resistant pathogens, especially when combined with educational interventions and infection control protocols.

Another means of reducing antimicrobial resistance is to use narrow-spectrum antimicrobials. There is evidence that some infections, such as CAP, can be successfully treated with narrow-spectrum antibiotics. Unfortunately, ICU patients have often received prior antimicrobial treatment, making it more likely that they will be infected with an antibiotic-resistant organism. Thus, initial empiric treatment with a broad-spectrum agent is often necessary until culture results are available.[49] Another means of controlling antibiotic-resistant Gram-negative bacilli is to restrict the use of antibiotics that have been frequently associated with particular pathogens. This is particularly true in the case of third-generation cephalosporins, the extensive use of which has played an important role in the emergence of both ESBL and MDR *P. aeruginosa* and *Acinetobacter* species.[32,50]

Combination Therapy Versus Monotherapy

Combination therapy has been used in the management of many different types of infections in the hope that antimicrobials with different mechanisms of action may offer synergistic benefits, allow the use of lower doses, and delay or prevent the emergence of antimicrobial-resistant pathogens.[51] Several studies using animal and computer models have suggested that combination therapy is superior to monotherapy. However, several recent reviews comparing β-lactam monotherapy with β-lactam and aminoglycoside combination therapy have indicated that monotherapy is preferable for certain conditions, particularly documented sepsis and fever with neutropenia. Although fatality rates remain the same, the addition of an aminoglycoside to β-lactams for the treatment of sepsis should be discouraged because of an increased risk for adverse events (eg, renal toxicity).[52] With regard to the empiric treatment of fever and neutropenia, β-lactam and aminoglycoside combination therapy (eg, a new, broad-spectrum β-lactam plus an older β-lactam) offers no advantage over β-lactam monotherapy. Monotherapy is associated with better survival, a lower rate of treatment failure, and a lower rate of adverse events.[53] Furthermore, no combination therapy offers any advantage over monotherapy with regard to the development of antimicrobial resistance.[51,53-55]

A recent study demonstrated no significant advantages of combination therapy over monotherapy in the treatment of VAP in patients with certain restrictions. The Canadian Critical Care Trials Group conducted a multicenter trial involving patients in 28 Canadian and US ICUs. Immunocompetent adults (N=740) who were receiving mechanical ventilation and had suspected VAP after 4 days in the ICU were randomized in an open-label fashion to either I.V. meropenem and ciprofloxacin or I.V. meropenem alone. Treatment was adjusted based on culture results and sensitivities: if culture was positive, a single antimicrobial with the narrowest spectrum was administered, and if culture demonstrated no growth, study antimicrobials were discontinued (except in cases with a high pretest likelihood of VAP). The adequacy of empiric antimicrobial treatment and mortality at 28 days did not differ significantly between the combination group and the monotherapy group.[56] Study caveats included omission of patients most likely to have a drug-resistant infection (<6% of patients had either methicillin-resistant *S. aureus* or *Pseudomonas* infection), stringent patient surveillance and review of culture results, and disregard of initial therapy as treatment was rapidly de-escalated (suggesting that the majority of patients did not have serious VAP).[56]

The potential beneficial effects of combination therapy were illustrated by Micek and colleagues. In this retrospective cohort study, 305 patients with a *P. aeruginosa* bloodstream infection were identified during a 6-year period. Hospital mortality was greater for patients receiving inappropriate initial antibiotic therapy (n=75; mortality, 30.7%) than for those receiving appropriate initial treatment (n=230; mortality, 17.8%; *P*=0.018). Multiple regression analysis identified inappropriate initial treatment as an independent determinant of hospital mortality. Appropriate initial therapy was more common among patients receiving empiric combination treatment than among those receiving empiric monotherapy (79.4% vs 65.5%; *P*=0.011). Therefore, initial combination therapy for *P. aeruginosa* bloodstream infection may minimize inappropriate antimicrobial treatment.[57] Monotherapy in suspected infection may expose patients to inappropriate initial therapy and subsequent mortality, whereas patients can receive de-escalated monotherapy with an appropriate antimicrobial and have positive outcomes once the organism has been identified.

Infections with *P. aeruginosa* and *A. baumannii* strains that are highly resistant to all antimicrobials except for polymyxins pose a particular challenge to clinicians. Double and triple combination therapies have proved effective against MDR *P. aeruginosa* and *A. baumannii*. Mechanisms of positive interaction between agents are generally not known. Rapid permeation of the outer cell membrane by polymyxin B may enhance the penetration and activity of imipenem and rifampin. It is important to note that although combinations of antimicrobials demonstrate bactericidal activity in vitro, their clinical efficacy, utility, and applicability have not been thoroughly investigated, and several unknowns remain.[12,58]

De-escalation and Tailoring Therapy

In de-escalation, initial treatment with broad-spectrum antimicrobials to cover the most probable causative pathogens is followed by antimicrobial streamlining driven by microbiologic findings (ie, isolation by culture with susceptibility testing of pathogens). This method is thought to offer maximum benefit for the patient while reducing the risk for selection pressure for resistance.[28] For example, Ibrahim and colleagues implemented hospital guidelines for the treatment of VAP in which the initial use of a broad combination of antibiotics was followed in most cases by the discontinuation of 1 or 2 agents. Despite initial broad-spectrum treatment, no significant increase in antibiotic-resistant VAP occurred, and no differences were observed in hospital mortality or length of stay after implementation of the guidelines.[59] In some instances, de-escalation may not aid the individual patient but may help the ICU by reducing selection pressure for resistance. De-escalation is necessary to avoid more prolonged administration of a broad-spectrum agent than is justified by available information.[60] De-escalation has not been shown to impair patient outcomes (ie, increase mortality, length of stay, and cost of therapy).[61]

Antimicrobial Cycling

Antimicrobial cycling is another strategy to reduce emergence of antimicrobial resistance. In treatment cycling, a class of antimicrobials or a specific agent is withdrawn for a specified time interval (eg, months or years) and then reintroduced later in an effort to limit the development of bacterial resistance to the cycled antimicrobial agents. Theoretically, this method allows use of the antimicrobials that offer the greatest overall activity against predominant ICU pathogens, resulting in more effective treatment of nosocomial infections.[49] However, mathematical modeling analyses of antimicrobial cycling suggest that this method is unlikely to impede evolution or the spread of antibiotic resistance. The heterogeneous use of antimicrobials

is predicted to be more effective than antimicrobial cycling; this strategy involves the simultaneous use of several drug classes throughout the hospital, with each patient receiving one specific class of antimicrobial.[62] According to the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, the data are insufficient to recommend the routine use of antimicrobial cycling as a method of preventing or reducing antimicrobial resistance over an extended period.[63]

Principles of Antimicrobial Stewardship

It is well established that when antimicrobials to which the probable infecting organism is susceptible are chosen for empiric therapy, the chance of clinical success is greater than when an inappropriate treatment is chosen. Ideally, antimicrobial treatment should be initiated based on the accurate identification of the pathogen responsible for the infection and the results of susceptibility testing; however, this may take as long as 72 hours because of limitations in current diagnostic methods. The dilemma for clinicians who treat infectious diseases in the critically ill is that increases in MDR organisms mean that broad-spectrum agents should be used sparingly, even though prompt, aggressive treatment is necessary to avoid morbidity and mortality. A clinical decision on empiric therapy must be made when the need to treat outweighs the need to wait for microbiologic confirmation, a situation that occurs most frequently among critically ill patients who become febrile. As described earlier, mortality in the ICU almost doubles when initial treatment is inadequate. Other risk factors that warrant consideration include prior antibiotic treatment and prolonged mechanical ventilation. Risk must be assessed for each patient individually before treatment decisions are finalized.[28]

Antimicrobial stewardship encompasses the appropriate selection, dosing, route of administration, and duration of therapy. Its chief goal is to optimize clinical outcomes while minimizing the unintended consequences of antimicrobial use, such as toxicity, the selection of pathogenic organisms, and the emergence of resistance. The combination of antimicrobial stewardship with a comprehensive infection control program has proved to limit the emergence and transmission of antimicrobial-resistant pathogens. Moreover, antimicrobial stewardship is aimed at reducing overall healthcare costs without negatively affecting the quality of healthcare.[63] A comprehensive antimicrobial stewardship program is based on 2 key strategies:

1. A prospective audit of antimicrobial use including direct interaction with and feedback to the prescriber, performed by an infectious disease specialist or clinical pharmacist specializing in infectious disease; and
2. Formulary restriction and preauthorization, which can result in immediate and significant reductions in antimicrobial use and cost.

(Note that the effectiveness of preauthorization requirements in controlling resistance is less clear.)[63]

Supplements to core active antimicrobial stewardship strategies include education, guidelines and clinical pathways, antimicrobial order forms, streamlining and de-escalation protocols, dose optimization, and parenteral to oral conversion.[63]

Summary

Recent data document the emergence of MDR Gram-negative pathogens worldwide and underscore the urgent need for effective pharmacologic treatment of nosocomial infections. Knowledge of the molecular mechanisms, risk factors, and causes of resistance can aid clinicians in treatment selection based on prevalent pathogens within their communities and institutions. Strategies to combat emergence include stringent infection control interventions, including active surveillance, hand hygiene, contact isolation precautions, and environmental decontamination. Combining antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant pathogens and can reduce healthcare costs without compromising the quality of healthcare.

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CME Post-test

1. ***P. aeruginosa* is difficult to manage in the hospital or ICU because it is resistant to a number of antimicrobials of different classes, including the following:**
   a. ampicillin, amoxicillin-clavulanate, and tetracyclines
   b. common disinfectants and cleaning supplies used in hospital environments
   c. trimethoprim-sulfamethoxazole and narrow- and extended-spectrum cephalosporins
   d. ceftazidime and cefepime

2. **Obritsch and colleagues examined antimicrobial resistance trends in *P. aeruginosa* isolates based on 1993 to 2002 data from the ISS and discovered that the MDR rate _____.**
   a. was approximately 17% from 1993 to 2002
   b. increased from 4% in 1993 to 14% in 2002
   c. increased from 9% in 1993 to 11% in 2002
   d. decreased from 22% in 1993 to 21% in 2002

3. **Which of the following agent(s) is/are active against *P. aeruginosa* and *A. baumannii*?**
   a. Carbapenems
   b. Sulbactam and ampicillin
   c. Antistaphylococcal penicillins
   d. Carbapenems and amikacin

4. **Which of the following contribute to carbapenem resistance in *P. aeruginosa* and *A. baumannii*?**
   a. Alanine, lysine, and dynein
   b. Myosin, serine, and metallo-β-lactamases
   c. Serine, metallo-β-lactamases, and OXA-enzymes
   d. OXA-enzymes and myosin

5. **Risk factors for colonization or infection with ESBL bacteria include which of the following:**
   a. total antimicrobial use and prolonged stay in European or Asian ICUs
   b. total antimicrobial use, prolonged stay in European or North American ICUs, and use of ciprofloxacin
   c. use of ciprofloxacin, indwelling catheter, and prolonged hospital or ICU stay
   d. use of ciprofloxacin, third-generation cephalosporins, trimethoprim-sulfamethoxazole; total antimicrobial use; indwelling catheter; and length of hospital or ICU stay

6. **By what means do Gram-negative bacilli such as *P. aeruginosa* and *A. baumannii* infect the intestinal tract?**
   a. Fecal contamination of wounds or devices
   b. Ingestion of infected food
   c. Translocation across intestinal lining or fecal contamination of wounds or devices
   d. Ingestion of infected food or fecal contamination of wounds or devices

7. **Which of the following cause pathogens' emerging resistance to antimicrobials?**
   a. Difficulty in assessing the pathogens in ICUs
   b. Lack of education about *P. aeruginosa* and *A. baumannii*
   c. Rejection of novel antimicrobial developments by pathogens
   d. Overuse or misuse of broad-spectrum agents and increased intestinal colonization arising from use of antibiotics

8. **To prevent antimicrobial resistance in healthcare settings, the CDC campaign recommends that healthcare professionals _____.**
   a. frequently disinfect the environment with alcohol-based antiseptics, which purge surfaces of Gram-negative bacilli and limit the number of new infections
   b. prevent infections to decrease antimicrobial use, optimize antimicrobial use, effectively diagnose and treat infections, and prevent transmission of infection from patient to patient
   c. educate other healthcare professionals about the benefits of cleaning and environmental decontamination, and designate cleaning tasks to specific individuals
   d. report new infections to the CDC and isolate colonized or infected patients when necessary

9. **On the topic of infection control measures for controlling the spread of MDR Gram-negative bacteria, the medical literature provides _____.**
   a. a substantial number of well-conducted studies delineating infection control measures that have been effective and ineffective
   b. multiple reports of successful containment of MDR *P. aeruginosa* outbreaks in the community
   c. multiple reports of successful containment of MDR *A. baumannii* outbreaks by using strategies such as hand hygiene, environmental decontamination, and limited use of medical devices
   d. no reports of successful outbreak control of MDR Gram-negative bacteria

10. The antimicrobial mortality study of Kollef and colleagues involving 2,000 participants concluded that among patients receiving inadequate antimicrobial treatment, the hospital mortality rate was _____.
a. <25%
b. >50%
c. 65%-75%
d. ≥80%

11. Iregui and colleagues found that lack of immediate appropriate antimicrobial treatment corresponded with significantly higher mortality rates in patients with which of the following conditions:
a. VAP and ESBL *E. coli* and *Klebsiella* infections
b. tuberculosis
c. lower respiratory tract infections and VAP
d. urinary tract infections

12. Some studies have concluded that for combating Gram-negative bacteria, combination therapy does not offer any advantages over monotherapy. Which of the following statements is false?
a. Initial combination therapy for *P. aeruginosa* bloodstream infection may minimize inappropriate antimicrobial treatment.
b. According to one study, the difference between the mortality rates of the combination therapy and monotherapy groups was not significant.
c. Antimicrobial cycling is more effective than combination therapy or monotherapy.
d. Recently, a study indicated that monotherapy may be more effective in patients with sepsis.

13. Antimicrobial de-escalation _____.
a. involves initial treatment with narrow-spectrum antimicrobials followed by add-on therapy to cover all pathogens
b. is an approach that is always beneficial to the patient
c. may not aid all patients but may be beneficial to the ICU by reducing selection pressure for resistance
d. may impair patient outcomes

14. Because use of broad-spectrum antimicrobial agents is linked to increases in MDR organisms, _____.
a. broad-spectrum empiric therapy is never appropriate
b. broad-spectrum empiric therapy should be implemented only when the institution has a very high rate of MDR pathogens
c. physicians should assess individual patients' risk factors for infection with MDR pathogens before implementing broad-spectrum empiric therapy
d. institutions should encourage use of narrow-spectrum antibiotics for community-acquired infections, even in ICU patients

15. The chief goal of antimicrobial stewardship is to _____.
a. lower costs associated with nosocomially acquired Gram-negative infections
b. optimize clinical outcomes while minimizing the unintended consequences of antimicrobial use
c. enforce the use of clinical practice guidelines and clinical pathways to ensure appropriate antimicrobial use
d. eliminate the use of combination antimicrobial therapy

UNIVERSITY OF KENTUCKY

Answer Sheet & Evaluation Form

Emerging Modalities to Combat Resistant Gram-Negative Pathogens in Critically Ill Patients: *Part 1: Changes in Gram-Negative Resistance Over Time*

Date of Release: July 2007 **Expiration Date:** July 31, 2008

Directions: A score of 70% or higher on the post-test awards physicians up to 1.5 *AMA PRA Category 1 Credits*™. To claim continuing education credit, individuals must complete the self-study activity, post-test, and evaluation. Please submit your answers only once through one of the methods listed below.

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1.	a	b	c	d	**9.**	a	b	c	d
2.	a	b	c	d	**10.**	a	b	c	d
3.	a	b	c	d	**11.**	a	b	c	d
4.	a	b	c	d	**12.**	a	b	c	d
5.	a	b	c	d	**13.**	a	b	c	d
6.	a	b	c	d	**14.**	a	b	c	d
7.	a	b	c	d	**15.**	a	b	c	d
8.	a	b	c	d					

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1. Extent to which the objectives were achieved:	1	2	3	4	5
2. Potential effect on your practice:	1	2	3	4	5
3. Detail of information presented:	1	2	3	4	5
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