Impact of Antibiotic Resistance on the Treatment of Gram-negative Sepsis

Lindsey R. Baden, MD and Barry I. Eisenstein, MD†*

Address
*Division of Infectious Disease, Brigham and Women's Hospital, and Harvard Medical School, PBB-A4, 15 Francis Street, Boston, MA 02115, USA.
E-mail: lbaden@partners.org

†Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02115, USA.

Current Infectious Disease Reports 2000, **2**:409–416
Current Science Inc. ISSN 1523–3847

Resistance among gram-negative organisms has greatly complicated the care of the septic patient. An understanding of the likely source of infection, the epidemiologic risk of the patient being exposed to an antibiotic-resistant organism, and the specific vulnerabilities of the host are essential to the proper selection of empiric antimicrobial therapy. In this report, we discuss the epidemiology, antibiotic resistance mechanisms, microbiology, treatment strategies, and diagnostic and therapeutic innovations in the approach to the septic patient.

Introduction

Sepsis is a severe clinical problem in the United States, as more than 300,000 cases occur annually. Not only is sepsis a serious cause of morbidity, it is also the third leading cause of infectious deaths in this country, with a mortality rate of 30% to 40% [1•] Gram-negative organisms are the etiologic agents in approximately 40% of sepsis cases [2]. These organisms colonize the GI tract in high concentrations and have certain virulence properties that facilitate development of invasive disease [3•]. The emergence of antibiotic-resistance determinants has made sepsis therapy extremely challenging. This report discusses the myriad of issues raised by the complex dynamics of the human microbiologic ecosystem and its continued evolution.

Several important groups of gram-negative organisms cause human disease, including the following: enteric (*Escherichia*, *Klebsiella*, *Serratia*, *Enterobacter*, *Citrobacter*, and *Proteus*), nonenteric (*Pseudomonas*, *Aeromonas*, *Stenotrophomonas*, and *Acinetobacter*), diarrheal (*Salmonella*, *Shigella*, and *Campylobacter*), anaerobic (*Bacteroides*), and respiratory (*Haemophillus*, *Legionella*). Of these gram-negative organisms, the enterics and the nonenterics typically cause the greatest burden of serious nosocomial disease. These groups of bacteria are found in different reservoirs; the enterics in the GI tract and the nonenterics typically in aqueous environments.

Epidemiology of Gram-negative Sepsis and Antibiotic Resistance

Enterococci have developed resistance to ampicillin, aminoglycosides, and most recently, vancomycin. Global dissemination of vancomycin-resistant enterococci (VRE) has been rapid since it was first identified in 1986 in France. In the United States, vancomycin resistance among enterococci has expanded from 0.9% of all isolates in 1989 to 25% in 1998. Thus, VRE have generated much concern about the development and dissemination of other antimicrobial-resistance determinants [4•,5••]. Fortunately, VRE is a relatively avirulent pathogen, typically causing disease in the most seriously ill patients. This is not the case for many gram-negative organisms, however.

The development of gram-negative sepsis is a function of several important factors, including exposure to an organism (either a virulent strain or exposure to a virulent or nonvirulent strain after loss of a host defense mechanism), specific host vulnerabilities, inoculum-related factors, antibiotic susceptibilities, and the likely infected body site. The typical first step in disease is the colonization event, which requires adherence of the organism either to a mucosal surface or to a foreign body, such as an indwelling catheter or endotracheal tube. Significant progress has been made, at the molecular level, to understand the specificity (*ie*, tissue or foreign-body tropism) of many of these interactions [3•].

The nature of the organisms that colonize patients depends on several important factors, including a predisposing medical condition, such as cystic fibrosis with airway colonization by *Pseudomonas* and *Burkholderia*, or bronchiectasis with colonization by *Pseudomonas*. Environmental exposures, such as ingestion of contaminated food or nosocomial contact, play a determining role, as do selective environmental pressures, such as antibiotic use, in either inpatient or outpatient (*eg*, for treatment of acne or prophylaxis against *Pneumocystis carinii*) scenarios [6]. Of these, nosocomial acquisition is a major concern, as vulnerable sick patients often spend significant time in the hospital.

The risk of being infected by a resistant organism is clearly related to prior exposure to resistant bacteria. Thus,

Table 1. Relative frequency of selected pathogens, by site of infection and type of intensive care unit, 1992–1997

Pathogen	Bloodstream infection CCU (*n* = 1159)	Bloodstream infection MICU (*n* = 2971)	Pneumonia CCU (*n* = 1635)	Pneumonia MICU (*n* =4389)	Urinary tract infection CCU (*n* = 2321)	Urinary tract infection MICU (*n* = 4956)
Coagulase-negative staphylococci	37	36	2	1	3	2
Staphylococcus aureus	24	13	21	20	3	2
Enterococcus species	10	16	2	2	14	14
Escherichia coli	3	3	4	4	28	14
Enterobacter species	3	3	9	9	4	5
Candida albicans	2	6	6	5	10	21
Klebsiella pneumoniae	2	4	8	8	6	6
Serratia marcescens	2	1	4	4	1	0.7
Pseudomonas aeruginosa	2	3	14	21	7	10
Other *Candida* species	2	3	0.2	1	4	5
Candida glabrata	2	2	3	0.2	3	5
Acinetobacter species	1	2	3	6	0.2	1
Other fungi	1	0.8	2	1	5	8
Proteus mirabilis	0.6	0.5	2	2	4	2
Citrobacter species	—	0.5	—	2	—	1
Streptococcus pneumoniae	0.4	—	2	—	0	—
Haemophilus influenzae	0.1	—	3	—	0	—
Other	7	6	16	14	8	3

CCU—cardiac care unit; MICU—medical intensive care unit.
Adapted from National Nosocomial Infections Surveillance System [5••], Richards *et al.* [14•], and Richards *et al.* [15•].

an understanding of the organism reservoir and the selective pressures in that environment is central to assessing the risk of a patient becoming infected with an antibiotic-resistant organism. For example, the risk of acquiring an antibiotic-resistant *Salmonella* or *Campylobacter* strain has little to do with hospitalization and more to do with animal husbandry practices [7–9], whereas infection with an antibiotic-resistant *Klebsiella* or *Pseudomonas* strain is clearly related to the nosocomial environment [10••,11].

Within the context of the nosocomial environment, understanding the putative reservoirs for certain organisms facilitates an understanding of the types of infections they cause; *Pseudomonas* has a predilection to cause ventilator-associated pneumonia (VAP), in part because of its ability to survive and multiply to high concentrations in water, and accumulate in the respiratory tubing of the ventilatory circuit.

Data from the National Nosocomial Infections Surveillance (NNIS) [12] and the European Prevalence of Infection in Intensive Care (EPIC) study [13] indicate that more than 80% of nosocomial infections are related to the urinary tract (31%), lungs (31%), or bloodstream (19%). Typically, these infections are associated with a breech in the normal host defenses (*eg*, urinary catheter, endotracheal tube, central venous catheter). Of these infections, pneumonia and bloodstream infections (BSI) carry significant morbidity. Table 1 demonstrates the distribution of infecting organisms, as elucidated by the NNIS surveillance system, according to type of intensive care unit (ICU), medical (MICU) or cardiac care (CCU).

It is important to note that gram-negative organisms are the dominant pathogens in pulmonary and urinary tract infections (UTI), accounting for 40% to 50% of isolates, with the most important microbial contributors being *Pseudomonas aeruginosa* and *Escherichia coli*. Approximately 15% of nosocomial BSI are caused by gram-negative organisms; *E. coli*, *Enterobacter*, *Klebsiella*, *Serratia*, and *Pseudomonas* are the most prevalent [5••,14•,15•]. Given the increased use of broad-spectrum antimicrobials in the nosocomial environment, it is not surprising that the overall proportion of MICU gram-negative BSI has decreased slightly over the past 10 years, from 23% in the period 1986 through 1989 to 17% in the period 1992 through 1997, with a shift in the proportion of more virulent pathogens, such as *Enterobacter* and *Pseudomonas* [16].

The risk of being colonized by an antibiotic-resistant organism is related to the patient's prior antimicrobial exposure history. The Intensive Care Antimicrobial Resistance Epidemiology phase-two (ICARE2) data revealed a decrease in colonization rates among outpatients, compared with inpatients and ICU patients, as shown in Fig. 1 [10••]. ICARE2 is a laboratory-based surveillance system using a subset of 41 hospitals participating in the NNIS system, in part established because resistant organisms were appearing in patients presenting from the community. As expected, the authors found that overall antibiotic use in the ICU, inpatient wards, and outpatient arena correlates with the prevalence of microbial resistance (*eg*, high rate of quinolone use and high prevalence of quinolone-resistant organisms in the outpatient setting).

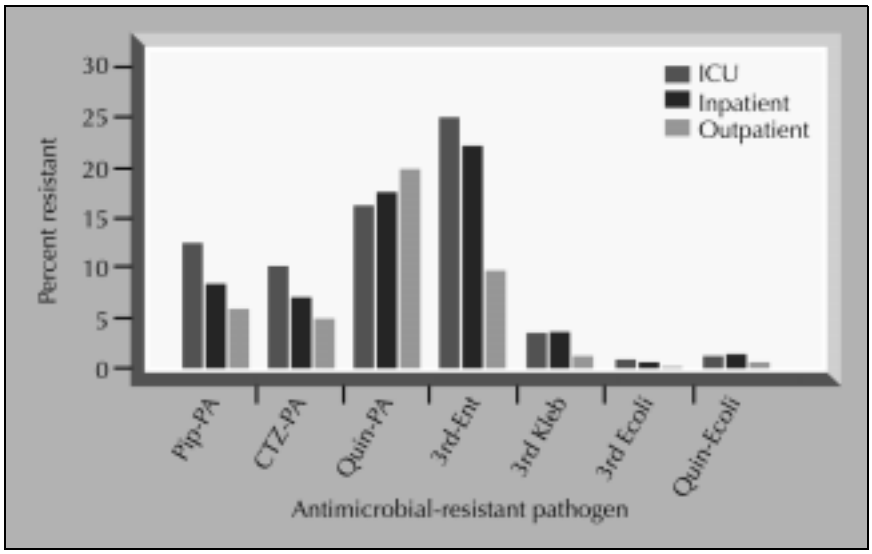

Figure 1. Comparison of antimicrobial resistance, by pathogen, for ICU patients, inpatients, and outpatients. CTZ-PA—*Pseudomonas aeruginosa* resistant to ceftazidime; Pip-PA—*Pseudomonas aeruginosa* resistant to piperacillin; Quin-*E coli* = *E. coli* resistant to quinolones; Quin-PA—*Pseudomonas aeruginosa* resistant to quinolones; 3rd-*E coli*—*Escherichia coli* resistant to third-generation cephalosporins; 3rd-Ent—*Enterobacter* resistant to third-generation cephalosporins; 3rd-Kleb—*Klebsiella pneumoniae* resistant to third-generation cephalosporins;*Adapted from* Fridkin *et al*. [10••].

Table 2. Percent of isolates resistant to common antibiotics and percent increase in resistance over 5 years

Organism	Antibiotic to which organism exhibits resistance	Number of isolates tested, 1998	Percentage resistance, 1998	Percentage increase in resistance, 1993–1998
Pseudomonas aeruginosa	Imipenem	1203	17.10%	32%
P. aeruginosa	Ceftazidime	1931	21.00%	1%
P. aeruginosa	Quinolones	1831	23.30%	89%
Enterobacter species	Third-generation cephalosporins	1185	34.00%	5%
Klebsiella pneumoniae	Third-generation cephalosporins	748	10.70%	7%
Escherichia coli	Third-generation cephalosporins	1005	3.20%	29%

Adapted from National Nosocomial Infections Surveillance System [5••].

As seen in Table 2, the NNIS data demonstrate a substantial presence of resistant gram-negative organisms in 1998 and indicate that the proportion of resistant organisms had increased rapidly in 1998, compared with the preceding 5 years [5••,14•,15•]. There are geographic trends in the distribution of resistant organisms, with the SENTRY study reporting 30.6% and 6.2% ceftazidime-resistant *Enterobacter* species isolated in the United States and Canada, respectively.

This type of geographic variability occurs not only between countries but also between different regions of the United States [17–19]. Of the ceftazidime-resistant *Enterobacter cloacae* isolates encountered in the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) program, 40% were in the Northeast, and only 12% were in the Northwest. Of the ceftazidime-resistant *Enterobacter aerogenes* isolates encountered in the SCOPE program, 48% were in the Southeast, whereas 13% were in the Northwest [20••].

Considering that approximately 50% of ICU infections are caused by aerobic gram-negative rods, the microbiology of nosocomial infection is shifting to organisms that are more difficult to treat, and the selective antibiotic pressure in our nosocomial environment is constant, it is not surprising that strains of organisms such as *Pseudomonas*, *Acinetobacter*, *Serratia*, and *Stenotrophomonas* have emerged that are resistant to all clinically used antibiotics.

There are no convincing data suggesting that the presence of antibiotic resistance determinants leads to enhanced virulence; rather, they diminish our ability to treat established infections. Given the constant antimicrobial pressure in the nosocomial environment, organisms resistant to multiple antibiotics have been selected. Thus, in patients infected with antibiotic resistant strains, we see the sequelae of inadequately treated infection, either from delay in the institution of adequate antibiotic therapy or the inability to treat the infection. In many major medical centers, multidrug-resistant gram-negative organisms have appeared, and all too often have forced the closing of heavily colonized intensive care and burn units.

Mechanisms of Antibiotic Resistance

Gram-negative bacteria exhibit several important mechanisms of resistance to antimicrobial therapy, including diminished antibiotic penetration, altered target, antibiotic inactivation, and efflux mechanisms. The genes encoding these phenotypes may be chromosomal or plasmid in

origin, inducible or constitutive. With broad use of antibiotics, multiply resistant determinants have been coselected. A detailed review of antimicrobial resistance mechanisms can be found elsewhere [21–23].

Two mechanisms of resistance emerged as clinically important in the 1990s: chromosomally inducible AmpC resistance and plasmid-borne, extended-spectrum β-lactamase (ESBL) resistance [4•,24,25].

AmpC-type resistance is typically associated with the hyperproduction of a chromosomally-mediated, broad-spectrum β-lactamase, and is often found among isolates of *Enterobacter*, *Citrobacter*, indole-positive *Proteus*, *Providencia*, and *Serratia*. Certain β-lactam antibiotics usually induce this enzyme. Yu *et al*. [26] showed that clinical failure often occurs when serious *Enterobacter* infections are treated with a cephalosporin, despite apparent in vitro cephalosporin susceptibility. This clinical failure was shown to be due to the induction of a chromosomal AmpC resistance determinant. Thus, cephalosporins should be used carefully in this setting.

A multitude of resistance plasmids have been identified in gram-negative bacteria. These determinants confer resistance to a large variety of antimicrobial agents. In the 1980s, *Klebsiella pneumoniae* strains resistant (by an ESBL) to third-generation cephalosporins and aztreonam were identified in Europe (1983) and the United States (1988).

Recently, several reports have raised serious concerns about the efficacy of β-lactam, monobactam, and cephalosporin antibiotics in the treatment of infections caused by ESBL-containing organisms. One case report demonstrated that cefotaxime was ineffective therapy for a patient with a serious *Klebsiella pneumoniae* infection that was cefotaxime-susceptible by in vitro criteria. This isolate was noted to be ceftazidime-resistant and to have an ESBL [27]. Whether this and other clinical failures in the presence of ESBLs are caused by an inoculum effect, β-lactamase hyperproduction, porin channel changes [28], or other mechanisms, these worrisome observations have led to a change in the approach to the determination of in vitro resistance and to the treatment of this type of infection.

It is difficult to know the true prevalence of ESBLs, as the resistance to oxyimino–β-lactam antibiotics does not routinely reach the resistance threshold in the microbiology laboratory. This has lead to a reworking of the National Committee for Clinical Laboratory Standards (NCCLS) breakpoints. If an ESBL is present, then the efficacy of all third-generation cephalosporins, monobactams, extended-spectrum β-lactams, and β-lactam–β-lactamase inhibitor combinations are suspect [29]. Imipenem, cefepime, and the cephomycins (*eg*, cefotetan, cefoxitin) are effective agents, as well as antibiotics of a different class.

Diagnostic Issues

One of the greatest exasperations a clinician caring for a septic patient can experience is having to wait one to two days for culture results to determine whether the patient is infected, and then waiting longer to learn the identity and the susceptibility profile of the infecting organism. With improvements in culturing technology, we are now able to receive positive blood cultures within hours, rather than days. However, despite this shorter delay, the clinician is still required to initiate empiric therapy in the face of the likelihood of highly resistant flora.

With the molecular biological revolution, we have seen the emergence of new tests, typically based on polymerase chain reaction (PCR) technology, enabling the rapid identification of specific pathogens using the patient's blood or using fluid from the site of the infection. Obviously, this technology is prone to the same challenges of interpretation (*eg*, "Is this colonization or disease?) that the clinician currently faces in the ICU. To help with both diagnosis and prognosis, new assays are focusing on the concentrations (or presence) of mediators in the inflammatory cascade or on circulating bacterial moieties, such as lipopolysaccharide [30,31•].

A broad array of pathogens can now be identified by these techniques, including viruses (human immunodeficiency virus, cytomegalovirus), fungi (*Candida*, *Aspergillus*), and bacteria (VRE, *E. coli*, *Mycobacterium tuberculosis*, *Bacteroides*) [32–35]. The consequential ability to provide pathogen-directed therapy at the bedside would enable more focused (*ie*, narrow-spectrum) antimicrobial use, thus diminishing the selective pressure that leads to resistance selection in the first place.

The clinical significance of antimicrobial susceptibility break points, as determined by the microbiology laboratory, has not been determined rigorously for most infections, as emphasized in the ESBL experience noted above. Given an improved understanding of the genetic basis for resistance, new diagnostics for the determination of resistance have emerged. Utilizing new technologies, such as PCR, the presence of known resistance determinants, such as the *mecA* gene in *Staphylococcus* (the majority of methicillin resistance exhibited by *Staphylococcus aureus* is due to the chromosomal presence of this gene), can be rapidly determined [36].

Where there are multiple resistance determinants, such as the *vanA* and *vanB* genes in enterococci, multiplex PCR or chip technology can be developed to determine the presence of and to distinguish between resistance determinants [32]. As the number of resistance determinants grows, the technology to determine the presence or absence of a determinant becomes more complex.

Unfortunately, the variety of resistance mechanisms of gram-negative bacteria are much more heterogeneous than are the resistance mechanisms of gram-positive bacteria. As resistance can be a function of changes in the capsule, porin channels, or efflux pumps, the complexity of determining its presence may be more difficult for some types of resistance than it is for others. Of course, these technologies are limited by what we know to look for. Thus, the need for routine culturing remains.

Therapeutic Strategies

Establishing the optimal therapy for a patient with sepsis requires the clinician to synthesize a large amount of data, including putative source, epidemiologic risk, predisposing medical conditions, and local organism resistance patterns. It is critical to determine the likely infecting source, which may represent the reason for hospitalization or be the result of a life-saving intervention, such as the insertion of a central venous catheter or endotracheal tube. Identifying the source greatly assists in the identification of the most likely infecting pathogen(s).

The risk of colonization and subsequent infection by a drug-resistant organism is clearly associated with the patient's exposure to it. Thus, understanding the reservoir and subsequent mode of human acquisition of a given drug-resistant pathogen helps understand the risk of acquiring it.

In the case of an infection that is predominantly transmitted in the community (*eg*, pneumococcal pneumonia, tuberculosis, gonorrhea), the risk of infection by a drug resistant organism is a function of the burden of resistance in the community in question.

However, most serious gram-negative infections (*ie*, BSI, VAP, UTI) are acquired nosocomially, and reflect the resistance pattern of the respective care environment. Using data from the SENTRY program, Table 3 shows the $MIC_{50/90}$ and in vitro susceptibility of the four most important nosocomial gram-negative organisms [20••].

These data, which represent the state of resistance in the United States as a whole, are useful in understanding the types of resistant organisms that any US health-care center is at risk to acquire. It is critical to have an ongoing surveillance program for antimicrobial resistance, as well as to understand the resistance patterns in one's local institution.

Community-acquired urosepsis is less likely to be due to an antibiotic resistant organism than nosocomially-acquired urosepsis is; thus, different antibiotic strategies are required. The cornerstone of effective antimicrobial therapy is minimizing the organism burden; draining all infected collections is essential. Such intervention both eliminates the infection and lessens the opportunity for the emergence of resistance.

Treatment of serious gram-negative infections often involves a "double-coverage" approach to antimicrobial therapy, not only as empiric therapy when a resistant organism is likely, but also to achieve broad empiric coverage, develop therapeutic synergy, and prevent the emergence of resistance. In the acutely ill septic patient, broad coverage, hedging against the resistant pathogen, is necessary.

Synergistic therapy is defined as combining two therapeutic agents to enhance inhibition or, preferably, killing. In the synergistic relationship, each antibiotic enhances the efficacy of the other, so the activity level of the combination is greater than the solo activity levels of both agents, added together. A typical synergistic bactericidal therapy combines a cell-wall-active agent and a ribosomally-active agent.

Despite the in vitro demonstration of synergism against a variety of organisms, clinically significant synergistic therapy has been proven in only a handful of settings, such as enterococcal endocarditis, *Pseudomonas* infection in the neutropenic patient, and perhaps severe *Klebsiella* infection.

Despite the argument that, statistically, combination therapy should prevent the emergence of resistance, the contrary result was reported in at least one study, of *Enterobacter* bacteremia. In six of 31 cases (19%), the infecting organism developed resistance to third-generation cephalosporins; four of the six patients were treated with a cephalosporin-aminoglycoside combination [26].

Although only limited data support the benefit of synergistic therapy, most infectious diseases experts favor treating life-threatening gram-negative infections with a β-lactam–aminoglycoside combination, given the suggestion of synergy between these agents [37]. Clearly, using an aminoglycoside in a hypotensive patient augments the risk of nephrotoxicity; however, inadequate antimicrobial therapy generally subjects the patient to a substantially greater clinical risk.

Given the concern about aminoglycoside nephrotoxicity, many practitioners have utilized β-lactam–flouroquinolone combinations as empiric therapy. But, as there is little clinical data supporting the value of this combination, we do not favor it as empiric therapy in the critically ill septic patient. Once the identity of the infecting organism is known, the antibiotic therapy should be appropriately tailored, with careful attention paid to chromosomally latent but inducible resistance, as noted above. In determining appropriate empiric therapy, it is critical to consider the resistance patterns of the organisms to which the patient was likely exposed.

New Targets and Approaches

Active assessment of adjuvant therapies for severe sepsis continues. More than two dozen trials have investigated agents that attack the immune dysregulation of sepsis—including glucocorticoids, bradykinin antagonists, platelet-activating factor antagonists, monoclonal antibodies against tumor necrosis factor, soluble TNF receptors, prostaglandin antagonists, and interleukin 1 receptor antagonists—and have yielded no clear evidence of clinical benefit [1,38, 39,40•]. Monoclonal antibodies to endotoxin and other pathologic moieties in sepsis have been equally disappointing in their lack of demonstrated therapeutic benefit. One of the most promising new therapies for the treatment of sepsis is recombinant activated protein C [41]. Recently, a phase III study of this compound was stopped early, by the sponsor, due to a recommendation (presumably relating to reduced mortality) by the Data and Safety Monitoring Board. The data from this study is likely to be presented shortly to the Food and Drug Administration.

One of the difficulties associated with conducting this type of study is that resistant organisms render empiric antibiotic

Table 3. Activity of specific antimicrobial agents against common nosocomial gram-negative bloodstream isolates, US and Canada, January to June 1997

Antimicrobial agent	*Escherichia coli* (769 reports) Activity* (susceptibility†)		*Klebsiella* (311 reports) Activity* (susceptibility†)		*P. aeruginosa* (189 reports) Activity* (susceptibility†)		*Enterobacter* (151 reports) Activity* (susceptibility†)	
Ampicillin	8 / 16	(52.4%)	> 16 / > 16	(2.7%)	> 16 / > 16	(0.0%)	> 16 / > 16	(1.4%)
Piperacillin	2 / > 128	(57.0%)	8 / > 128	(80.7%)	4 / 64	(93.0%)	4 / > 128	(63.9%)
Ticarcillin	8 / > 128	(53.6%)	> 128 / > 128	(2.3%)	32 / 128	(86.6%)	8 / > 128	(59.2%)
Amoxicillin-clavulanate	8 / 16	(68.8%)	4 / 16	(89.7%)	> 16 / > 16	(1.6%)	> 16 / > 16	(2.8%)
Ticarcillin-clavulanate	4 / 64	(67.1%)	4 / 32	(88.2%)	32 / 128	(87.6%)	8 / > 128	(58.5%)
Piperacillin-tazobactam	2 / 4	(95.5%)	4 / 16	(94.0%)	4 / 32	(92.4%)	4 / > 64	(68.8%)
Cefazolin	≤ 2 / 16	(88.0%)	> 2 / 16	(86.0%)	> 16 / > 16	(1.1%)	> 16 / > 16	(1.4%)
Cefuroxime	4 / 8	(94.9%)	4 / 8	(90.2%)	> 16 / > 16	(0.0%)	> 16 / > 16	(29.9%)
Cefoxitin	4 / 8	(93.0%)	4 / 8	(90.5%)	> 32 / > 32	(1.1%)	> 32 / > 32	(2.0%)
Cefotaxime	≤ 0.25 / ≤ 0.25	(98.3%)	≤ 0.25 / ≤ 0.25	(97.3%)	> 32 / > 32	(18.5%)	0.5 / > 32	(69.5%)
Ceftazidime	≤ 0.12 / 0.5	(98.0%)	0.25 / 1	(96.4%)	2 / 16	(87.1%)	0.5 / 16	(69.4%)
Cefepime	< 0.12 / 0.25	(99.3%)	≤ 0.12 / 0.25	(98.7%)	2 / 16	(87.0%)	≤ 0.12 / 4	(99.3%)
Aztreonam	≤ 0.12 / ≤ 0.12	(97.6%)	≤ 0.12 / 0.25	(96.1%)	8 / > 16	(77.4%)	≤ 0.12 / > 16	(70.7%)
Imipenem	0.25/0.5	(99.5%)	0.25 / 0.5	(100.0%)	2 / 8	(88.0%)	0.5 / 2	(98.6%)
Meropenem	≤ 0.06 / ≤ 0.06	(99.6%)	≤ 0.06 / ≤ 0.06	(100.0%)	0.5 / 2	(95.2%)	≤ 0.06 / 0.25	(99.3%)
Amikacin	4 / 8	(98.5%)	2 / 4	(99.0%)	4 / 8	(98.4%)	2 / 4	(100.0%)
Gentamicin	1 / 2	(96.0%)	1 / 1	(95.3%)	2 / 8	(89.7%)	1 / 2	(94.3%)
Tobramycin	1 / 2	(96.7%)	1 / 1	(95.1%)	1 / 2	(95.7%)	1 / 2	(93.9%)
Ciprofloxacin	≤ 0.015 / 0.03	(97.2%)	0.03 / 0.25	(96.3%)	0.12 / 2	(89.1%)	0.03 / 0.5	(92.2%)
Levofloxacin	≤ 0.5 / ≤ 0.5	(97.6%)	≤ 0.5 / ≤ 0.5	(97.7%)	≤ 0.5 / 4	(84.9%)	≤ 0.5 / 1	(93.2%)
Sparfloxacin	≤ 0.25 / ≤ 0.25	—	≤ 0.25 / ≤ 0.25	—	1 / > 2	—	≤ 0.25 / 1	—
Gatifloxacin	≤ 0.03 / 0.06	—	0.12/0.25	—	1 / > 4	—	0.06 / 0.5	—
Tetracycline	≤ 4 / > 8	(72.5%)	≤ 4 / 8	(85.4%)	> 8 / > 8	(3.3%)	≤ 4 / 8	(83.0%)
Trimeth-sulfameth‡	≤ 0.5 / > 1	(74.3%)	≤ 0.5 / > 1	(87.4%)	> 1 / > 1	(2.2%)	≤ 0.5 / 1	(84.4%)

*Minimal inhibitory concentration ($MIC_{50/90}$).
†Percentage in vitro susceptibility.
‡Trimethoprim-Sulfamethoxazole.
Adapted from Pfaller *et al.* [20••].

therapy inadequate [2]. There are several targets under active study, such as protein kinase inhibitors and anti-CD14 antibodies. One area of study with potential future interest is "antisense technology," in which inactive complementary DNA strains are designed to target resistance determinants, leading to their inactivation.

Conclusion

In this report, we have reviewed the microscopic and macroscopic aspects of antimicrobial resistance. The emergence of antibiotic resistance is a dynamic evolutionary process continually adapting to the selective pressure of our antibiotic therapies and health-care environments. There are many innovations on the horizon for the diagnosis and treatment of the septic patient; however, the choice of empiric therapy must always reflect the microbial microcosm from which each patient presents.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bone RC, Grodzin CJ, Balk RA: **Sepsis: a new hypothesis for pathogenesis of the disease process.** *Chest* 1997, **112:**235–243.
2. Ziegler EJ, Fisher CJ Jr, Sprung CL, *et al.*: **Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group.** *N Engl J Med* 1991, **324:**429–436.
3. • Eisenstein BI, Zaleznik DF: **Enterobacteriaceae.** In *Principles and Practice of Infectious Diseases.* Edited by Mandell GL, Bennett JE, Dolin R. Philadelphia: Churchill Livingstone; 1999:2294–2310.

This chapter comprehensively reviews the Enterobacteriacae.

4. • Gold HS, Moellering RC Jr: **Antimicrobial-drug resistance.** *N Engl J Med* 1996, **335:**1445–1453.

This article reviews the emergence of several important mechanisms of resistance in the 1990s.

5. •• Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention. *National Nosocomial Infections Surveillance (NNIS) System Report, Data, Summary from October 1986-April 1998,* Issued June 1998. Atlanta: Public Health Service, US Department of Health and Human Services; 1998:1–25.

This report analyzes data collected by the NNIS System, an ongoing national surveillance system monitoring nosocomial infection rates, organisms and resistance patterns at more than 250 hospitals. The report can be downloaded from the CDC website at <http://www.cdc.gov/ncidod/hip/NNIS>.

6. Miller YW, Eady EA, Lacey RW, *et al.*: **Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci on the skin of contacts.** *J Antimicrob Chemother* 1996, **38:**829–837.
7. Levy SB: **Multidrug resistance--a sign of the times [editorial; comment].** *N Engl J Med* 1998, **338:**1376–1378.
8. Endtz HP, Ruijs GJ, van Klingeren B, *et al.*: **Quinolone resistance in** *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J Antimicrob Chemother* 1991, **27:**199–208.
9. Glynn MK, Bopp C, Dewitt W, *et al.*: **Emergence of multidrug-resistant** *Salmonella enterica* serotype typhimurium DT104 infections in the United States. *N Engl J Med* 1998, **338:**1333–1338.
10. •• Fridkin SK, Steward CD, Edwards JR, *et al.*: **Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals.** *Clin Infect Dis* 1999, **29:**245–252.

This report analyzes antibiotic resistance patterns and concomitant antimicrobial use at 41 US hospitals.

11. Yinnon AM, Butnaru A, Raveh D, *et al.*: *Klebsiella* **bacteraemia: community versus nosocomial infection.** *QJM* 1996, **89:**933–941.
12. Emori TG, Culver DH, Horan TC, *et al.*: **National nosocomial infections surveillance system (NNIS): description of surveillance methods.** *Am J Infect Control* 1991, **19:**19–35.
13. Vincent JL, Bihari DJ, Suter PM, *et al.*: **The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study.** *EPIC International Advisory Committee JAMA* 1995, **274:**639–644.
14. • Richards MJ, Edwards JR, Culver DH, Gaynes RP: **Nosocomial infections in coronary care units in the United States. National Nosocomial Infections Surveillance System.** *Am J Cardiol* 1998, **82:**789–793.

This is a careful analysis of the pathogens causing infections in US CCUs, from the NNIS database.

15. • Richards MJ, Edwards JR, Culver DH, Gaynes RP: **Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System.** *Crit Care Med* 1999. **27:**887–892.

This is a careful analysis of the pathogens causing infections in US MICUs, from the NNIS database.

16. Fridkin SK, Welbel SF, Weinstein RA: **Magnitude and prevention of nosocomial infections in the intensive care unit.** *Infect Dis Clin North Am* 1997, **11:**479–496.
17. Miller GH, Sabatelli FJ, Hare RS, *et al.*: **The most frequent aminoglycoside resistance mechanisms--changes with time and geographic area: a reflection of aminoglycoside usage patterns? Aminoglycoside Resistance Study Groups.** *Clin Infect Dis* 1997, **24(Suppl 1):**S46–62.
18. Dornbusch K, King A, Legakis N: **Incidence of antibiotic resistance in blood and urine isolates from hospitalized patients. Report from a European collaborative study. European Study Group on Antibiotic Resistance (ESGAR).** *Scand J Infect Dis* 1998, **30:**281–288.
19. Barsic B, Beus I, Marton E, *et al.*: **Antibiotic resistance among gram-negative nosocomial pathogens in the intensive care unit: results of 6-year body-site monitoring.** *Clin Ther* 1997, **19:**691–700.
20. •• Pfaller MA, Jones RN, Doern GV, Kugler K: **Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997).** *Antimicrob Agents Chemother* 1998, **42:**1762–1770.

These authors investigate antimicrobial resistance patterns for blood stream pathogens from 38 sites in the US and Canada.

21. Jones RN, Pfaller MA, Marshall SA, *et al.*: **Antimicrobial activity of 12 broad-spectrum agents tested against 270 nosocomial blood stream infection isolates caused by non-enteric gram- negative bacilli: occurrence of resistance, molecular epidemiology, and screening for metallo-enzymes.** *Diagn Microbiol Infect Dis* 1997, **29:**187–192.
22. Virk A, Steckelberg JM: **Clinical aspects of antimicrobial resistance [review].** *Mayo Clin Proc* 2000, **75:**200–214.
23. Medeiros AA: **Evolution and dissemination of β-**lactamases accelerated by generations of **β-**lactam antibiotics. *Clin Infect Dis* 1997, **24(Suppl 1):**S19–S45.

24. Pfaller MA, Jones RN, Marshall SA, *et al.*: **Inducible amp C β-lactamase producing gram-negative bacilli from blood stream infections: frequency, antimicrobial susceptibility, and molecular epidemiology in a national surveillance program (SCOPE).** *Diagn Microbiol Infect Dis* 1997, **28:**211–219.
25. Pitout JD, Sanders CC, Sanders WE Jr: **Antimicrobial resistance with focus on β-lactam resistance in gram-negative bacilli.** *Am J Med* 1997, **103:**51–59.
26. Chow JW, Fine MJ, Shlaes DM, *et al.*: *Enterobacter* **bacteremia: clinical features and emergence of antibiotic resistance during therapy.** *Ann Intern Med* 1991. **115:**585–590.
27. Karas JA, Pillay DG, Muckart D, Sturm AW: **Treatment failure due to extended spectrum β-lactamase** [letter]. *J Antimicrob Chemother* 1996, **37:**203–204.
28. Jacoby GA: **Genetics of extended-spectrum β-lactamases.** *Eur J Clin Microbiol Infect Dis,* 1994. **13(Suppl 1):**S2–S11.
29. Rice LB, Carias LL, Bonomo RA, Shlaes DM: **Molecular genetics of resistance to both ceftazidime and β-lactam–β-lactamase** inhibitor combinations in *Klebsiella pneumoniae* and in vivo response to **β-lactam therapy.** *J Infect Dis* 1996, **173:**151–158.
30. Romaschin AD, Harris DM, Ribeiro MB, *et al.*: **A rapid assay of endotoxin in whole blood using autologous neutrophil dependent chemiluminescence.** *J Immunol Methods* 1998, **212:**169–185.
31. • Carlet J: **Rapid diagnostic methods in the detection of sepsis [review].** *Infect Dis Clin North Am* 1999, **13:**483–494, xi.
This is a useful review of emerging diagnostic considerations in sepsis.
32. Dutka-Malen S, Evers S, Courvalin P: **Detection of glycopeptide resistance genotypes and identification to the species level of clinically relevant enterococci by PCR.** *J Clin Microbiol* 1995, **33:**1434.
33. Einsele H, Hebart H, Roller G, *et al.*: **Detection and identification of fungal pathogens in blood by using molecular probes.** *J Clin Microbiol* 1997. **35:**1353–1360.
34. Flahaut M, Sanglard D, Monod M, *et al.*: **Rapid detection of** *Candida albicans* in clinical samples by DNA amplification of common regions from *C. albicans*-secreted aspartic proteinase genes. *J Clin Microbiol* 1998, **36:**395–401.
35. Kane TD, Alexander JW, Johannigman JA: **The detection of microbial DNA in the blood: a sensitive method for diagnosing bacteremia and/or bacterial translocation in surgical patients.** *Ann Surg* 1998, **227:**1–9.
36. Wallet F, Roussel-Delvallez M, Courcol RJ: **Choice of a routine method for detecting methicillin-resistance in staphylococci.** *J Antimicrob Chemother* 1996, **37:**901–909.
37. Dellinger RP: **Current therapy for sepsis.** *Infect Dis Clin North Am* 1999. **13:**495–509.
38. Cronin L, Cook DJ, Carlet J, *et al.*: **Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature.** *Crit Care Med* 1995, **23:**1430–1439.
39. Lefering R, Neugebauer EA: **Steroid controversy in sepsis and septic shock: a meta-analysis.** *Crit Care Med* 1995. **23:**1294–1303.
40. • Zeni F, Freeman B, Natanson C: **Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment [editorial; comment].** *Crit Care Med* 1997, **25:**1095–1100.
These authors provide a comprehensive discussion of anti-inflammatory therapies in the treatment of sepsis.
41. Murakami K, Okajima K, Uchiba M, *et al.*: **Activated protein C attenuates endotoxin-induced pulmonary vascular injury by inhibiting activated leukocytes in rats.** *Blood* 1996, **87:**642–647.