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Emerging issues in the management of infections caused by multidrug-resistant gram-negative bacteria

ABSTRACT

Accumulating evidence indicates that treating seriously ill infected patients with active antibiotics early in the course of infection is critical to improving outcomes. The most common reason for ineffective empiric therapy is resistance to the agents used. Gram-negative bacteria are becoming increasingly resistant to many commonly used antibiotics, and some cases require older, more toxic antibiotics for adequate microbial coverage. The diversity of resistance mechanisms that underly multidrug resistance makes developing effective new antimicrobial agents very difficult, especially against problematic species such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. This growing problem requires a multipronged strategy that includes adherence to infection control principles, parsimonious and rational use of current antimicrobial agents, and development of new agents active against multidrug-resistant pathogens.

KEY POINTS

Multidrug-resistant gram-negative bacteria continue to grow in importance in hospitals with high percentages of vulnerable patients. Recognizing the resistance patterns present in hospitals is key, as are empiric treatment regimens that address resistance phenotypes.

Attention to infection control measures is critical to reducing the spread of resistance, as are coherent strategies for minimizing overall antibiotic use.

Rational use of newer antibiotics that offer some activity against resistant pathogens will be important for maintaining these agents' clinical utility.

Dr. Rice reported that he has received consulting/advisory fees from Wyeth Pharmaceuticals, Elan Corp., Merck & Co., Novexel, and Johnson & Johnson and has received honoraria from Wyeth and Elan for speaking or writing.

The author reported that he prepared this article without assistance from any medical education company.

In the past decade, patients and physicians have benefited from the introduction of several antimicrobial agents targeted toward the treatment of infections caused by drug-resistant gram-positive pathogens, primarily methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. These agents include quinupristin-dalfopristin (Synercid), linezolid (Zyvox), daptomycin (Cubicin), and tigecycline (Tygacil) **(Table 1)**. Of these, only tigecycline has activity that extends to gram-negative pathogens,[1] although its activity is not sufficient to justify use in the treatment of infections caused by *Pseudomonas aeruginosa*.

This focus on gram-positive pathogens has been justified, given the relative dearth of agents active against these species prior to the introduction of the newer antibiotics. However, while substantial progress was made against gram-positive pathogens, a progressive increase in resistance among gram-negative pathogens has continued unabated. In many intensive care units (ICUs), multidrug-resistant gram-negative bacilli such as *P aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* now pose the greatest therapeutic challenge, especially for the empiric treatment of patients with systemic inflammatory response syndrome or frank sepsis.

This article will discuss the importance of effective therapy for good outcomes in critically ill infected patients, explore the mechanisms by which gram-negative bacteria have become resistant to multiple antibiotics, and review options for the treatment of multidrug-resistant gram-negative pathogens.

EMPIRIC THERAPY AND OUTCOMES: APPROPRIATE INITIAL THERAPY MATTERS

A large body of evidence has accumulated over the past decade indicating that appropriate antibacterial therapy, administered early, has a significant impact on the outcomes of serious bacterial infections **(Table 2)**.[2–7]

In an early study of ventilator-associated pneumonia from a single ICU with a small number of patients, Luna et al[2] reported substantially higher mortality

TABLE 1
Recently licensed intravenous antimicrobial agents and their activities

	Year of US approval	Extended gram-positive activity*	Broad gram-negative activity
Quinupristin-dalfopristin (Synercid)	1999	+	–
Linezolid (Zyvox)	2000	+	–
Moxifloxacin (Avelox)	2001	–	+
Ertapenem (Invanz)	2001	–	+
Daptomycin (Cubicin)	2003	+	–
Tigecycline (Tygacil)	2005	+	+

* Including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.

TABLE 2
Comparative mortality rates with adequate and inadequate initial antimicrobial therapy in recent studies of patients with serious bacterial infections

	Mortality rates	
Study	Adequate initial therapy	Inadequate initial therapy
Luna et al[2]	38%	91%
Rello et al[3]	15.4%	37.0%
Kollef and Ward[4]	31.3%	56.8%
Ibrahim et al[5]	28.4%	61.9%
Vallés et al[6]	37.0%	69.4%
Harbarth et al[7]	24%	39%

(91%) in patients given inadequate initial antimicrobial therapy than in those given agents active against the identified pathogen(s) (38%). The majority of inadequately treated microorganisms in this 1997 study were resistant gram-negative bacteria (*Acinetobacter* species, *K pneumoniae*, and *P aeruginosa*).

In a separate study of ventilator-associated pneumonia published that same year, Rello et al[3] found a greater than 20% increase in mortality in patients given inadequate initial antimicrobial therapy (see **Table 2** for specific rates). Most of the pneumonia cases in this study were "late" pneumonias, and *P aeruginosa* was the predominant pathogen identified.

In a 1998 study, Kollef and Ward[4] reported a mortality rate of 56.8% when a resistant pathogen was identified on mini-bronchoalveloar lavage compared with 31.3% when empiric antimicrobial regimens were active against the identified pathogen.

More recent studies have examined the impact of adequate therapy on mortality associated with bacteremia and sepsis. In a study from a university-affiliated ICU, Ibrahim et al[5] reported a mortality rate of 61.9% for inadequately treated patients with bloodstream infections compared with 28.4% for patients who received adequate therapy. *Candida* species and multidrug-resistant gram-positive bacteria predominated.

In a multicenter observational study of community-acquired bacteremia, Vallés et al[6] found that survival in the first 48 hours among patients who presented with septic shock improved by more than 25% with appropriate antimicrobial therapy **(Table 2)**. As expected with community-acquired infections, gram-positive bacteria predominated, and *Escherichia coli* represented 60% of the identified gram-negative bacteria.

Most recently, Harbarth et al[7] analyzed data gathered from a multicenter study of the safety and efficacy of the soluble tumor necrosis factor receptor fusion protein lenercept, and they found a 15% increase in mortality among patients given inadequate as opposed to adequate initial antimicrobial therapy **(Table 2)**. The most frequent bacteria for which inadequate therapy was administered in this study were *P aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* species, methicillin-resistant *S aureus*, and enterococci.

It has become evident that effective therapy for ventilator-associated pneumonia and bacteremia due to a variety of microorganisms requires an initial regimen that demonstrates in vitro activity against the causative pathogen. The most common reason for inadequate therapy is resistance to the administered regimen. Therefore, understanding the mechanisms of resistance and therapy alternatives for problematic gram-negative bacteria is of profound importance.

EXPRESSION OF MULTIDRUG RESISTANCE IN GRAM-NEGATIVE BACTERIA

The expression of multidrug resistance in gram-negative bacteria hinges primarily on the presence of two characteristics:

Porins, pump mutations defend gram-negative bacteria against beta-lactams

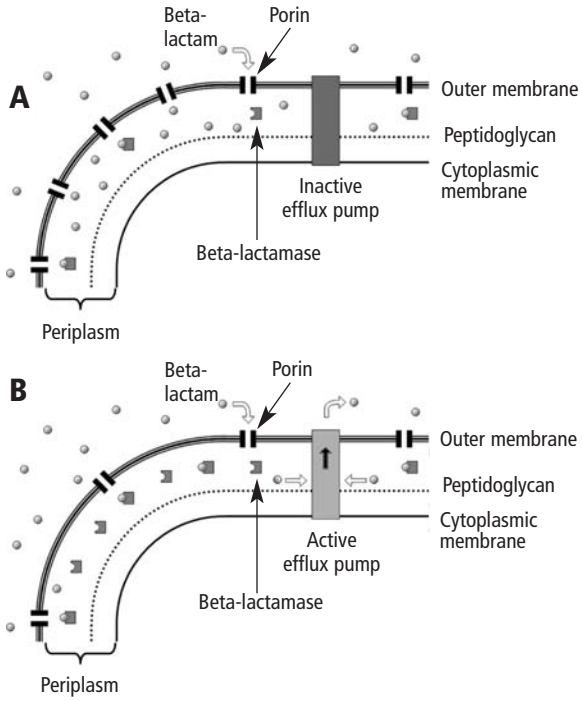

FIGURE 1. The role of porins and pump mutations in defending gram-negative bacteria against beta-lactam antibiotics. **(A)** Under circumstances in which porins are plentiful and passage through them is relatively quick, a beta-lactam has a significant advantage in that it can enter the cell in large numbers, overwhelming the number of lactamases present for defense and inhibiting enough penicillin-binding proteins to result in cell death. **(B)** After exposure to beta-lactams and other antimicrobial agents, some bacteria (notably *Pseudomonas aeruginosa*) are able to take several defensive actions. They reduce the quantity of porins in the outer membrane, retarding the beta-lactam's entry into the periplasmic space. They activate RND pumps, which "vacuum" the beta-lactams from the periplasmic space and expel them into the surrounding media. They also can increase the quantity of beta-lactamase that is produced. Under these circumstances, even a beta-lactamase that shows relatively weak activity in vitro can mount a sufficient defense to prevent cell death.

- The ability to access, then express, a variety of resistance determinants that may come from other species
- The ability to marshal intrinsic mechanisms that tend to amplify levels of resistance expressed by acquired mechanisms.

Control of periplasmic space is key

Gram-negative bacteria are structured in such a way that, to gain access to the cell, an invading compound must first traverse the outer membrane and enter the periplasmic space, a narrow region that extends from the outer membrane to the cytoplasmic membrane **(Figure 1)** and within which lies the cell wall. In the vicinity of the cytoplasmic membrane, cell wall precursors are brought out from the cytoplasm and attached to the growing and remodeling cell wall by penicillin-binding proteins, which are the targets of all beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams). Thus, inhibition of penicillin-binding proteins does not require antibiotic entry into the cell itself, but simply into the periplasmic space. Controlling the periplasmic space is therefore extraordinarily important to a bacterium's survival in an antibiotic-rich environment, and this control is exerted through both nonspecific and specific mechanisms.

Nonspecific mechanisms: Porins and efflux pumps

Most solutes must enter the outer membrane of the bacterial cell by passing through protein channels known as porins.[8] All porins are not created equal, and some allow solutes to pass through more quickly than others.[8] The rate at which solutes pass through porins is referred to as the permeability of the outer membrane. Among human pathogens, *P aeruginosa* and *A baumannii* have among the most impermeable of outer membranes, giving them an immediate survival advantage in antimicrobial-rich environments. In contrast, *E coli* has a relatively porous outer membrane.[8]

Under appropriate conditions, some bacteria can reduce expression of outer membrane porins to limit entry into the periplasmic space. Perhaps the most explicit example of this is *P aeruginosa* and its expression of resistance to imipenem.[9] Of course, porins exist for purposes other than to admit antibiotics to the periplasmic space, so reductions in their content are likely to confer a selective disadvantage in an environment free of antibiotics. It is therefore not unusual for porin mutants to become less prevalent when selective pressure from antimicrobials is no longer applied.

Another mechanism for controlling the content of the periplasmic space is the expression of multidrug efflux pumps. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including antibiotics) from within cells into the external environment; multidrug efflux pumps can extrude a wide range of compounds. Research over the past decade has elucidated the impact that multidrug efflux pumps have on the expression of antibiotic resistance.

The most common and clinically important efflux pumps in gram-negative bacteria are the so-called RND (resistance–nodulation–cell division) pumps.[10] RND pumps have an outer membrane component, a cytoplasmic membrane component, and a third component that connects and holds together the other

two. Although primarily designed to extrude materials from the cytoplasm into the surrounding media, these pumps also have an opening into the periplasmic space.[11] This would theoretically allow efflux of compounds that are in the periplasmic space as well, which would explain the observation that expression of RND-type pumps has discernable impact on levels of resistance to different beta-lactam antibiotics, which do not enter the cytoplasm of bacterial cells.

Specific mechanisms: Increased beta-lactamase expression

Porin and pump mechanisms of resistance are essentially nonspecific, since porins exist to transport a variety of molecules and since pumps, while having characteristic substrate profiles, extrude a variety of compounds. In addition to these nonspecific mechanisms, gram-negative bacteria can specifically control antimicrobial action within the periplasmic space by expressing beta-lactamases. As opposed to the beta-lactamases of gram-positive bacteria (which lack outer membranes), those expressed by gram-negative bacteria are not released into the surrounding media but are largely trapped within the periplasmic space. The ability to increase expression of beta-lactamases allows gram-negative bacteria to "pack" the periplasmic space with enzymes **(Figure 1)**. Under these circumstances, even relatively weak beta-lactamases can confer a high enough level of resistance to be clinically significant.[9] When increased expression of beta-lactamase is combined with porin reductions or RND pump activations, resistance levels can be substantial.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Klebsiella pneumoniae

K pneumoniae differs from the other two multidrug-resistant gram-negative bacteria, *P aeruginosa* and *A baumannii*, in some important respects. Like the vast majority of gram-negative bacteria (*Salmonellae* organisms being the only known exception), *K pneumoniae* expresses a beta-lactamase that is encoded on the chromosome. Unlike the enzymes of *P aeruginosa* and *A baumannii*, however, this enzyme is constitutively (rather than inducibly) expressed and is a penicillinase with relatively weak activity against cephalosporins.[12]

Because *K pneumoniae* does not produce a cephalosporinase, it cannot easily develop resistance to cephalosporins simply by changing the regulation of its chromosomal beta-lactamase gene. Instead, *K pneumoniae* has become resistant to cephalosporins through the acquisition of cephalosporin-hydrolyzing enzymes (extended-spectrum beta-lactamases, or ESBLs).[13] In most cases, such an expansion of the substrate spectrum can be accomplished by one or two point mutations in narrow-spectrum beta-lactamase genes. These mutant genes are frequently encoded on transferable plasmids that also encode resistance to a variety of other antimicrobial agents, including trimethoprim-sulfamethoxazole, tetracyclines, aminoglycosides, and, more recently, fluoroquinolones.[14,15]

It is not clear to what extent *K pneumoniae* uses RND-type multidrug efflux pumps to express resistance to beta-lactam antibiotics. There is at least one such pump in *K pneumoniae*, activation of which has been associated with resistance to the new glycylcycline antibiotic tigecycline.[16] It is very clear, however, that *K pneumoniae* frequently uses reductions in outer membrane porins to amplify resistance. The majority of ESBL-producing *K pneumoniae* isolates in some studies have had reductions in one or more outer membrane proteins.[17] Moreover, ESBL genes are frequently found downstream of promoters that contain mutations known to increase expression.[18] Finally, ESBL-producing *K pneumoniae* strains frequently express a number of different beta-lactamases, further amplifying the quantity of beta-lactamase in the periplasmic space.[19]

One consequence of increased beta-lactamase quantity is that beta-lactamase inhibitors, which are generally quite effective at inhibiting ESBLs, become overwhelmed. As a result, in many studies the majority of ESBL-producing *K pneumoniae* isolates are also resistant to inhibitor combinations, even though the ESBLs themselves are usually susceptible to inhibition.[20]

For many years, the most reliable agents for multidrug resistant *K pneumoniae* were the carbapenems, since they were resistant to hydrolysis by ESBL-type enzymes.[21] Recently, however, *K pneumoniae* strains resistant to imipenem have appeared in different geographic locales and have spread widely in New York City. These strains produce beta-lactamases designated *K pneumoniae* carbapenemase (KPC).[22] The strains that express them are resistant to all beta-lactam antibiotics and frequently to fluoroquinolones and aminoglycosides as well. They are currently creating major therapeutic challenges in hospitals throughout the New York City area and threaten to spread elsewhere.[22]

Pseudomonas aeruginosa

P aeruginosa has as many tools for developing resistance to antibiotics as any bacterium ever studied. As noted above, the outer membrane porins of *P aeruginosa* are "slow" porins, resulting in reduced access of antibiotics to the periplasmic space.[8] In addition, *P aeruginosa* is readily able to reduce porin quantities to restrict access.

Analysis of the *P aeruginosa* genome indicates the likely presence of 12 different RND-type efflux pumps, seven of which have been characterized, with six of those seven extruding antibiotics.[23] *P aeruginosa* also has an inducible chromosomal cephalosporinase.[9] Finally, *P aeruginosa* can acquire a variety of beta-lactamases and aminoglycoside-modifying enzymes to expand the spectrum of resistance expressed.

In most instances, it appears that *P aeruginosa* uses a variety of tools to express multidrug resistance. In 2001, Dubois et al[24] reported on an outbreak of *P aeruginosa* infections in an ICU setting in which resistance to virtually all antibiotics was expressed. The strains remained moderately susceptible to cefepime (Maxipime) and amikacin. In all, 69 patients were infected with this organism. Resistance was due to a combination of efflux pump activation, porin reduction, and beta-lactamase expression. Fortunately, patients infected with this strain responded to therapeutic doses of cefepime and amikacin.

P aeruginosa also may encode metallobeta-lactamases that hydrolyze carbapenems.[25] These enzymes have been described primarily from Japan, where the use of carbapenems is more extensive than in the United States. Metalloenzymes have a broad spectrum of activity, and strains that express them are often resistant to all other beta-lactam agents (except, in some cases, aztreonam [Azactam]).[26] Multidrug resistance in *P aeruginosa* accompanied by susceptibility to aztreonam should alert clinicians to the possibility that a metallobeta-lactamase may be present.

Acinetobacter baumannii

A baumannii is similar to *P aeruginosa* in many respects, particularly in the variety of intrinsic mechanisms it uses to confer and amplify resistance. *A baumannii* porins, like those of *P aeruginosa*, are "slow,"[27] and resistance in *A baumannii* has been tied to reductions in porin quantities.[28]

Two RND-type efflux pumps have been characterized in *A baumannii*, and their combined spectrum of activity is quite broad.[29,30] *A baumannii* encodes two different chromosomal beta-lactamases, one that is a broad-spectrum cephalosporinase and a second that can hydrolyze carbapenems.[31] Acquired beta-lactamases also may amplify resistance to carbapenems.[32]

A baumannii can cause serious infections in immunocompromised patients, and outbreaks have been reported in many geographic regions. These outbreaks are focused mainly in ICUs, with ventilator-associated pneunomia, wound infections, and bloodstream infections predominating.[33] As with *P aeruginosa*, significant outbreaks of *A baumannii* infection have occurred in ICUs in the New York City area.[34,35] The strains responsible for these outbreaks tend to be resistant to multiple agents, including carbapenems. *A baumannii* has also been an important cause of serious infections in injured US soldiers returning from the Middle East, and many of these strains have expressed multidrug resistance.[36]

THERAPEUTIC OPTIONS

Before considering therapeutics, it is worth emphasizing that assiduous attention to infection control measures is critical for reducing exposure to multidrug-resistant pathogens and aborting outbreaks. Maximum judiciousness in administering antimicrobial agents is also important, since prior exposure to antibiotics is a frequent and important risk factor for colonization and infection with multidrug-resistant bacteria. Still, patients will at times become infected with multidrug-resistant bacteria, so it is important to understand what therapeutic options are available for seriously ill patients.

Options for multidrug-resistant *K pneumoniae*

Strains of *K pneumoniae* that are not multidrug-resistant are susceptible to a wide variety of commonly used antimicrobial agents, including aminoglycosides, beta-lactam/beta-lactamase inhibitor combinations, carbapenems, cephalosporins, fluoroquinolones, monobactams, and trimethoprim-sulfamethoxazole. Since many ESBL-producing strains of *K pneumoniae* encode their ESBL enzymes on large, multidrug-resistant plasmids, options for these strains are often reduced to carbapenems. In the limited clinical studies that are available, carbapenems also appear to yield the best therapeutic outcomes and are therefore recommended for treating infections known to be caused by ESBL-producing bacteria.[21,37] In selected circumstances, when in vitro susceptibility is confirmed, beta-lactam/beta-lactamase inhibitor combinations and fluoroquinolones may be used effectively. Data on the potential efficacy of the fourth-generation cephalosporin cefepime for treating ESBL infections are conflicting, so this agent cannot be confidently recommended as routine therapy for these infections at this time.

Finding alternatives for the recently emerged KPC-producing *K pneumoniae* strains is more difficult. As shown in **Table 3**, many of these strains are resistant to multiple antibiotics.[38] At present, several hospitals are using the peptide antibiotics polymyxin B or colistin (Coly-Mycin M), also known as polymyxin E, as first-line therapy for infections caused by these

strains. Another alternative is tigecycline, the recently licensed glycylcycline that exhibits excellent activity against *K pneumoniae* strains. In clinical trials supporting its licensing, tigecycline was successful in treating 46 of 52 patients with intra-abdominal infections involving *K pneumoniae*.[39] More clinical data will be required before an assessment can be made of tigecycline's efficacy against additional multidrug-resistant strains.

Options for multidrug-resistant *P aeruginosa* and *A baumannii*

Antimicrobial therapy of infections caused by *P aeruginosa* or *A baumannii* is always a challenge, even for strains with typical susceptibility patterns. Strains that are susceptible at the start of therapy often emerge resistant before the end of therapy. The resulting fear of resistance often prompts the use of combination therapy despite a lack of data to support combination therapy as a mechanism for preventing the emergence of resistance in these species. Thus, in selecting treatments for these difficult-to-treat species, we are generally operating at the edges of commonly accepted evidence-based practices.

The circumstances are even more daunting when infection is caused by strains known to be resistant to multiple drugs. Physicians are then often left with the difficult choice between commonly used antimicrobial agents that are only marginally effective in vitro or infrequently used and toxic therapies that are effective in vitro. Unfortunately, physicians in critical care settings increasingly face circumstances in which no commonly used antimicrobial agents are active in vitro against the infecting pathogen. In such circumstances, the peptide antibiotics polymyxin B and colistin are sometimes the only viable choices. Historically, these peptide antibiotics have been associated with renal toxicity and neurotoxicity. Their use diminished with the availability of broad-spectrum beta-lactam antibiotics.

Unfortunately, clinical experience with colistin and polymyxin B is scarce. Reported use of these agents against modern multidrug-resistant pathogens is rare, retrospective, and without adequate controls, which makes assessing their true efficacy difficult. The retrospective nature of the reports also often makes it difficult to accurately assess the true importance of *P aeruginosa* or *A baumannii* as a pathogen in specific cases. Finally, the serious underlying diseases that predispose to infection with these bacteria often complicate estimation of the infection's contribution to a patient's death. Despite these limitations, it is worthwhile to review the available literature on the use of these agents for these important infections.

TABLE 3
Activity of antimicrobial agents against KPC-producing, carbapenem-resistant *K pneumoniae* from Brooklyn, NY

	Susceptibility results for 96 isolates (%)		
	Susceptible	Intermediate	Resistant
Piperacillin-tazobactam (Zosyn)	0	1	99
Cefotetan (Cefotan)	59	18	23
Ceftazidime (various)	2	0	98
Cefepime (Maxipime)	40	30	30
Gentamicin (various)	61	6	33
Amikacin (various)	45	52	3
Ciprofloxacin (various)	2	0	98
Doxycycline (various)	66	10	24
Polymyxin B (Polymyxin B)	91	0	9
Tigecycline (Tygacil)	100	0	0

KPC = *Klebsiella pneumoniae* carbapenemase
Adapted from Bratu et al.[38]

Polymyxin B. In a recent study on the clinical efficacy of polymyxin B, Sobieszczyk et al[40] retrospectively analyzed 29 courses of this therapy in 25 patients with serious respiratory infections. All patients were also treated with a second antibiotic. Sixteen of the courses were in patients infected with *A baumannii* (7 resistant to all other antibiotics), 12 were in patients infected with *P aeruginosa* (5 resistant to all other antibiotics), and 1 was in a patient with *Alcaligenes xylosoxidans*. End-of-treatment mortality, the primary outcome measure, was 21%, and the outcome was judged to be favorable at the end of 22 of the 29 courses of therapy (76%). Only one course of intravenous polymyxin B was judged to be associated with significant nephrotoxicity.

Colistin. Three recent studies, all retrospective, have looked at the efficacy of colistin in treating serious gram-negative infections.[41–43]

TABLE 4
Activity of imipenem and tigecycline against 49 multidrug-resistant *Acinetobacter baumannii* strains

	MIC (μg/mL)			Susceptibility of isolates (%)		
	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Imipenem-cilastatin (Primaxin)	1–128	32	128	20	2	78
Tigecycline (Tygacil)	1–4	2	2	92	8	0

MIC = minimum inhibitory concentration
Adapted, with permission, from Pachon-Ibanez et al.[47]

Garnacho-Montero et al[41] analyzed 35 cases of ventilator-associated pneumonia caused by *A baumannii*. Twenty-one of these episodes were susceptible only to colistin and were treated with colistin; the remaining 14 cases were susceptible to and treated with imipenem-cilastatin plus a second antibiotic. Clinical cure rates were 57% in both groups, and nephrotoxicity was judged to be equivalent between the groups.

Markou et al[42] reported on 28 critically ill patients treated with colistin for sepsis, 24 of whom had 26 courses and lived 48 hours so that they were deemed evaluable. Twenty episodes were due to *P aeruginosa* and 6 to *A baumannii*. Decreased fever and improved vital signs were noted in 17 of 26 colistin-treated patients for at least 48 hours, and 7 of 11 patient with bacteremia had an initial clinical response. Serious renal impairment was judged to occur in less than 10% of treatment courses.

Kasiakou et al[43] reported on 50 patients receiving 54 courses of colistin for treatment of serious infections (predominantly pulmonary and bloodstream infections) due to *A baumannii* (27 patients), *P aeruginosa* (21 patients), and *K pneumoniae* (2 patients). Virtually all patients received one or two other antimicrobial agents concomitantly. Clinical response (cure or improvement) was observed in 36 of 54 episodes (66.7%), and renal insufficiency was observed in 8% of patients.

Bottom line on peptide antibiotics. In aggregate, these small retrospective studies suggest that polymyxin B and colistin may be effective therapies for serious gram-negative infections, but better-controlled and prospective studies clearly are needed to truly define the role of these agents. On the positive side, neither agent appears to be as toxic as was once thought.

Our knowledge of these peptide antibiotics has suffered from an important limitation to date: the lack of an appropriate understanding of the pharmacodynamic parameters that will optimize their clinical efficacy. A few recent in vitro studies have investigated the pharmacodynamics of colistin and polymyxin B against *P aeruginosa*.[44–46] In general, they have found that these agents are concentration-dependent killers and have suggested that the ratio of area under the curve to minimum inhibitory concentration (AUC:MIC) is the most important parameter. They also have revealed the emergence of resistant mutants with continued dosing, a problem that has likewise been noted with nebulized forms of polymyxin B used to treat patients with cystic fibrosis.

Tigecycline. Although not effective against *P aeruginosa*, tigecycline may be an alternative for treating serious infections due to *A baumannii*. One recent in vitro study examining multidrug-resistant isolates indicates that tigecycline retains excellent activity against *A baumannii* strains that are resistant to imipenem and multiple other beta-lactam agents, confirming previous studies **(Table 4)**.[47] There are currently no published reports on the efficacy of tigecycline in treating clinical infections due to *A baumannii*. More clinical experience is required before tigecycline can be confidently recommended for treating serious infections due to *A baumannii*.

UNCERTAIN OUTLOOK FOR NEW ANTIMICROBIALS

Unfortunately, large pharmaceutical firms' investment in antibacterial therapy has waned considerably in the past decade.[48] Moreover, among the antibacterial agents that are being developed, the majority are focused on treating infections due to gram-positive bacteria.

There are several reasons for this decline. First, most gram-negative bacteria that we encounter remain susceptible to several classes of available antibiotics. Second, antibiotics are not among the most profitable drug classes being developed, even when successful. Perhaps even more important is the reality that most of the easy targets for antibacterial

therapy have already been discovered, which considerably increases the difficulty and cost of discovering new targets. Moreover, resistant gram-negative bacteria present a particular challenge since many of their resistance mechanisms are nonspecific, generic mechanisms designed to protect the organism against a wide range of toxic substances. Whereas it is easy to envision a compound that will avoid a beta-lactamase, it is much more difficult to develop a compound that will resist efflux by one of the 12 putative efflux pumps we believe *P aeruginosa* possesses.

CONCLUSIONS AND RECOMMENDATIONS

Multidrug-resistant gram-negative bacteria are with us to stay and will continue to grow in importance in hospitals that have high proportions of vulnerable patients and use excessive quantities of antibiotics. It is unlikely that a quick fix for this problem will come from the pharmaceutical industry in the near future. We must therefore use the tools available to us to reduce the spread of resistance. Attention to infection control measures is critical. Moreover, coherent strategies for minimizing total antibiotic use will be important. In addition, rational use of newer antibiotics that do offer some activity against these resistant pathogens will be important for maintaining these agents' clinical utility into the future.

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