Review

Gram-negative antibiotic resistance: there is a price to pay

Thomas G Slama

Indiana University School of Medicine, 8240 Nabb Road #300, Indianapolis, Indiana 46260, USA

Corresponding author: Thomas G Slama, slamaidi@aol.com

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Abstract

Resistance rates are increasing among several problematic Gram-negative pathogens that are often responsible for serious nosocomial infections, including *Acinetobacter* spp., *Pseudomonas aeruginosa*, and (because of their production of extended-spectrum β-lactamase) Enterobacteriaceae. The presence of multiresistant strains of these organisms has been associated with prolonged hospital stays, higher health care costs, and increased mortality, particularly when initial antibiotic therapy does not provide coverage of the causative pathogen. Conversely, with high rates of appropriate initial antibiotic therapy, infections caused by multiresistant Gram-negative pathogens do not negatively influence patient outcomes or costs. Taken together, these observations underscore the importance of a 'hit hard and hit fast' approach to treating serious nosocomial infections, particularly when it is suspected that multiresistant pathogens are responsible. They also point to the need for a multidisciplinary effort to combat resistance, which should include improved antimicrobial stewardship, increased resources for infection control, and development of new antimicrobial agents with activity against multiresistant Gram-negative pathogens.

Introduction

The treatment of serious bacterial infections in clinical practice is often complicated by antibiotic resistance. Based on their clinical experience, most clinicians - but not all [1,2] - believe that antibiotic resistance is increasing, is associated with increased morbidity and mortality, and is expensive. The importance of each of these points depends on the person's perspective: the first is most important to clinicians, the subsequent two to patients, and finally the last point to hospital administrators and health care payors. Recognizing the growing problem of antibiotic resistance, as well as the decreasing investment being made in antimicrobial research and development, the Infectious Diseases Society of America created the Antimicrobial Availability Task Force in March 2003 [3]. This group of national experts was charged with reviewing trends in antibiotic research and development in concert with the rise in antibiotic resistance and then proposing various solutions to ensure the availability of effective antibiotics in the future. Their policy report, issued in July 2004, was entitled 'Bad bugs, no drugs: as antibiotic R&D stagnates, a public health crisis brews'. Although the report has had a favorable impact on government legislation, much more remains to be done.

The Antimicrobial Availability Task Force identified six particularly problematic pathogens, including three Gram-negative organisms: *Acinetobacter baumannii*, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and *Pseudomonas aeruginosa*. The other problematic organisms were the Gram-positive pathogens methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium*, and the filamentuous fungi *Aspergillus* spp. [3]. Without a doubt, MRSA is the organism that has received the most attention, largely driven by clinical need rather than by large sums of money. It is likely that interest in the other problematic pathogens will also be driven by clinical need and not by investment to increase awareness. Some experts consider two additional water-borne, non-fermenting Gram-negative pathogens, namely *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, both of which are related to *P. aeruginosa*, to be problematic organisms [4].

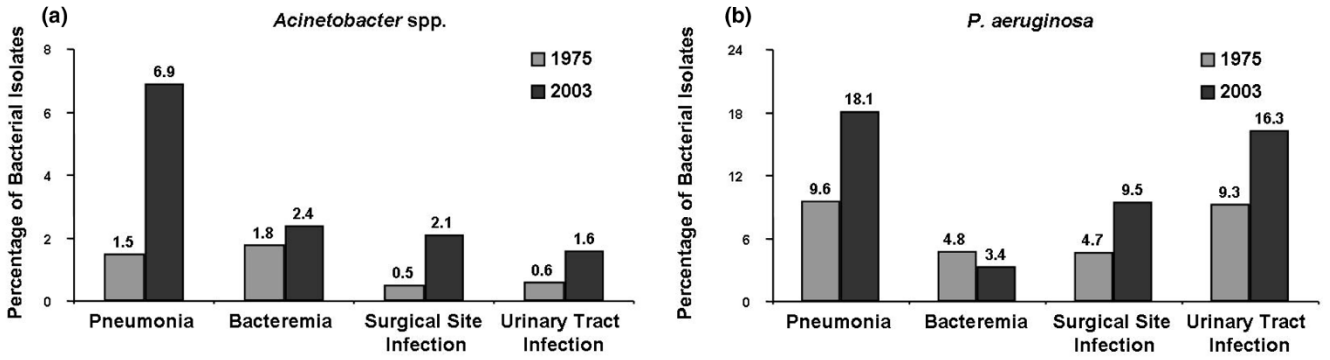
Gram-negative pathogens of concern in nosocomial infections

Acinetobacter spp.

Although long thought to be relatively avirulent, the *Acinetobacter calcoaceticus-baumannii* complex is emerging as a multiresistant nosocomial and community-acquired pathogen [3]. It was the most common wound isolate in Vietnam, Desert Storm, and Middle East war injuries, as well as in wounds associated with the 2004 Asian tsunami [5,6]. It is unclear whether the source of *A. baumannii* is associated

APACHE = Acute Physiology and Chronic Health Evaluation; ESBL = extended-spectrum β-lactamase; ICU = intensive care unit; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; NNIS = National Nosocomial Infections Surveillance; VAP = ventilator-associated pneumonia.

Figure 1



Acinetobacter spp. and *Pseudomonas aeruginosa* isolates: 1975 and 2003. Shown are the percentages of bacterial isolates associated with **(a)** *Acinetobacter* spp. and **(b)** *P. aeruginosa* by infection type in the National Nosocomial Infections Surveillance System for 1975 and 2003. Data from 1975 are from hospital-wide surveillance whereas those from 2003 are from intensive care unit surveillance [8].

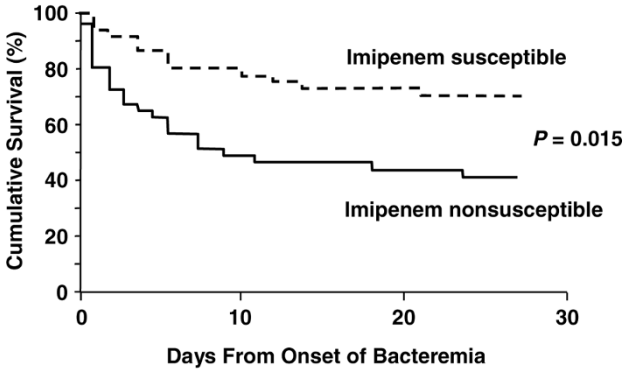
with field hospitals or larger medical centers after the soldiers were evacuated from the war zone. Nevertheless, treatment of soldiers with infected wounds is now directed to ensure coverage of this pathogen.

A. baumannii is an increasingly common cause of ventilator-associated pneumonia (VAP). In recent years, many things have changed in how VAP is treated. VAP patients are now routinely given shorter courses of antibiotic therapy (7 to 10 days), except in cases caused by *P. aeruginosa*. However, despite efforts to use Acute Physiology and Chronic Health Evaluation (APACHE) II or other scores, there remains a need to improve patient evaluation during antibiotic therapy. Does the patient still have adult respiratory distress syndrome? Is the patient still acidotic? How bad is the multiple organ system failure? In an increasing number of cases, at least in Germany and at the Walter Reed Army Medical Center (Washington, DC), VAP caused by *A. baumannii* presents as a multilobar infiltrate that often cavitates and develops pleural effusions and fistula formation. It is not uncommon in such cases to find persistently positive endotracheal specimens or open-lung biopsies with multiresistant strains of *A. baumannii* (resistant to three or more representatives of the major antibiotic categories) [7]. Data from the National Nosocomial Infections Surveillance (NNIS) system indicate that the incidence of nosocomial infections caused by *Acinetobacter* spp. increased between 1975 and 2003 (Figure 1) [8].

The incidence of *Acinetobacter* spp. in nosocomial pneumonia increased from 1.5% to 6.9% during this period, and similarly the incidence in bloodstream infections increased from 1.8% to 2.4%, in surgical site infections from 0.5% to 2.1%, and in urinary tract infections from 0.6% to 1.6%. Importantly, multiresistant strains of *Acinetobacter* spp. are being isolated with increasing frequency in many of these nosocomial infections. These pathogens have rapidly developed resistance to currently available antimicrobials via a wide range of mechanisms, including production of aminoglycoside-modifying enzymes, ESBLs, and carbapenemases, as well as through changes in outer membrane proteins, penicillin-binding proteins, and topoisomerases [9,10]. It is therefore not surprising that *Acinetobacter* spp. have emerged as 'selected' pathogens. In many areas it is common to find strains of *Acinetobacter* spp. that are resistant to all aminoglycosides, cephalosporins, and fluoroquinolones [11]. As a result, empiric therapy has become problematic and relapses more common. It is important to remember that *Acinetobacter* infections occur in intensive care units (ICUs), postoperative suites, and other hospital settings where antibiotic treatment is initially overseen by intensivists and hospitalists and not by infectious disease specialists. The importance of early aggressive treatment of *Acinetobacter* cannot be stressed enough.

The impact that multiresistant *Acinetobacter* spp. have on patient outcome is illustrated by a recent retrospective, risk-adjusted, cohort study conducted in patients with *Acinetobacter* bacteremia [12]. Patients infected with imipenem-resistant strains had a significantly higher 30-day mortality rate than did those infected with imipenem-susceptible strains (57.5% versus 27.5%; $P = 0.007$; Figure 2). In the vast majority of cases the imipenem-resistant stains had a multidrug resistance phenotype, characterized by resistance to three or more other antibiotic classes. Notably, patients with imipenem-resistant strains were significantly more likely to receive inappropriate antibiotic therapy initially that did not provide coverage against the isolated *Acinetobacter* strain (65.0% versus 20.0%; $P < 0.001$). Moreover, patients who were treated inappropriately at the start had a higher 30-day mortality rate than did those given appropriate initial antibiotic therapy (67.6% versus 23.9%; $P < 0.001$). The difference between groups in mortality was particularly evident over the first 5 days, indicating that initial treatment is of paramount importance.

Figure 2



Impact of imipenem resistance on mortality of patients with *Acinetobacter* bacteremia. Reprinted with permission from Kwon and coworkers [12]. Copyright © 2007 Oxford University Press.

ESBL-producing Enterobacteriaceae

The most common mechanism of resistance among *Escherichia coli*, *Klebsiella pneumoniae*, and other Enterobacteriaceae is through the production of β-lactamases, which - depending on the enzyme - inactivate certain β-lactam antibiotics [13]. The ESBLs are a heterogeneous group of enzymes that are encoded by plasmid-borne genes. ESBLs now number 532 distinct enzymes and convey varying degrees of resistance to cephalosporins, penicillins, β-lactamase inhibitors, and monobactams [1,13]. The prevalence of ESBL-producing strains varies by geography (particularly in urban areas), type of hospital, and patient age. For example, in the SENTRY Antimicrobial Surveillance Program, the rate of ESBL-producing strains of *Klebsiella* spp. in bloodstream infections between 1997 and 2002 was 43.7% in Latin America but 21.7% in Europe and 5.8% in North America ($P < 0.001$) [14]. Among North American strains recovered in 2001 from patients in ICUs, the ESBL-producing phenotype was found in 11.2% of *E. coli* isolates and 16.2% of *Klebsiella* spp. [15]. Importantly, during the past 2 to 3 years there have been reports of ESBL-producing strains that also produce carbapenemases [16].

The impact that ESBL production has on patient outcome and hospital costs was evaluated in a recent matched-cohort study [17]. Twenty-one patients infected with ESBL-producing *E. coli* or *Klebsiella* spp. at sites other than the urinary tract were compared with 21 patients with non-ESBL infections matched for pathogen, patient age, co-morbid conditions, anatomic site of infection, hospital location, date of hospitalization, and initial antibiotics received. The two groups were well matched with respect to demographic and clinical characteristics, except that patients with ESBL-positive strains had been hospitalized for a longer period before onset of the infection (24 days versus 11 days; $P = 0.035$) and were more likely to have recently received antibiotics (42.9% versus 4.8%; $P = 0.027$). Patients infected with ESBL-producing strains had significantly higher infection-related hospital costs than did those with non-ESBL-producing strains ($41,353 versus $24,902 per patient; $P = 0.034$), which was largely driven by a prolonged length of stay in the hospital. Patients with ESBL-producing strains required an additional length of stay of 9.7 days (95% confidence interval 3.2 days to 14.6 days; $P = 0.006$). In both groups, hospital bed costs accounted for approximately 55% of total costs, whereas antibiotic costs represented only 2% to 3% of the total. Initial antibiotic therapy was less likely to be successful in patients infected with the ESBL-positive strains (47.6% versus 85.7%; $P = 0.027$), reflecting a difference in success rates for noncarbapenem β-lactam antibiotics and fluoroquinolones. In contrast, treatment was successful in all patients who received a carbapenem, regardless of ESBL phenotype. Patients who failed initial antibiotic therapy were significantly more likely to receive sequential antibiotic therapy, thus increasing their length of stay and hospital costs.

Similar results were obtained in an earlier case-control study involving 33 patients infected with ESBL-producing *E. coli* or *K. pneumoniae* and 66 matched control individuals [18]. Patients with ESBL-producing strains had significantly greater median hospital charges than did those with non-ESBL-producing strains ($66,590 versus $22,231 per patient; $P < 0.001$). On multivariate analysis, which controlled for APACHE II score and hospitalization duration before infection, ESBL-producing strains increased costs by an average of 1.71-fold (95% confidence interval 1.01-fold to 2.88-fold; $P = 0.04$) relative to controls. Hospital stays were also 1.7 times longer after correction for APACHE II scores ($P = 0.01$), although this difference largely disappeared when correction was also made for the duration of hospitalization before infection.

A larger case-control study compared 99 bacteremic patients with ESBL-producing strains of *E. coli*, *Klebsiellia* spp., or *Proteus* spp. with 99 control patients with bacteremia caused by non-ESBL strains [19]. Patients with ESBL-positive strains had significantly higher average hospital costs ($46,970 versus $16,877 per patient; $P < 0.001$), longer median hospital stays after the onset of bacteremia (11 days versus 5 days; $P < 0.001$), and higher in-hospital mortality (35% versus 18%; $P = 0.01$) compared with control individuals. After adjusting for potential confounding variables in multivariate analyses, ESBL production remained independently associated with increased hospital costs ($P = 0.003$), longer hospital stays ($P = 0.001$), and higher in-hospital mortality ($P = 0.008$). Moreover, patients with ESBL-positive strains were much more likely than control individuals to have a delay of at least 48 hours until initiation of appropriate antibiotic therapy (66% versus 7%; $P < 0.001$).

The importance of selecting appropriate initial antibiotic therapy to patient outcome is illustrated by a prospective

study of 455 consecutive cases of *K. pneumoniae* at 12 hospitals in seven countries [20]. Eighty-five cases were caused by an ESBL-producing strain, and of these 20 patients (23.5%) died within 14 days of the first positive blood culture. Failure to administer an appropriate antibiotic with *in vitro* activity against the isolate within the first 5 days resulted in significantly higher mortality than treatment with an appropriate antibiotic (63.6% versus 14.1%; $P = 0.001$). Patients who received a carbapenem - either alone or in combination with another antibiotic - during that 5-day period had 83% lower risk for 14-day mortality than did those who received noncarbapenem antibiotics ($P = 0.012$). Moreover, on multivariate analysis carbapenem use was found to be independently associated with decreased mortality.

Taken together, these studies consistently show that ESBL-producing Enterobacteriaceae are associated with a delay in initiation of appropriate antibiotic therapy, which consequently prolongs hospital stays and increases hospital costs. More importantly, failure to initiate appropriate antibiotic therapy from the start appears to be responsible for higher patient mortality.

P. aeruginosa

P. aeruginosa is an invasive Gram-negative bacterial pathogen that is responsible for a wide range of severe nosocomial infections, including pneumonia, urinary tract infections, and bacteremia [3]. Importantly, this pathogen is intrinsically susceptible to only a limited number of antibacterial agents because of the low permeability of its cell wall [21]. Consequently, infections are often difficult to treat and may be life-threatening, particularly if the causative strain is multiresistant. As a result, considerable attention has been focused on *P. aeruginosa* in the hospital setting. As for *A. baumannii*, the incidence of *P. aeruginosa* in most nosocomial infections increased between 1975 and 2003 according to the NNIS System (Figure 1) [8]. During this period, the incidence of *P. aeruginosa* increased from 9.6% to 18.1% in nosocomial pneumonia, from 9.3% to 16.3% in urinary tract infection, and from 4.7% to 9.5% in surgical site infection. However, it declined slightly from 4.8% to 3.4% in bloodstream infections, largely reflecting the increasing frequency of certain Gram-positive pathogens, particularly coagulase-negative staphylococci and enterococci. In the 2001 SENTRY Surveillance Program report [15], *P. aeruginosa* was the second most common pathogen isolated from ICU patients, trailing only *S. aureus* [15].

In addition to its intrinsic resistance, *P. aeruginosa* has also acquired resistance via multiple mechanisms, including production of β-lactamases and carbapenemases, upregulation of multidrug efflux pumps, and finally cell wall mutations leading to a reduction in porin channels [21]. Many small antibiotics, including β-lactams and quinolones, require these aqueous porin channels in order to enter *P. aeruginosa*. In addition, mutation of genes encoding antibacterial targets such as DNA gyrase for fluoroquinolones contributes to resistance in *P. aeruginosa*. According to the NNIS System, resistance in *P. aeruginosa* is increasing. For nosocomial infections in ICU patients, 32% of strains were resistant to third-generation cephalosporins (cefepine or ceftazidine) in 2003, representing a 9% increase over the preceding 5-year period [22]. Similarly, 30% of strains were resistant to fluoroquinolones, representing a 15% increase. Perhaps most alarming was the observation that 21% of strains were resistant to imipenem in 2003, which represented a 47% increase over the previous 5-year period. These findings indicate that using these antibiotics to treat nosocomial infections caused by *P. aeruginosa* will result in a significant number of clinical failures.

The impact that multidrug resistance in *P. aeruginosa* has on mortality and cost is illustrated by several studies. In a retrospective analysis of patients with *P. aeruginosa* bacteremia at a large university hospital over a 10-year period, 51 out of 358 cases (14.2%) were multiresistant to ciprofloxacin, ceftazidime, imipenem, gentamicin, and piperacillin [23]. Patients with multiresistant *P. aeruginosa* had significantly higher in-hospital mortality than did those with more susceptible strains (67% versus 23%; $P = 0.001$). In another study, multiresistant *P. aeruginosa* was isolated from 22 hospitalized patients [24]. The mean cost of admission in this cohort was $54,081 per patient, which was substantially higher than the $22,116 cost per patient for those infected with susceptible strains of *P. aeruginosa.*

The emergence of resistance during treatment of *P. aeruginosa* infections has a dramatic effect on outcome and cost. In a cohort of 468 patients with *P. aeruginosa* infections, 30 patients developed resistance during treatment, defined by a fourfold increase in minimum inhibitory concentration (MIC) relative to the baseline isolate, which resulted in a change in interpretive class [25]. In the multivariate analysis, patients in whom resistance emerged had significantly longer median hospital stays (24 days versus 7 days; $P < 0.001$) and higher in-hospital mortality rates (27% versus 8%; $P = 0.02$) than did those who did not have treatment-emergent resistance. Comparable results have been reported for treatment-emergent resistance in other Gram-negative pathogens, such as *Enterobacter* spp. [26].

Clinical challenges in treating patients with resistant organisms

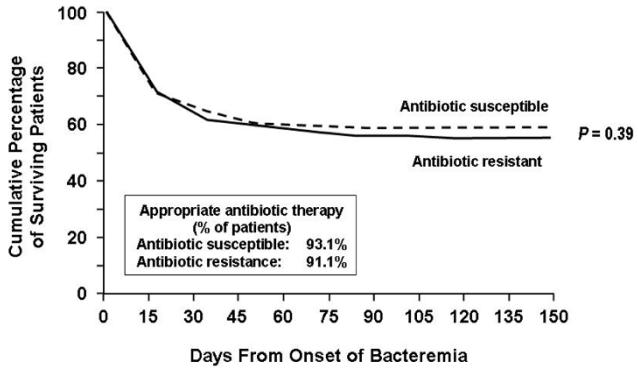
The clinical studies highlighted in the preceding sections illustrate that patients infected with resistant strains of key Gram-negative pathogens have increased mortality, longer hospital stays, and higher hospital costs than those infected by susceptible strains. This evidence underscores the need for hospitals to start reacting in a proactive manner rather than in a reactive one to combat the rising resistance rates. Although resistance is an important factor, it is important to recognize that several other problems also contribute to poor

outcomes and high costs. First and foremost is the selection of initial antibiotic therapy before susceptibility test results become available. Patients who receive inadequate initial antibiotic therapy that does not provide coverage of the causative pathogen have poorer clinical outcomes, longer lengths of stay, and higher costs than those who received an appropriate antibiotic from the start [4]. Second, clinical laboratories are struggling to provide optimal and rapid susceptibility testing. However, hospitalists and intensivists often may not recognize subtle differences in susceptibility results. An MIC of 4 μg/ml for one drug does not mean that the pathogen has an MIC of 4 μg/ml for all members of that drug class. In turn, this may lead to slower identification of resistant pathogens and, ultimately, poorer clinical outcomes. Finally, efforts by hospital administrators to continually cut costs may lead to elimination of key personnel involved in overseeing infection control on a daily basis.

If resistant pathogens and inappropriate initial antibiotic therapy are associated with poor outcomes and high costs, then, conversely, high rates of appropriate initial antibiotic therapy should overcome any difference in outcomes and costs between resistant and susceptible strains. In a retrospective, observational cohort study, 328 patients admitted to the ICU were identified with nosocomial, microbiologically documented Gram-negative bacteremia [27]. Of these, 120 cases (36.6%) were caused by ceftazidime-resistant pathogens, which in the study hospital was considered to indicate an ESBL-producing strain or a hyperproducer of Amp C β-lactamases. Patients with susceptible and resistant strains had similar demographic and clinical characteristics at the onset of Gram-negative bacteremia, except that patients with resistant strains had been hospitalized longer before bacteremia onset than those with susceptible strains (18 versus 8 days; $P < 0.001$). In general, patients with resistant strains were more likely to be infected with *Acinetobacter* spp. and *Enterobacter* spp., whereas those with susceptible strains were more likely to be infected with *E. coli.* The frequencies of infection with other Enterobacteriaceae and *P. aeruginosa* were similar in the two groups. Overall, appropriate initial antibiotic therapy was administered to 93.1% of patients with susceptible stains and 91.1% of those with resistant strains. Notably, mortality rates - whether measured in the hospital or at 14 or 28 days - did not differ between bacteremic patients with susceptible or resistant strains (Figure 3). Although patients with resistant strains required, on average, at least 1 additional week in the hospital, the length of hospital stay after bacteremia onset did not differ.

The cost of Gram-negative resistance is further illustrated by a recent study of 617 surgical patients with Gram-negative rod infections [28]. In this analysis, antibiotic resistance was defined by resistance to all drugs in one or more of the major antibiotic classes. Patients with infection caused by resistant bacteria had greater severity of illness at admission than did those with susceptible strains; there was a higher rate of use

Figure 3



Impact of high rates of appropriate antibiotic therapy on mortality in patients with Gram-negative bacteremia. Antibiotic resistance was defined as *in vitro* resistance to ceftazidime [27]. Reprinted with permission. Copyright © 2002 Infectious Diseases Society of America.

of invasive support measures at the time infection was diagnosed among these patients. The most common pathogens responsible for resistant infections were *Pseudomonas* and *Acinetobacter* spp. After taking differences in baseline parameters into account in the regression analysis, antibiotic resistance independently predicted higher hospital costs, with an attributable cost increase of $10,255 per patient ($P = 0.0001$).

Real costs of controlling infection

Several factors contribute to the real costs associated with controlling infection. These include the cost of new antimicrobial development - now estimated at $1 billion per drug - as well as the need for increased surveillance within each hospital to determine which pathogens are problematic by patient type and by hospital ward. The costs associated with enforced isolation procedures to control spread of resistant pathogens, as well as those for implementing improved antibiotic usage policies to limit emergence of resistant strains, must also be considered, but these will only be successful if they are supported by the hospital administration. Finally, education remains a critical component of any effort to control infection, but it will most likely be successful when targeted to interns, residents, and medical students who have not yet developed specific treatment habits.

As the general population ages and people live longer, additional strain will be placed on the delivery of quality health care at reasonable prices. Whether the focus is on infection control or another health care issue, who is going to help? Large pharmaceutical companies will only develop new antimicrobial agents if the federal government provides financial incentives through better patent protection or acceptable reimbursement rates. If it does not, then antibiotic development will become the purview of small companies,

which will be bought and sold as they move agents through the clinical development process. Hospitals will initiate surveillance programs or policy changes in order to improve infection control but only if they prove to save money. Similarly, third-party payors will support use of new antibiotics or procedures provided that they can maintain profit margins. Legislators may help depending on where and how much national pressure is delivered by various organizations and lobbyists. Finally, physicians will take steps to improve infection control, but they will require evidence, and then they still will often make individual decisions rather than following a recommended algorithm for patient management.

The list of new antimicrobials in clinical development for treatment of Gram-negative infections unfortunately remains small. Some of these agents are promising, especially the carbapenems and cephalosporins currently in development, because they have greater activity than other members of their respective antibiotic class against key pathogens such as *P. aeruginosa* and MRSA.

Conclusion

In summary, *A. baumannii*, ESBL-producing Enterobacteriaceae, and *P. aeruginosa* are key Gram-negative pathogens that are involved in serious nosocomial infections. Multiresistant strains are particularly problematic, conveying increased mortality, longer hospital stays, and higher hospital costs over and above the values associated with susceptible strains of these pathogens. Moreover, the consistency of these findings across studies, as well as across these key pathogens, underscores the clinical and economic significance of antibiotic resistance. Successful treatment requires a 'hit hard and hit fast' approach with an antibiotic that provides coverage of these important Gram-negative organisms, including multiresistant strains. Finally, co-operation between doctors, hospital administrators, third-party payors, legislators, and pharmaceutical companies is needed in order to find ways to prevent further increases in antibiotic resistance and limit the costs associated with it.

Competing interests

The author declares that they have no competing interests.

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