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The Bacterial Cell Wall as an Antimicrobial Target

ISSUE EDITOR

Karen **Bush**

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Indiana University Bloomington

TABLE OF CONTENTS

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Introduction to *Antimicrobial Therapeutics Reviews*

The bacterial cell wall as an antimicrobial target

Bacterial cell walls are unique structures that serve as ideal targets for antimicrobial drugs. Agents that interfere with bacterial cell wall biosynthesis or cell integrity have been used therapeutically with high efficacy and good safety since the 1940s.[1,2] Because there is no comparable structure in mammalians, bacterial cell wall inhibitors can exhibit high target specificity with side effect profiles that are not target related, unlike some other classes of antibiotics. In addition, cell wall–active agents are frequently bactericidal in their action, providing the opportunity for complete bacterial clearance in serious infections.

Antibiotics that target the cell wall generally have their origins in natural products, many from soil isolates that have produced commercially successful antibiotics or closely related analogs. Among these are the penicillins, cephalosporins, carbapenems, and monobactams from the β-lactam class, and the cationic peptides in the naturally occurring polymyxin family, agents that are among our last hopes for treatment of infections caused by many multidrug-resistant Gram-negative bacteria. Glycopeptides and other large macrocylic natural products, such as vancomycin and daptomycin, are enjoying widespread use following the global dissemination of methicillin-resistant staphylococci beginning in the 1990s. However, it is becoming clear that we need to look beyond natural products for our next generation of antibacterial drugs.

Although cell wall–active agents targeting the bacterial wall are among the mainstays of our antibacterial armamentarium, resistance to these agents, and all antibiotics, has increased at a dramatic rate, such that some have even proposed that we may be approaching an "era of untreatable infections."[3] Therefore, new approaches to antibacterial agents are urgently needed. Because of the success of agents that interact with cell wall targets, it is logical to examine the role of the cell wall, and the mechanism of action of cell wall–active agents, to evaluate the potential for novel agents in these areas.

In this *Annals* volume, the contributors explore the various roles of the bacterial cell wall as related to the physiology of bacteria and to the development of antibacterial drugs. To set the stage for the volume, Master *et al.*[4] provide surveillance data in the first article, demonstrating the levels of resistance in key pathogens over the period of 2007–2011. Although resistance has remained somewhat flat for some drug–bug combinations during this time, the levels of resistance to cell wall–active agents are sufficiently high to cause great concern for the utility of some of these agents.

Egan and Vollmer then provide an updated review on the physiology of cell wall division[5] as background to later discussions about mechanisms of action and mechanisms of resistance of various cell wall–active agents. Silver then provides a comprehensive analysis of the various screening targets related to peptidoglycan biosynthesis,[6] with an emphasis on those targets that still

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may hold potential for future drug discovery/drug development programs. As a complementary review, Johnson *et al.* discuss bacterial cell wall recycling,[7] with mechanistic insights that may provide additional drug targets involved in synergistic interactions with known targets for drugs like the β-lactams.

β-Lactams are the most widely used class of antibiotics[8] and thus attract much of the attention in the remainder of the volume. Talbot[9] provides a discussion of the future of β-lactam antibiotics, taking into consideration various resistance mechanisms specific for this class, but also the potential for new agents in the pipeline that may address these issues. An updated review on the increasing numbers and types of β-lactamases, the enzymes responsible for much of the resistance to the β-lactam antibiotics, is then provided by Bush,[10] followed by the article by Palzkill,[11] who describes structural and functional aspects of the particularly deleterious metallo-β-lactamases. In a somewhat optimistic light, Shlaes discusses new investigational β-lactam–β-lactamase inhibitor combinations that may address at least some β-lactam–resistance problems.[12] A different approach to β-lactam resistance is taken by Page,[13] who illustrates the use of siderophore conjugates that enhance the antimicrobial activity of various antibiotic classes, especially the β-lactams, by using bacterial iron uptake mechanisms.

Other classes of agents that target the bacterial cell wall include the peptide and lipopeptide antibiotics. Structural and functional aspects of host defense peptides are presented by Yount and Yeaman,[14] with a discussion of various cell wall targets that may lead to new strategies for the development of novel peptide antibiotics. The final article in this volume describes the cyclic lipopeptide daptomycin, an agent that targets the Gram-positive cell wall and membrane. Bayer *et al.*[15] depict the diverse resistance mechanisms leading to daptomycin resistance in *Staphylococcus aureus*, providing new insights into the action of this novel agent.

Bacterial cell walls remain attractive targets for future antimicrobial drug discovery. Although resistance issues have compromised the use of many of our previous agents for treatment of infections caused by multidrug-resistant Gram-negative bacteria, promising new β-lactam–β-lactamase inhibitor combinations that can address many of these pathogens are in late-stage clinical development. Previously unexploited cell wall targets may provide us with viable inhibitors for future development. Perhaps the greatest challenge, however, will be to convince pharmaceutical research and development organizations that antibacterial research is worth sufficient investment to conduct the studies necessary to identify novel cell wall–active antimicrobial agents with commercial potential.

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Recent trends in resistance to cell envelope–active antibacterial agents among key bacterial pathogens

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Cell envelope–active agents, particularly β-lactams, play a pivotal role in the treatment of bacterial infections and the extent to which their activity is affected by the emergence of multidrug-resistant organisms is of concern. We analyzed the Surveillance Network (TSN) database to evaluate resistant trends for key cell envelope–active drugs among ESKAPE pathogens. Analysis demonstrated that the activity of these drugs has been notably influenced by the emergence of multidrug resistance; this was especially evident for the β-lactam drugs. For example, *Acinetobacter baumannii* resistance to imipenem increased from 23.9% to 34.3%, and resistance to piperacillin–tazobactam increased from 37.0% to 49.7% between 2007 and 2011. During the same time period *Klebsiella pneumoniae* resistance to imipenem increased from 0.8% to 3.8%. As β-lactams are a cornerstone of anti-infective therapy, it is important to closely monitor the activity of the agents being used today and to aggressively pursue new strategies that can augment current drugs and thwart ever-emerging β-lactam resistance mechanisms that are continuously encountered.

Keywords: resistance; cell envelope; antibacterial; pathogens

Background

The bacterial cell envelope (including the outer membrane, cell wall, and cytoplasmic membrane) has been a primary target for antibacterial development for over 70 years. Focusing on this target has met with great success. The general lack of an analogous physiological structure in human cells has minimized toxicity issues, and the vital nature of this structure to bacterial viability has resulted in most drugs being bactericidal. Further, by far the most prominent class of drugs in this genre, the beta-lactams (β-lactams) are "chemically malleable" in that a seemly endless array of structures can be produced. These modifications have been used to enhance pharmacological properties (allowing for both oral and parenteral forms of many β-lactams to be used), to increase the antibacterial potency of preexisting β-lactams, and to develop molecules refractory to various β-lactam resistance mechanisms that evolve among bacterial populations. By leveraging these attributes β-lactams have been the most effective and valuable class of antibiotics developed and used to date.

Given the pivotal role that cell envelope–active agents, particularly β-lactams, play in the treatment of bacterial infections, the extent to which their current and future effectiveness is affected by the emergence of multidrug-resistant organisms is of great concern.[1–5] The resistance issue encompasses both Gram-positive and Gram-negative species,[6–8] and the enzymatic strategies against β-lactams that Gram-negative bacteria employ seem to be changing on an almost daily basis.[7,9] Particular concern regarding resistant pathogens is focused on the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species).[10,11,4] Therefore, a recent perspective on resistance trends among these organisms with regard to key cell envelope–active agents, particularly β-lactams, was warranted.

Method of analysis

To gain a recent perspective on the resistance trends occurring in the United States, we used the Surveillance Network (TSN) as the data source for all of the

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Table 1. TSN regional distribution

Region	State	No. of laboratories
N. E. Central	IL, OH, MI, WI	19
S. E. Central	AL, KY, TN	11
Mid-Atlantic	NJ, NY, PA	26
Mountain	AZ, NM	24
New England	CT, MA, ME, VT	10
Pacific	CA, OR, WA	33
S. Atlantic	DC, DE, FL, MD, NC, VA, WV	57
N. W. Central	KS, MN, MO, ND, NE	9
S. W. Central	LA, OK, TX	28
		Total = 217

analyses presented. TSN is an electronic database of strain-specific antimicrobial susceptibility test data generated by clinical microbiology laboratories across the United States as a result of their routine diagnostic testing.[12] The laboratories are divided into nine geographic regions: North East Central, South East Central, Mid-Atlantic, Mountain, New England, Pacific, South Atlantic, North West Central, and South West Central (Table 1). There are over 200 laboratories from whom the data are collected directly from the institutions' laboratory information systems on a regular basis and accumulated in a central database. Participant laboratories serve hospitals that range in size from less than 100 beds to more than 500 beds. Community, university, and government hospitals are represented. Information includes organism identification, the susceptibility profile for all drugs tested, specimen source, patient location, age, and gender. All data are available for analysis based on any one or more of the parameters mentioned.

TSN analyses presented here primarily focused on key cell envelope–active drugs (predominately β-lactams) and the ESKAPE pathogens. The volume of data for each organism analyzed is as follows: *S. aureus* (885,860 drug–organism data points), *E. faecalis* (303,713 drug–organism data points), *E. faecium* (109,777 drug–organism data points), *E. coli* (6,098,400 drug–organism data points), *K. pneumoniae* (1,308,285 drug–organism data points), *Enterobacter* spp. (520,640 drug–organism data points), *P. aeruginosa* (1,249,167 drug–organism data points), and *A. baumannii* (108,747 drug–organism data points). These data are based on testing done with single patient, nonduplicate isolates. Except for the *S. aureus* analysis, the resistance trends from 2007 through 2011 were based on isolates from all patient types, locations, and specimen sources grouped together.

Results and discussion

S. aureus

According to CLSI guidelines,[13] *S. aureus* resistance to oxacillin (i.e., methicillin-resistant *S. aureus* [MRSA]) indicates resistance to all other currently available anti-staphylococcal β-lactams (ceftaroline being an exception discussed later). Therefore, MRSA was the only β-lactam resistance profile tracked in (Fig. 1) where the MRSA trends were analyzed according to patient location. Overall and for each patient location (inpatient, ICU, and

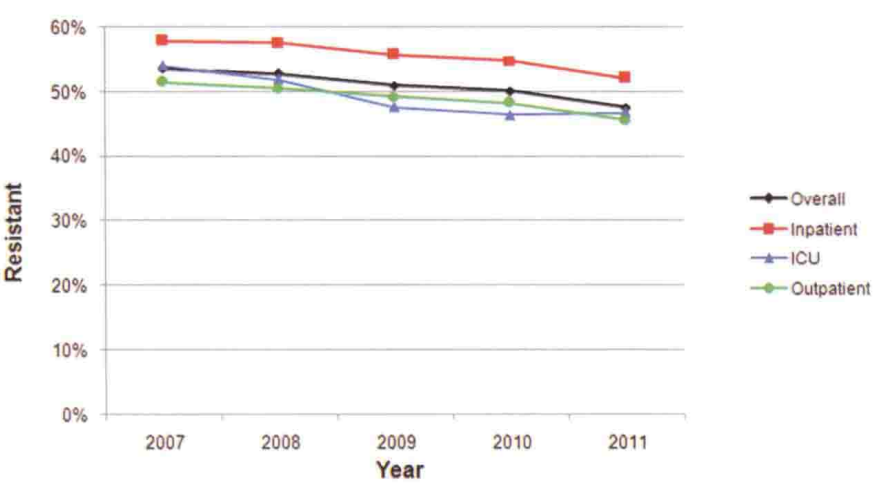

Figure 1. MRSA trends according to patient location.

Table 2. *S. aureus* (MRSA) vancomycin total (*N*) and percentage susceptible (*S*), intermediate (*I*), and resistant (*R*)

S. aureus (MRSA)				Drug: vancomycin			
Year	Total	*S* (*N*)	*S* (%)	*I* (*N*)	*I* (%)	*R* (*N*)	*R* (%)
2007	116,663	116,484	99.80%	156	0.10%	23	0.00%
2008	100,723	100,547	99.80%	148	0.10%	28	0.00%
2009	84,211	84,134	99.90%	60	0.10%	17	0.00%
2010	80,418	80,363	99.90%	35	0.00%	20	0.00%
2011	73,936	73,912	100.00%	13	0.00%	11	0.00%

outpatient) MRSA rates have decreased from 2007 to 2011. Among ICU patients the decrease was from 54% to 46.7%; notably, the MRSA rates among outpatients were not substantially different from the rates seen among inpatients and ICU patients. The decrease in MRSA rates may be due to increased use and effectiveness of infection-control practices, such as active surveillance and hand hygiene programs. Although the MRSA rates appeared to be decreasing in each patient population, nearly half of all *S. aureus* encountered in 2011 were MRSA.

In TSN database there were 571 results for *S. aureus* (169 MRSA) and ceftaroline (the only currently available β-lactam with anti-MRSA activity).[14–16] Using the FDA susceptible breakpoint of ≤ 1 μg/mL, we determined that 100% of the isolates were susceptible to ceftaroline. For non-β-lactams to date there have been only 13 *S. aureus* strains confirmed as being resistant to vancomycin (D. Sahm, principal investigator, NARSA Network), and no additional confirmed isolates have been encountered through TSN. From 2007 to 2011 0.06% of *S. aureus* isolates were reported as intermediate to vancomycin (Table 2) and no pattern of increased rates over time was observed. Over the years analyzed there were 199,097 results on daptomycin for *S. aureus* and the resistance rate averaged 0.03% (Table 3).

E. faecalis *and* E. faecium

Analysis of trends for the key three cell envelope–active agents for enterococci (ampicillin, daptomycin, and vancomycin) demonstrated the stark difference between *E. faecalis* and *E. faecium* resistance patterns (Fig. 2). For ampicillin and daptomycin the average resistance rates between 2007 and 2011 for *E. faecalis* were 0.98% and 0.24%, respectively. Over that time vancomycin resistance was consistently between 3.4% and 3.9%. In contrast, as of 2011 ampicillin and vancomycin resistance rates among *E. faecium* were 88% and 75%, respectively. Also, daptomycin resistance increased year after year, from 2.5% in 2007 to 12% in 2011. Clearly, resistance among enterococci is predominately an issue with *E. faecium*. However, based on TSN data, we determined that there were 141,024 results on vancomycin for *E. faecalis* and 50,171 results of *E. faecium*, indicating that *E. faecalis* is still the most prominent enterococcal species in the clinical setting by almost a 3:1 ratio.

Table 3. *S. aureus* (MRSA) daptomycin total (*N*) and percentage susceptible (*S*), intermediate (*I*), and resistant (*R*)

S. aureus (MRSA)				Drug: daptomycin			
Year	Total	*S* (*N*)	*S* (%)	*I* (*N*)	*I* (%)	*R* (*N*)	*R* (%)
2007	14,075	14,070	100.00%	0	0.00%	5	0.00%
2008	17,261	17,251	99.90%	1	0.00%	9	0.10%
2009	18,766	18,758	100.00%	0	0.00%	8	0.00%
2010	22,479	22,476	100.00%	0	0.00%	3	0.00%
2011	29,987	29,977	100.00%	0	0.00%	10	0.00%

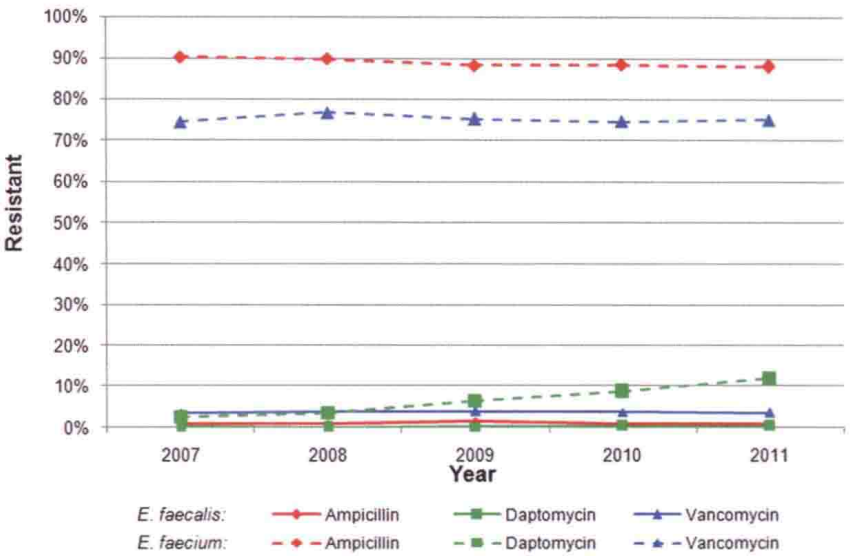

Figure 2. Resistance trends for *E. faecalis* and *E. faecium*.

E. coli, K. pneumoniae, *and* Enterobacter spp.

Although *E. coli* is not among the ESKAPE pathogens, it is by far the most prominent enteric species encountered in infections in the United States. For example, in TSN query for imipenem activity from 2007 to 2011 there were 1,149,678 results for *E. coli* alone and 344,946 results for *K. pneumoniae* and *Enterobacter* spp. combined. Therefore, tracking resistance patterns for this highly prominent organism is clearly warranted. As shown in (Fig. 3A), analysis of trends for four key β-lactam representatives (cefepime, ceftazidime, piperacillin/tazobactam, and imipenem) showed that resistance to all of the agents except imipenem has slightly increased from 2007 to 2011 (cefepime, 1.2–2.3%; ceftazidime, 1.6–3.9%; piperacillin/tazobactam, 0.7–2%); however, the resistance rates for all agents was less than 5%. Imipenem resistance among *E. coli* remained quite uncommon, with an average rate of 0.5% over the years studied.

K. pneumoniae resistance rates to all four β-lactams were greater than those seen for *E. coli* (Fig. 3B). From 2009 to 2011 ceftazidime resistance rates leveled off around 10%, and cefepime rates have remained consistent between 4% and 4.8%. Resistance rates for piperacillin/tazobactam have fluctuated between 4.7% and 7.6%. Most notable was the steady increase in imipenem resistance rates from 0.8% in 2007 to 3.8% in 2012. As shown in (Fig. 3B), this has resulted from a steady year after year increase in resistance rates.

Enterobacter spp. resistance to ceftazidime has been level from 2009 to 2011, with rates in the 20% range (Fig. 3C). Since 2009, piperacillin/tazobactam resistance has hovered between 10% and 13%, while cefepime resistance has remained consistently low, between 1.8% and 2%. Since 2009, imipenem resistance has increased from 0.45% to 2.1%.

P. aeruginosa *and* A. baumannii

For these two key ESKAPE pathogens, five β-lactams and polymyxin/colistin trends were analyzed (Fig. 4). Notable for *P. aeruginosa* (Fig. 4A) was that the resistance rates for all five β-lactams studied (cefepime, ceftazidime, imipenem, piperacillin/tazobactam, and aztreonam) have remained fairly constant from 2007 to 2011. In 2011, the resistance rates for cefepime, ceftazidime, imipenem, piperacillin/tazobactam, and aztreonam were 8.5%, 9.6%, 13.1%, 11.3%, and 12.2%, respectively. Although not done as part of this analysis, it would be of interest to evaluate what percentage of *P. aeruginosa* isolates were resistant to multiple β-lactams. The resistance rates for the outer membrane targeted agents colistin and polymyxin B also have remained somewhat constant over the time period examined, fluctuating between 2.3% and 3.2%.

Although the resistance rates for all the β-lactams studied for *A. baumannii* have fluctuated over the

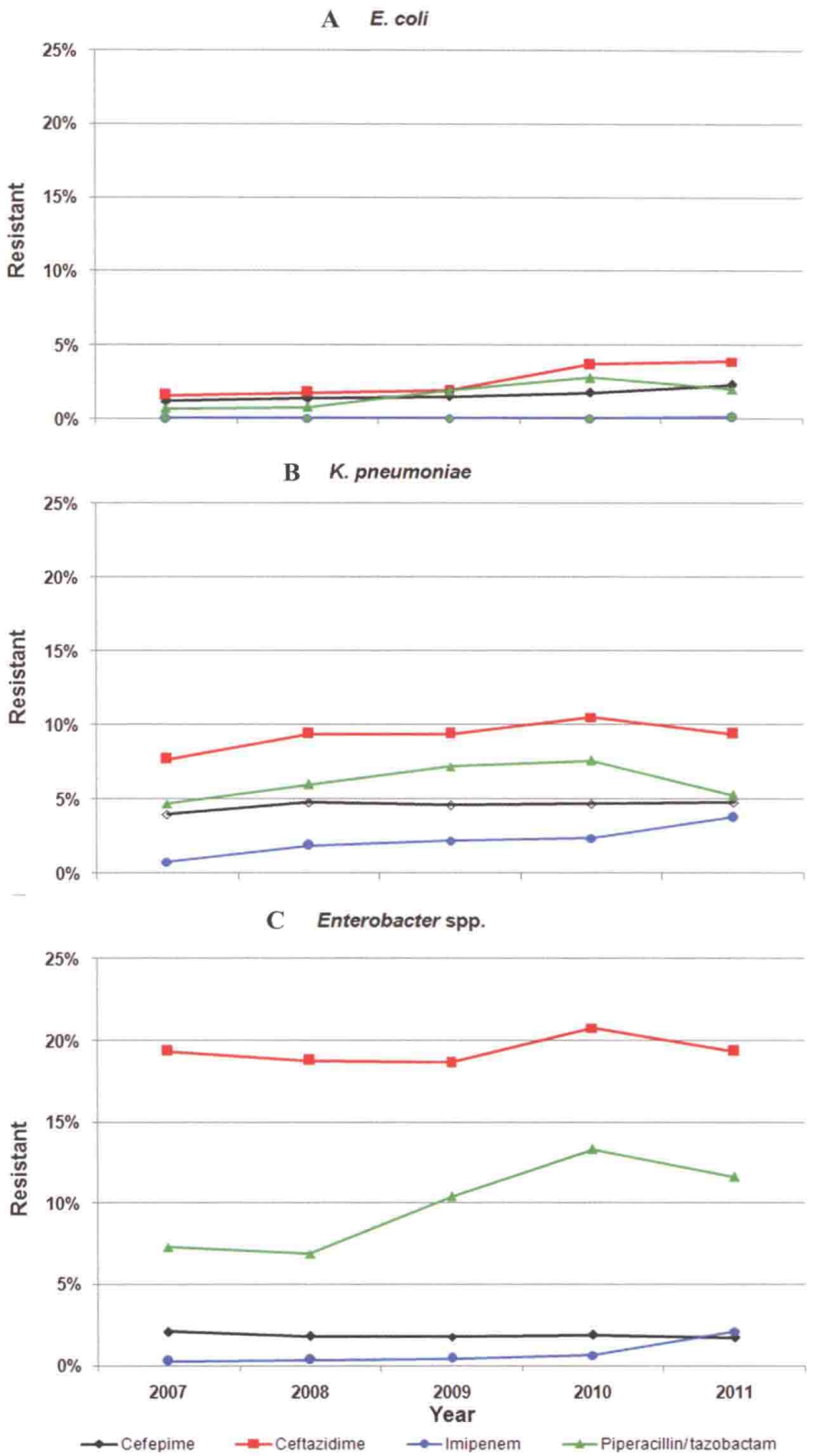

Figure 3. Resistance trends for *E. coli*, *K. pneumoniae*, and *Enterobacter*.

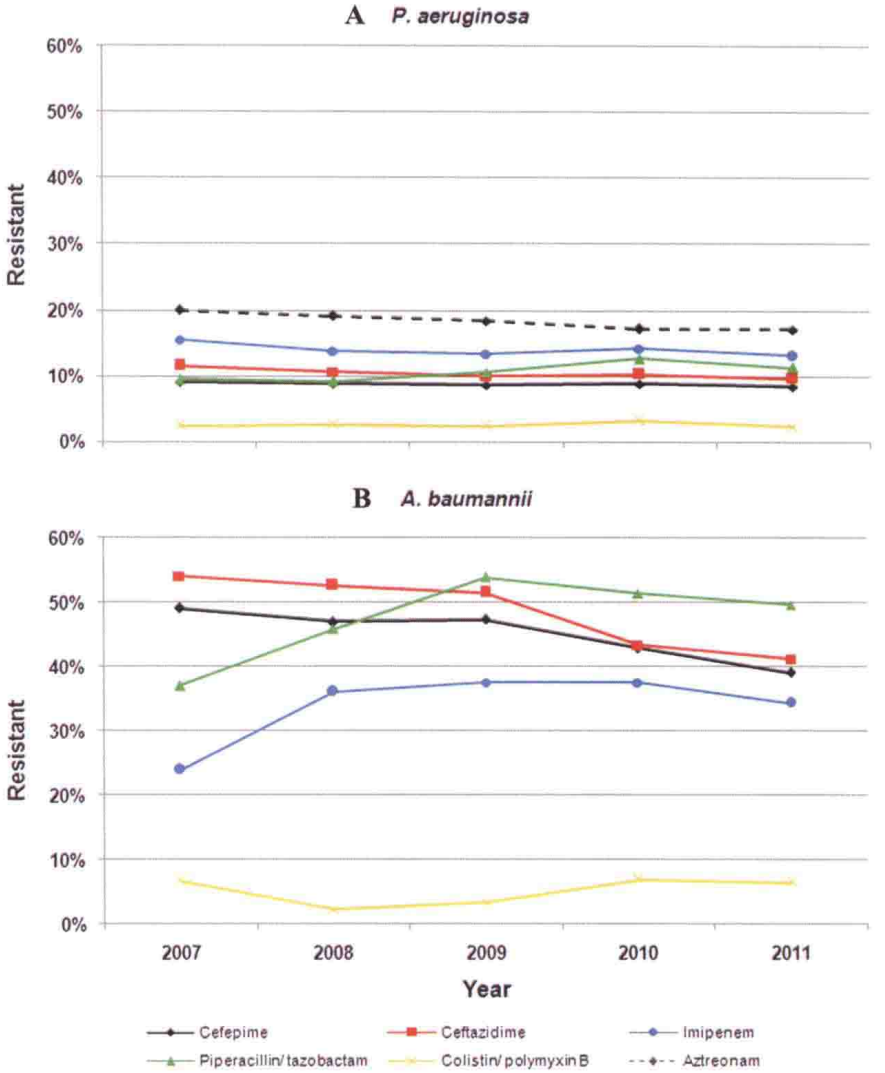

Figure 4. Resistance trends for *P. aeruginosa* and *A. baumannii.*

time period evaluated, as of 2011 the resistance rate for imipenem was greater than 30%, approximately 40% for ceftazidime and cefepime, and close to 50% for piperacillin/tazobactam. Also notable is that since 2009 the resistance rate for colistin/polymyxin B has increased from 3.4% to 6.5%. The reasons for this increase are difficult to discern, but may be due to increased use of colistin/polymyxin B or clonal spread of multidrug-resistant strains.

Summary

The analysis of TSN data demonstrated that among the ESKAPE pathogens, agents that target the cell envelope have not "escaped" the emergence of resistance and multidrug resistance expressed by these organisms. This was especially evident among the β-lactam drugs. As the β-lactams have been a cornerstone of anti-infective therapy for so many years, it is hard to imagine that another class of drugs could be discovered or developed that would supplant the critical role β-lactams are expected to play in the treatment of bacterial infections. Therefore it is important to closely monitor the activity performance of the agents being used today and to aggressively pursue new strategies that can augment current drugs and thwart the β-lactam resistance mechanisms that continue to emerge.

Conflicts of interest

The authors declare no conflicts of interest.

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