Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

[1]Division of Geographic Medicine and Infectious Diseases, Tufts University and Tufts Medical Center, Boston, Massachusetts; [2]Talbot Advisors, Wayne, Pennsylvania; [3]Division of Infectious Diseases, Rady Children's Hospital San Diego, and [4]University of California at San Diego, San Diego, [5]Division of Infectious Diseases, Harbor–University of California at Los Angeles (UCLA) Medical Center, and [6]Los Angeles Biomedical Research Institute, Torrance, and [7]The David Geffen School of Medicine at UCLA, Los Angeles, California; [8]Division of Infectious Diseases, Providence Portland Medical Center and Oregon Health Sciences University, Portland; [9]Medical Service, Louis Stokes Cleveland Veterans Administration Medical Center, and [10]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio; [11]Department of Medicine, University of Virginia School of Medicine, Charlottesville; and [12]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

The Infectious Diseases Society of America (IDSA) continues to view with concern the lean pipeline for novel therapeutics to treat drug-resistant infections, especially those caused by gram-negative pathogens. Infections now occur that are resistant to all current antibacterial options. Although the IDSA is encouraged by the prospect of success for some agents currently in preclinical development, there is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future. Furthermore, we remain concerned that the infrastructure for discovering and developing new antibacterials continues to stagnate, thereby risking the future pipeline of antibacterial drugs. The IDSA proposed solutions in its 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews," and recently issued a "Call to Action" to provide an update on the scope of the problem and the proposed solutions. A primary objective of these periodic reports is to encourage a community and legislative response to establish greater financial parity between the antimicrobial development and the development of other drugs. Although recent actions of the Food and Drug Administration and the 110th US Congress present a glimmer of hope, significant uncertainly remains. Now, more than ever, it is essential to create a robust and sustainable antibacterial research and development infrastructure—one that can respond to current antibacterial resistance now and anticipate evolving resistance. This challenge requires that industry, academia, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the US Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services work productively together. This report provides an update on potentially effective antibacterial drugs in the late-stage development pipeline, in the hope of encouraging such collaborative action.

BACKGROUND

Infections caused by antibiotic-resistant bacteria continue to challenge physicians in 2008. We face growing resistance among gram-positive and gram-negative pathogens that cause infection in the hospital and in the community [1–3]. Rice [2] recently reported these as the "ESKAPE" pathogens *Enterococcus faecium*,

The IDSA is a national medical society that represents infectious diseases physicians, scientists, and other health care professionals dedicated to promoting health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has >8400 members, was founded in 1963 and is based in Arlington, VA. For more information, visit http://www.idsociety.org/. This work was developed by the IDSA's Antimicrobial Availability Task Force (AATF): John Bartlett (chair) and Helen W. Boucher, John S. Bradley, John E. Edwards Jr, David Gilbert, W. Michael Scheld, Brad Spellberg, George H. Talbot, and Robert Guidos (AATF staff). The IDSA Board of Directors approved the report on 3 September 2008.

Received 8 September 2008; accepted 3 October 2008; electronically published 26 November 2008.

Reprints or correspondence: Dr. Helen W. Boucher, FACP, Div. of Geographic Medicine and Infectious Diseases, Tufts Medical Center, 750 Washington St., Box 238, Boston, MA 02111 (hboucher@tuftsmedicalcenter.org).

Clinical Infectious Diseases 2009; 48:1–12

1058-4838/2009/4801-0001$15.00
DOI: 10.1086/595011

Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and *Enterobacter* species) to emphasize that they currently cause the majority of US hospital infections and effectively "escape" the effects of antibacterial drugs. Data from the Centers for Disease Control and Prevention (CDC) show rapidly increasing rates of infection due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), and fluoroquinolone-resistant *P. aeruginosa* [4]. More people now die of MRSA infection in US hospitals than of HIV/AIDS and tuberculosis combined [5, 6]. Furthermore, panantibiotic-resistant infections now occur. Several highly resistant gram-negative pathogens—namely *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa,* and carbapenem-resistant *Klebsiella* species and *Escherichia coli*—are emerging as significant pathogens in both the United States and other parts of the world. Our therapeutic options for these pathogens are so extremely limited that clinicians are forced to use older, previously discarded drugs, such as colistin, that are associated with significant toxicity and for which there is a lack of robust data to guide selection of dosage regimen or duration of therapy [4, 7–10]. The growing number of elderly patients and patients undergoing surgery, transplantation, and chemotherapy and dramatic increases in population in neonatal intensive care units will produce an even greater number of immunocompromised individuals at risk of these infections [11].

Over the past several years, the Infectious Diseases Society of America (IDSA) has worked with US Congress, the Food and Drug Administration (FDA), the National Institutes of Health, the CDC, and other stakeholder groups to highlight this problem. Most recently, the IDSA issued a "Call to Action for the Medical Community" in the hope of raising awareness [3].

Despite ongoing efforts and some successes, only 1 new antibacterial—doripenem—has been approved since our earlier report (figure 1), and the number of new antibacterial drugs approved for marketing in the United States continues to decrease [12]. This report updates the 2006 report [12].

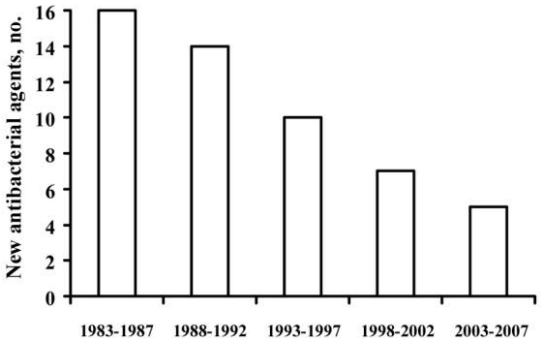

Figure 1. New antibacterial agents approved in the United States, 1983–2007, per 5-year period [2, 3].

METHODS

Sources were reviewed to identify antibacterial drug candidates in the development pipeline, as follows:

1. The 2007 Pharmaceutical Research and Manufacturers of America (PhRMA) report "Medicines in Development for Infectious Diseases" [13]
2. Abstracts from the 2006 and 2007 Interscience Conference on Antimicrobial Agents and Chemotherapy, which were searched for investigational antimicrobials
3. Interviews conducted by the IDSA Antimicrobial Availability Task Force (AATF) of leaders of 13 major pharmaceutical and 6 of the largest biotechnology companies identified by Spellberg et al. [14]; Web sites of these companies were also accessed, and data on drugs in development were reviewed
4. The ClinicalTrials.gov Web site was accessed and searched by condition, with a disease heading of "bacterial infections." Identified compounds were confirmed by accessing the Web site of the innovator company. Because of the high failure rate of compounds that have not successfully navigated phase 1 studies, only compounds in phases 2 or 3 of development are discussed.
5. The PubMed database was searched for relevant literature published from September 2005 through December 2007 by using the search terms "antimicrobial drug development," "investigational antimicrobials," and "novel antimicrobials."

As in our earlier report, we focus on new orally or intravenously administered antibacterial drugs that have progressed to phase 2 or 3 of development, because these agents are more likely to reach the clinic and are associated with substantial investment by pharmaceutical sponsors. Excluded were nonabsorbable antimicrobials administered via the gastrointestinal tract and new indications or formulations of approved drugs.

RESULTS

Table 1 includes 16 antimicrobial compounds in late-stage clinical development (phase 2 and later). Of these, 8 have activity against gram-positive organisms (hereafter, "anti–gram-positive drugs"). Telavancin has a dual mechanism and affects both cell wall and cell membrane. A second anti–gram-positive drug, TD-1792, is new since our 2006 report. TD-1792 is a multivalent cephalosporin that combines the activities of a glycopeptide and a β-lactam in 1 molecule [15]. According to a manufacturer-issued press release, a phase 2 study of TD-1792 showed efficacy comparable to that of vancomycin for complicated skin and skin-structure infection (cSSSI) caused by

gram-positive bacteria [16]. However, these data have not yet been published in a peer-reviewed context.

Three of the anti–gram-positive drugs—ceftobiprole, telavancin, and dalbavancin—are in continuing regulatory review following the issuance of approvable letters by the FDA for a cSSSI indication; all 3 reportedly met the prespecified end points in pivotal phase 3 studies [17–19]. Dalbavancin was deemed approvable in September 2005 and again in December 2007. Ceftobiprole was deemed approvable on 19 March 2008, subject to completion of study-site inspections, assessment of clinical and microbiological data provided by the sponsor to the FDA but not yet reviewed, and further characterization of diabetic patients with foot infections [20]. A Theravance press release noted that the FDA had concerns about "study monitoring issues at a single site" and planned further inspections [21]. A public FDA advisory committee meeting to review telavancin, oritavancin, and iclaprim occurred 18–20 November 2008 [22].

The final 2 anti–gram-positive drugs have an oral formulation: (1) iclaprim, with a mechanism of action similar to that of trimethoprim, and (2) RX-1741, a second-generation oxazolidinone. However, according to our interview with a senior executive at Arpida, iclaprim's manufacturer, development of the oral formulation is significantly behind that of the intravenous formulation.

Eight compounds have activity against both gram-positive and gram-negative organisms. Five of these compounds are new to the list. Of note, another 5 were discovered by Japanese innovator companies.

Doripenem is a carbapenem with greater in vitro potency than meropenem against *P. aeruginosa*; doripenem's activity against extended-spectrum β-lactamase (ESBL)–producing gram-negative organisms is similar to that of meropenem. The FDA recently approved doripenem for treatment of complicated intra-abdominal infection and complicated urinary tract infection [23]. Pivotal studies included patients with *P. aeruginosa* infection [24]. Results from 2 studies of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), demonstrated the noninferiority of doripenem to imipenem and piperacillin-tazobactam, respectively. The HAP-VAP indication was recently reviewed at an FDA Anti-Infective Drug Advisory Committee meeting, where it received a split vote that narrowly favored approval [25, 26].

Tomopenem [27] is a carbapenem with in vitro activity against *P. aeruginosa* (MIC_{90}, 4 μg/mL) but with less activity against imipenem-resistant strains (MIC_{90}, 16 μg/mL) [28]. Tomopenem has advanced to phase 2 of development for treatment of cSSSI and HAP (B. Dannemann, personal communication with G.H.T.), but its subsequent release by Roche to the Japanese innovator leaves its US development status in question [27].

The intravenous and oral aminomethylcycline PTK-0796 is being developed by Paratek Pharmaceuticals [29]. Like tigecycline, the spectrum of PTK-0796 includes MRSA, VRE, and some resistant gram-negative pathogens, including *A. baumannii* (MIC_{90}, 8 μg/mL) [30, 31]. A phase 2 study of PTK-0796 versus linezolid for treatment of cSSSI was recently completed [29]. Hopefully, these data will provide insight into the potential usefulness of this drug in the treatment of infection due to resistant bacteria, especially gram-negative pathogens.

Several other compounds in earlier stages of development may address the unmet need for antimicrobials that are active against resistant gram-negative pathogens. ME 1036, an intravenous carbapenem in phase 1 development, shows in vitro potency against resistant gram-positive organisms, including MRSA and VRE, and ESBL-producing *E. coli* and *K. pneumoniae* but no activity against *P. aeruginosa* [32–34]. PZ-601, an intravenous carbapenem manufactured by Protez, demonstrates potency against a broad spectrum of gram-positive (including MRSA) and gram-negative pathogens other than *P. aeruginosa* and *A. baumannii* [35, 36]. Recently, Novartis announced plans to acquire Protez, and a phase 2 cSSSI study began enrolling patients in May 2008 [37]. Sulopenem, an intravenous and oral penem being developed by Pfizer, is a broad-spectrum antibacterial with activity against gram-negative pathogens, including ESBL-producing Enterobacteriaceae, gram-positive pathogens, and anaerobes; it was initially developed in Japan.

BAL 30376 is a novel β-lactam–β-lactamase inhibitor combination developed by Basilea [38, 39]. This tripartite compound includes a siderophore monobactam with stability to class B β-lactamases, a bridged monobactam that inhibits class C β-lactamases, and the β-lactamase inhibitor clavulanate that inhibits class A β-lactamases. In vitro studies demonstrate the activity of BAL 3076 against a broad spectrum of gram-negative pathogens, including *Acinetobacter* species, nonfermenting bacilli (e.g., *P. aeruginosa* and *S. maltophilia*), and Enterobacteriaceae with known β-lactamases. This antibacterial potentially provides single-drug therapy for serious nosocomial gram-negative infections [38–40].

Another early-stage metallo-β-lactamase inhibitor, ME1071 (CP3242), which is being developed by Meiji Seika Kaisha, has shown clinically relevant in vitro and in vivo activity against *A. baumannii* (and *P. aeruginosa*) [41–43].

None of these agents addresses the growing need created by the emergence of carbapenemases. We found no antibacterial drugs with a pure gram-negative spectrum that have reached phase 2 development.

Table 2 shows an update of antistaphylococcal vaccines and immunoglobulins. Unfortunately, development of most of them has been terminated, and results of clinical studies are not yet public for the remaining few. Despite the enthusiasm

Table 1. Antibacterial compounds undergoing clinical development in phase 2 or later studies.

Spectrum and product (company)	New to list	Class (mechanism of action)	Novel mechanism of action	Formulation	Status	Innovator	Comments
Gram positive							
Ceftobiprole medocaril (Basilea/ Johnson and Johnson)	No	Cephalosporin (cell wall synthesis inhibitor)	No	IV	Phase 3 HAP met end points, failed in VAP subset; positive CAP results; NDA for cSSSI approvable March 2008	Peninsula Pharmaceuticals	In-licensed by Johnson and Johnson, 2005
Ceftaroline fosamil (Cerexa/ Forest)	No	Cephalosporin (cell wall synthesis inhibitor)	No	IV	Phase 3	Takeda Pharmaceutical	PPI-0903, TAK-599
Telavancin (Theravance)	No	Lipoglycopeptide (cell wall synthesis inhibitor)	Yes	IV	Approvable October 2007 for cSSSI, phase 3 HAP trials met end points (ECCMID 2008)	Theravance	
Dalbavancin (Pfizer)	No	Lipoglycopeptide (cell wall synthesis inhibitor)	No	IV	NDA approvable September 2005, December 2007	Vicuron Pharmaceuticals	Pfizer acquired by purchase of Vicuron Pharmaceuticals
Oritavancin (Targanta)	No	Glycopeptide (cell wall synthesis inhibitor)	No	IV	cSSSI NDA filed February 2008	Lilly	Licensed from InterMune
Iclaprim (Arpida)	No	Diaminopyrimidine (dihydrofolate reductase inhibitor)	No	IV, oral	Phase 2 HAP/phase 3 cSSSI IV, phase 1 oral; IV cSSSI NDA filed March 2008	Arpida	…
TD-1792 (Theravance)	Yes	Multivalent vanco-cephalosporin	Unknown	IV	Phase 2 cSSSI met end points	Theravance	…
RX-1741 (Rib-X)	Yes	Oxazolidinone	No	Oral	Phase 2 uncomplicated skin infection completed enrollment; phase 2 CAP enrolling	Rib-X	…
Gram positive and gram negative							
Faropenem (Replidyne)	No	Penem (cell wall synthesis inhibitor)	No	Oral	Phase 3; not approvable October 2006; phase 3 acute exacerbation of chronic bronchitis trials terminated April 2008; development terminated	Daiichi Suntory Pharmaceuticals	Additional studies (superiority) required and ongoing; licensed from Daiichi Suntory Pharmaceuticals (now Asubio Pharma) March 2004

PZ-601 (Protez)	Yes	Carbapenem with MRSA activity (cell wall synthesis inhibitor)	No	IV	Phase 2 cSSSI enrolling	Dainippon Sumitomo	Licensed from Dainippon Sumitomo; also known as SMP-216601; agreement for purchase by Novartis announced June 2008
Tomopenem (Daiichi Sankyo)	No	Carbapenem with MRSA activity (cell wall synthesis inhibitor)	No	IV	Phase 2; status of US development to be clarified	Daiichi Sankyo	Released by Roche to innovator; Daiichi Sankyo, formerly RO4908463, CS-023, and R-115685
Cethromycin (Advanced Life Sciences)	No	Macrolide (protein synthesis inhibitor)	No	Oral	Phase 3 CAP met end points; NDA planned for third quarter 2008	Advanced Life Sciences	Oral respiratory pathogen spectrum
EDP-420 (Enanta)	Yes	Bicyclolide; bridged macrolide structure (protein synthesis inhibitor)	No	Oral	Phase 2 CAP in Japan met end points; phase 2 in the United States to be confirmed	Enanta	Oral respiratory pathogen spectrum
PTK 0796 (Paratek)	Yes	Aminomethylcycline (protein synthesis inhibitor)	No	IV, oral	Phase 2 cSSSI completed	Paratek	…
NXL 103 (Novexel)	Yes	Streptogramin (protein synthesis inhibitor)	No	Oral	Phase 2	Sanofi-Aventis	Oral respiratory pathogen spectrum; formerly XRP2868
RX-3341 (Rib-X)	Yes	Quinolone with MRSA activity	No	IV	Phase 2 cSSSI initiated	Rib-X	Licensed in 2006 from Wakunaga Pharmaceuticals; formerly WQ- 3034 and ABT-492

NOTE. CAP, community-acquired pneumonia; cSSSI, complicated skin and skin-structure infections; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus;* NDA, new drug application; VAP, ventilator-associated pneumonia.

Table 2. Antistaphylococcal vaccines and immunoglobulins undergoing clinical development in phase 2 or later studies.

Product (company)	Mechanism of action	Formulation	Status	Comments
StaphVAX (NABI)	Polysaccharide conjugate vaccine	IM	Terminated	Phase 3 failed
Altastaph (NABI)	Hyperimmune, polyclonal immunoglobulin	IV	Terminated	Phase 2 study: prevention of infection in patients undergoing hemodialysis and low birth–weight infants; adjunctive therapy of persistent *Staphylococcus aureus* bacteremia; development halted
Aurexis (Inhibitex)	Humanized monoclonal antibody	IV	Terminated	Phase 2; no benefit over placebo
INH-A21 (Veronate, Inhibitex)	Donor-selected polyclonal human immune globulin enriched in antibody to cell surface adhesion proteins	IV	Phase 3	Prevention of infection in very low birth–weight infants; phase 3 failed
BSYX-A110 (Pagibaximab, Medimmune)	Antiliopetichoic acid monoclonal antibody	IV	Terminated	Prevention of infection in low birth–weight infants; acquired from GlaxoSmithKline and Biosynexus; phase 2 study complete 2004; Medimmune acquired by Astra-Zeneca 2007; development terminated (J. Rex, personal communication)
S. aureus genetically recombinant antibody (Aurograb; Neutec)	Human genetically recombinant antibody fragment that binds to the immunodominant cell surface antigen, GrfA, a staphylococcal ATP-binding cassette transporter protein	IV	Phase 3	Adjunctive study of staphylococcal infection; study completed June 2006; Neutec acquired by Novartis in 2006
S. aureus vaccine V710 (Merck)	Protein- or antigen-based vaccine	IM	Phase 2	Phase 2 study to evaluate the efficacy, immunogenicity, and safety of a single dose of V710 in adult patients scheduled for cardiothoracic surgery

NOTE. ATP, adenosine triphosphate; IM, intramuscular; IV, intravenous.

for these toxin- or virulence factor–based interventions, issues with manufacturing, study design, and patient selection have plagued development, which leaves the future of such strategies uncertain [44–47].

The results of our interviews with leaders of anti-infective development at Abbott, AstraZeneca, Bayer, GlaxoSmithKline, Lilly, Merck, Novartis, Ortho McNeil/Johnson & Johnson, Pfizer, Roche, Sanofi Aventis, Schering Plough, and Wyeth were disappointing. From these 13 pharmaceutical leaders, just 3 new compounds are in advanced clinical development: ceftobiprole and dalbavancin (under regulatory review) and PTK-0796. The small number of antibacterials in phase 2 or 3 development at these major companies, which once were the international leaders in anti-infective drug discovery and development, reflects the companies' decreased investment in this therapeutic area [3].

The 2007 PhRMA report includes 388 infectious diseases medicines and vaccines and 83 antibacterial drugs in development [13]. Careful review of these data reveals that most are preclinical and phase 1 compounds. Also included are topical and nonabsorbable antimicrobials, which we do not consider here, and several compounds for which development has been terminated. Finally, the PhRMA report does not focus on new molecular entities, and many of the listed drugs are previously approved agents that are being studied for new indications.

ANTIMICROBIAL DRUG-DEVELOPMENT NEEDS

The IDSA's AATF identified the following development needs for the particularly problematic ESKAPE pathogens [2].

E: *E. faecium* (VRE)

Consistently identified as the third most frequent cause of nosocomial bloodstream infection (BSI) in the United States, enterococcal BSIs remain a significant problem [48, 49]. Vancomycin resistance likewise continues to increase, with a rate of ~60% among *E. faecium* isolates [48]. Despite growing incidence, there is a paucity of meaningful data that address efficacy of our newer agents, such as linezolid, daptomycin, and tigecycline, in the therapy of these infections, and tolerability remains problematic [50–52].

S: *S. aureus* (MRSA)

Despite the addition of several new agents to treat MRSA infection, clinicians are routinely faced with treatment challenges involving patients with invasive disease. Although criteria for treating skin and skin-structure infection due to community-associated MRSA are evolving [53], the need is great for oral agents for step-down therapy for the group of patients who require initial parenteral therapy. Because of the prominence of toxin activity in these infections, protein synthesis inhibition may also be desirable [54, 55]. Novel classes are clearly needed for MRSA, because current drug classes exhibit treatment-limiting toxicities and emerging resistance [56–58]. Nondrug therapies, including vaccines and antibodies, are particularly attractive, because they may allow targeted preventive or adjunctive therapy for populations at particular risk, such as dialysis-dependent patients or surgical patients at high risk (e.g., cardiac surgery). Unfortunately, studies to date have failed to demonstrate efficacy for these agents.

K: ESBL-producing *E. coli* and *Klebsiella* species

Infection due to ESBL-producing *E. coli* and *Klebsiella* species continue to increase in frequency and severity. The number of enzymes and the number of organisms that exhibit cross-resistance to other classes of antimicrobials is growing, which makes selection of therapy even more challenging [4, 11, 27, 59, 60].

The impact of these infections was initially difficult to ascertain. However, a recent single-center study showed that BSI due to an ESBL-producing organism was an independent predictor of mortality, prolonged length of stay, delay in initiation of appropriate antimicrobial therapy, and increased hospitalization costs. In a meta-analysis of 16 studies reported for 1996–2003, ESBL-producing BSI was significantly associated with delayed initiation of effective therapy and increased crude mortality [61, 62].

Despite this growing, serious problem, the molecules in late-stage development, as well as the recently approved doripenem, represent only incremental advances over existing carbapenems [63].

More K: *K. pneumoniae* Carbapenemase-Hydrolyzing β-Lactamases

Carbapenem-resistant Enterobacteriaceae are increasingly recognized as the cause of sporadic and outbreak infections in the United States and Europe [64–69]. Plasmid-encoded carbapenemases were initially described in *K. pneumoniae* and were later recognized in *E. coli* and other Enterobacteriaceae [64, 70]. These organisms cause severe infections among residents of long-term-care facilities and are not easily detected in the clinical microbiology laboratory [71]. Little is known with regard to optimal antimicrobial therapy, and few drugs demonstrate activity. Tigecycline and the polymyxins, including colistin, have been used in individual cases with variable success [9]. Aggressive infection-control practices are required in aborting these outbreaks, and there are currently no antibacterials in advanced development for these resistant pathogens [66, 72].

A: *A. baumannii*

The incidence of infection due to MDR *Acinetobacter* species continues to increase globally [73, 74]. Recent studies of patients in the intensive care unit who had BSI and burn infection due to carbapenem-resistant *Acinetobacter* species demonstrate an increased mortality (crude mortality, 26%–68%), as well as increased morbidity and length of stay in the intensive care unit [75].

Tigecycline shows in vitro activity against gram-positive and gram-negative organisms, including MRSA, and *Acinetobacter* isolates. Although successful treatment of *A. baumannii* infection has been reported, reports of breakthrough infections have led to some caution with regard to the use of this newer agent to treat infection caused by this pathogen [74, 76–79].

Tigecycline received FDA approval in 2005 for treatment of cSSSI and complicated intra-abdominal infections. Although community-acquired pneumonia trials met primary end points, the HAP/VAP study was unsuccessful, thus leaving Tigecycline's role in HAP/VAP treatment unclear [27, 80].

Unfortunately, as in 2006, we cannot identify candidate compounds in late-stage development for treatment of MDR *Acinetobacter* infection; this pathogen is emblematic of the mismatch between unmet medical needs and the current antimicrobial research and development pipeline [75].

P: *P. aeruginosa*

Rates of infection due to resistant *P. aeruginosa* continue to increase in the United States and globally, as does resistance to both the quinolones and carbapenems. Aminoglycoside resistance is emerging as a significant problem [4, 81, 82]. Recent reports also document resistance to the polymyxins. Patients at risk include those in intensive care units, particularly if they are ventilator dependent, and individuals with cystic fibrosis [1, 27, 60]. To date, no drugs in clinical development address the issue of carbapenem resistance or MDR or offer a less toxic alternative to the polymyxins.

E: *Enterobacter* Species

Enterobacter species cause an increasing number of health care–associated infections and are increasingly resistant to multiple antibacterials [83, 84]. Infection due to *Enterobacter* species, especially BSI, is associated with significant morbidity and mortality [85]. As with other members of the Enterobacteriaceae, resistance occurs via ESBLs and carbapenemases (including *K. pneumoniae* carbapenemase-hydrolyzing β-lactamases) and inducible chromosomal cephalosporinases [83, 86]. Other than colistin and perhaps tigecycline, few antibacterials are active against these resistant organisms, and we found no drug in late-stage development for these pathogens [87, 88].

DISCUSSION

The number of antibacterials in phase 2 or 3 of clinical development remains disappointing, and the absence of agents designed to treat infection due to resistant gram-negative bacilli places patients with these infections in danger. At this time, there are no systemically administered antimicrobials in advanced development that have activity against either a purely gram-negative spectrum or bacteria already resistant to all currently available antibacterials.

Ascertaining the true number of compounds in development remains challenging. Although PhRMA reported 388 medicines and vaccines in testing, 83 of which are antibacterials, we found significantly fewer than 83 new molecular entities in advanced

clinical development. Because no comprehensive survey of antibiotic development was undertaken before the IDSA's reports of 2004 and 2006 [12, 14], we cannot determine whether the 388 medications and vaccines reported in development by PhRMA—or even just the new, systemic antibacterials listed in the present report—reflect an increase or decrease in the development pipeline over the past few years. What is certain is that the number of new antibacterials that make it through the complete development process and ultimately receive FDA approval has precipitously decreased over the past 25 years. Indeed, we found a 75% decrease in systemic antibacterials approved by the FDA from 1983 through 2007, with evidence of continued decrease in approvals, even during the most recent 5-year period (2003–2007) [3]. These data do not suggest a significant recent increase in antibacterial development. Recent reports about the decrease in discovery research efforts in large pharmaceutical companies and the decrease in antibacterial trials, most notably "early phase" clinical trials, further highlight the diminishing industry focus on antibacterial drug research and development [89, 90]. Only 5 major pharmaceutical companies—GlaxoSmithKline, Novartis, AstraZeneca, Merck, and Pfizer—still have active antibacterial discovery programs, and the number of antibacterial trials registered at ClinicalTrials.gov decreased between 2005 and 2007 [89, 90].

We do observe some small signs of success. The approval of doripenem is encouraging; its increased in vitro potency against *P. aeruginosa* may translate into clinical advantage. Positive results in phase 3 studies for telavancin, ceftobiprole (although not for the VAP subset in the HAP studies), and cethromycin are encouraging, although the regulatory delays are troubling. Several compounds in early development appear promising, but phase 2 clinical studies are not yet under way. We found evidence of potentially increased interest among large pharmaceutical companies in the recent announcements of collaborations between Mpex Pharmaceuticals and GlaxoSmithKline, Novexel and Forest Laboratories, and Protez and Novartis [37, 91, 92]. These relationships reflect some signs of renewed investment interest that must be nurtured very carefully if we hope to see a productive pipeline. Looking forward over the next 5–10 years, it is possible that the number of approved antibacterials will plateau at a level similar to that of the past 5 years (i.e., ~1 drug per year).

It is critical to emphasize that focusing on just the number of approved antibacterials does not necessarily "tell the full story" of the overall clinical impact of the new drugs. New antimicrobials should provide clear advances in treatment of infection, compared with already available therapies. As in our earlier report, the number of truly novel compounds with a new mechanism of action remains small. Most antibacterial drugs that are currently in the late-stage pipeline do not augur a major advance in our ability to treat infection due to resistant pathogens, and the overall number of compounds in development to treat gram-negative infection is small. The fact that much of the discovery effort is based in Japan is also noteworthy [27]. The IDSA is concerned about the lack of an active international drug-discovery infrastructure and the attendant consequences—in particular, the decrease in US- and European-based antibacterial discovery infrastructure.

IDSA's Proposed Strategy and Solutions

The IDSA's goal is to enable industry—in cooperation with academia, the National Institutes of Health, the FDA, the CDC, the Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services—to create a sustainable research and development infrastructure that can both respond to current antimicrobial resistance and anticipate evolving resistance. This effort requires attention to the specifics of microbial pathogenicity and the microbial epidemiology of human disease and must be coupled with appropriate acknowledgement of drug-development time lines and regulatory milestones, as well as appropriate legislative incentives.

To succeed, key stakeholders will need to adopt a long-term outlook and maintain ongoing consultation with infectious diseases experts, with the goal of establishing sustainable research and development programs to meet public health needs. Novel intravenous and oral drugs to treat both hospitalized and community-based patients are needed, as opposed to "me too" drugs that provide minimal improvement over existing therapies. Priority should be given to antimicrobials with the potential to treat serious infections that are resistant to current antibacterial agents.

A solution requires ongoing and increasing investment by pharmaceutical sponsors, both "big pharma" and innovative but typically smaller biotechnology companies; this will require mitigation of the current disincentives, as well as creation of new incentives, to make developing antibacterials a viable option for these companies. The AATF interviews with company leaders revealed the need for such incentives. Establishing targeted new incentives will allow development teams within large companies to compete more equitably with programs from other therapeutic areas that are developing drugs that treat chronic conditions (e.g., hypercholesterolemia) for finite research and development resources. For biotechnology companies, such incentives will make antibacterial development a viable option for venture capitalists and other investors.

Regulatory challenges, guidance, and progress. Over the past several years, the regulatory debate about development and approval of new antimicrobials focused on noninferiority study design, especially the appropriate size of the noninferiority margin for a given indication. The industry leaders whom we interviewed voiced concerns about large sample sizes leading to

cost-prohibitive studies, perceived demands for placebo-controlled trials in diseases for which antibacterials are part of treatment guidelines (and for which ethics committees would not permit use of placebo), and the inability to define acceptable outcome measures. Representatives of both large pharmaceutical and smaller biotechnology companies also reported the difficulty caused when the FDA seemed to "change the rules" after providing advice on development programs.

A clear need remains for specific regulatory guidance. Every company representative interviewed by AATF members listed "regulatory uncertainty," or a lack of clear regulatory guidance, as a major disincentive to anti-infective drug development. A welcome advance that will, hopefully, remove some uncertainty is a draft FDA guidance that addresses how susceptibility testing interpretive criteria that are presented in product inserts (labeling) can be updated to reflect changes in the epidemiology of bacterial resistance [93]. In addition, in January 2008, FDA and the IDSA cosponsored a workshop focused on the design of trials for community-acquired pneumonia [94]. This meeting provided a venue for a full scientific discussion of many of the evolving issues in trial design for new community-acquired pneumonia therapies; the proceedings were published in the recent *Clinical Infectious Diseases* supplement on treatment of community-acquired pneumonia [95, 96]. The IDSA hopes that this was the first of many such exchanges and that these interactions and the resultant decisions will lead to clarity about issues of both trial design and overall program requirements for the development of new antimicrobial agents.

Appropriate incentives. Over the past 5 years, the IDSA has advocated federal action to spur new antibiotic development. The IDSA continues to work with federal policy makers and members of Congress to encourage the elimination of disincentives and encourage responsible incentives. The greatest need is for incentives that produce a sustainable research and development infrastructure that can both respond to current antimicrobial resistance and anticipate evolving resistance. Also needed is legislation that will strengthen the overall US approach to antimicrobial resistance—a "major blooming public health crisis" [89, p. 357].

We have seen small signs of success in partnerships and in recent congressional action. For example, in 2007, the Wellcome Trust awarded GlaxoSmithKline £4 million (~US$7.4 million) to accelerate development of compounds for treating infection with gram-negative pathogens. This public-private partnership illustrates a creative means to stimulate antibacterial drug development [97].

Moreover, in September 2008, Congress enacted IDSA-supported legislation that would provide a 3-year market exclusivity period for approval of a new indication for an already approved ″older″ antibacterial drug and a 5-year market exclusivity period for approval of a previously unapproved ″older″ antibacterial drug. Such exclusivity already has been available for other therapeutic categories. This provision will create parity for antibiotics. (Contained in S. 3560, the QI Program Supplemental Funding Act passed the US Senate on 25 September 2008 and passed the US House of Representatives on 27 September 2008. It was presented to the President on 29 September 2008.) Other pending legislation, S. 2351/H.R. 4200, if enacted, would provide a 50% research and development tax credit to developers of new infectious diseases products. Enactment of this incentive should be valuable for larger, profitable companies. To make this incentive relevant to start-up biotechnology companies, the incentive must be modified to permit the tax credit to be redeemed in future years when a profit is realized; alternatively, the credit must be sellable.

Additional legislative incentives specifically targeting priority antibacterial therapies (e.g., awards, grants, and longer terms of market exclusivity) and other helpful tools (diagnostics, vaccines) must be considered and enacted [3]. Other important legislative measures currently pending in Congress include the Strategies to Address Antimicrobial Resistance (STAAR) Act (S. 2313–H.R. 3697)—which is intended to strengthen federal antimicrobial resistance surveillance, prevention, control, and research efforts—and the Preservation of Antibiotics for Medical Treatment Act (S. 549–H.R. 962)—which is intended to phase out the use of antibacterials of critical clinical importance in human medicine for nontherapeutic (i.e., growth promotion) use in animals. The IDSA and many other medical, health care, and public health organizations have endorsed these bills. Ironically, although decreased inappropriate antibacterial use (e.g., antibiotic stewardship) is likely to decrease the problem of resistance, decreased antibacterial use also will lead, logically, to decreased interest by pharmaceutical companies in new drug development.

Conclusions

As in our earlier report, the late-stage clinical development pipeline for antibacterials remains unacceptably lean. Although some important molecules are in late-stage development for treatment of infection due to problematic pathogens, such as MRSA, few novel molecules have been advanced for treatment of the other ESKAPE pathogens. Importantly, no drugs have reached advanced stages of development for infection due to MDR gram-negative bacilli, such as *A. baumannii* and *P. aeruginosa,* and none represents more than an incremental advance over currently available therapies.

IDSA supports strengthening current approaches to antimicrobial resistance, to protect effectiveness of the drugs currently available. We must maximize hospital infection-control practices, to limit the spread of resistance. And most importantly, the United States must make the development of a sustainable antibacterial drug research and development infra-

structure a national priority. Only this will ensure a steady stream of new antibacterials to meet the needs of both our current patients and those of their children.

Acknowledgments

We express our appreciation to our colleagues, who provided insight and information. Leaders of anti-infective development at Abbott, Arpida, AstraZeneca, Bayer, Cerexa, Cubist, GlaxoSmithKline, Lilly, Merck, Mpex, Novartis, Ortho McNeil/Johnson & Johnson, Pfizer, Rib-X, Roche, Sanofi Aventis, Schering Plough, Targanta, Theravance, Trius Therapeutics, and Wyeth, as well as leaders at the FDA, the National Institutes of Health, and the CDC, graciously offered their time for interviews and provided timely updates that contributed to our ability to provide a timely report on the antimicrobial pipeline. We are indebted to Robert J. Guidos, Director of Public Policy and Government Relations, for his continued support of IDSA's AATF.

Potential conflicts of interest. H.W.B. serves as an advisor or consultant to Astellas, Basilea, Cubist, Johnson & Johnson, Merck, Pfizer, Targanta, and Theravance and has owned shares of Pfizer and Cubist. G.H.T. serves or has recently served as a consultant to Actelion, Bausch and Lomb, Calixa, Cerexa, Cubist, Ipsat, Nabriva, PTC, Rib-X, Shire, Targanta, Tetraphase, Theravance, ViroPharma, and Wyeth. J.S.B.'s employer has received research grants from AstraZeneca, Cubist, Johnson & Johnson, and Wyeth and reimbursement for J.S.B.'s role in consulting for AstraZeneca, Cubist, Johnson & Johnson, Wyeth, Forest/Cerexa, Pfizer, Schering Plough, and Trius. J.E.E. serves on the scientific advisory boards of Pfizer, Merck, and Gilead; has participated in educational programs regarding fungal infections funded by Pfizer, Merck, and Astellas; has received research laboratory support from Pfizer, Merck, and Gilead; and has participated in the Bristol-Myers Squibb Freedom to Discovery research program. D.G. serves as an advisor or consultant to Pfizer, Advanced Life Sciences, Pacific Bioscience, Schering-Plough, Roche, Wyeth, and Pfizer and is on the speakers' bureau for Merck. L.B.R. serves as a consultant to Advanced Life Sciences, Cadence Novexel Paratek, Pfizer, Johnson & Johnson, and Wyeth; is on the advisory board of Theradoc; and is on the speakers' bureau for Arpida and Targanta. W.M.S. serves on the advisory board of Pfizer, Cubist, and Glaxo-SmithKline. B.S. has received research support from Astellas, Gilead, Enzon, Novartis, Merck, and Pfizer; serves on the scientific advisory board of Merck; has consulted for Arpida, Basilea, and Cerexa; and owns equity in NovaDigm Therapeutics. J.G.B. serves on the HIV advisory boards for Bristol-Myers Squibb, Abbott Laboratories, and GlaxoSmithKline.

References

1. Giske CG, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother **2008**; 52:813–21.
2. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis **2008**; 197:1079–81.
3. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis **2008**; 46: 155–64.
4. National Nosocomial Infections Surveillance System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control **2004**; 32:470–85.
5. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. Clin Infect Dis **2006**; 42:389–91.
6. Boucher HW, Corey GR. Epidemiology of methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **2008**; 46(Suppl 5):S344–9.
7. Falagas ME, Bliziotis IA. Pandrug-resistant gram-negative bacteria: the dawn of the post-antibiotic era? Int J Antimicrob Agents **2007**; 29: 630–6.
8. Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 β-lactamases in New York City. Clin Infect Dis **2004**; 39:55–60.
9. Urban C, Bradford PA, Tuckman M, et al. Carbapenem-resistant *Escherichia coli* harboring *Klebsiella pneumoniae* carbapenemase β-lactamases associated with long-term care facilities. Clin Infect Dis **2008**; 46:e127–30.
10. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis **2005**; 40:1333–41.
11. Chopra I, Schofield C, Everett M, et al. Treatment of health-care-associated infections caused by gram-negative bacteria: a consensus statement. Lancet Infect Dis **2008**; 8:133–9.
12. Talbot GH, Bradley J, Edwards JE Jr, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: an update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin Infect Dis **2006**; 42:657–68.
13. PhRMA: medicines in development for infectious diseases. Washington, DC: Pharmaceutical Research and Manufacturers of America, **2007**.
14. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis **2004**; 38:1279–86.
15. Poulakou G, Giamarellou H. Investigational treatments for postoperative surgical site infections. Expert Opin Investig Drugs **2007**; 16: 137–55.
16. Theravance announces positive results from phase 2 clinical study with investigational antibiotic in patients with complicated skin and skin structure infections: TD-1792 achieves primary endpoint. South San Francisco, CA: Theravance, **2007**.
17. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis **2008**; 46:647–55.
18. Stryjewski ME, Graham DR, Wilson SE, et al. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis **2008**; 46: 1683–93.
19. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. Clin Infect Dis **2003**; 37:1298–303.
20. FDA issues approvable letter for ceftobiprole, a new anti-MRSA broad-spectrum antibiotic. 18 March 2008 ed. Basel, Switzerland: Basilea Pharmaceutica, **2008**.
21. Theravance receives additional information regarding FDA cancellation of Advisory Committee Meeting. South San Francisco, CA: Theravance, **2008**.
22. Food and Drug Administration. Advisory Committee Calendar. Available at: http://www.fda.gov/oc/advisory/accalendar/2008/2008ACcalendar.html#November. Accessed 13 November 2008.
23. United States Food and Drug Administration. Doripenem. Available at: http://www.fda.gov/cder/rdmt/InternetNME07.htm. Accessed 13 November 2008.
24. JS Solomkin, O Umeh, J Jiang, et al. Doripenem vs. meropenem with an option for oral step-down therapy in the treatment of complicated intra-abdominal infections [abstract L-487]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
25. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. Crit Care Med **2008**; 36:1089–96.
26. Johnson & Johnson. FDA requires additional information on DORI-

BAX for treatment of hospital-acquired pneumonia. Langhorne, PA: Johnson & Johnson, **2008**.
27. Talbot GH. What is in the pipeline for gram-negative pathogens? Expert Rev Anti Infect Ther **2008**; 6:39–49.
28. Koga T, Abe T, Inoue H, et al. In vitro and in vivo antibacterial activities of CS-023 (RO4908463), a novel parenteral carbapenem. Antimicrob Agents Chemother **2005**; 49:3239–50.
29. PTK 0796 completed a randomized, evaluator-blinded >200 patient phase 2 complicated skin and skin structure infection (cSSSI) clinical study with IV and oral step-down therapy compared to Zyvox. Boston: Paratek, **2007**.
30. Macone A, Donatelli J, Dumont T, Levy S, Tanaka S. In-vitro activity of PTK0796 against gram-positive and gram-negative organisms. In: Proceedings of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2003**.
31. Traczewski M, Brown S. PTK0796: in vitro potency and spectrum of activity compared to ten other antimicrobial compounds. In: Proceedings of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2003**.
32. Sahm D, Draghi D, Thornsberry C. Activity of ME1036, a novel anti-MRSA carbapenem, against gram-positive and gram-negative pathogens. In: Proceedings of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco, CA). Washington, DC: American Society of Microbiology, **2006**.
33. Kurazono M, Hirai Y, Takahata S, et al. Efficacy of ME1036 against *Enterobacteriaceae* harboring a variety of β-lactamases including ESBLs [abstract F-331]. In: Proceedings of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society of Microbiology, **2004**:197.
34. Brown SD, Traczewski MM. ME1036: in vitro potency and spectrum of activity [abstract F1-342]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
35. Pace J, Stevens T, Hamrick J, Hoban D, Bouchillon S, Xerri L. PZ-601 susceptibility of gram-positive pathogens causative for systemic and respiratory infections [abstract F1-230]. In: Proceedings of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco, CA). Washington, DC: American Society of Microbiology, **2006**.
36. Pace J, Stevens T, Hoban D, et al. PZ-601 susceptibility of important gram-negative bacterial species causative for community-acquired pneumonia (CAP), complicated skin and skin structure infections (cSSSI), and intra-abdominal infections (IAI) [abstract F1-229]. In: Proceedings of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco, CA). Washington, DC: American Society of Microbiology, **2006**.
37. Protez pharmaceuticals to be acquired by Novartis. Malvern, PA: Protez Pharmaceuticals, **2008**.
38. Page M, Desarbre E, Geier C, Hofer B. Activity of BAL30376 against gram-negative bacteria [abstract F1-229]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
39. Bowker K, Noel AR, MacGowan A, Walsh TR. In vitro potency of BAL30376 against gram-negative bacilli (GNB) [abstract F1-313]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
40. Schmitt-Hoffmann A, Gebhardt K, Gaucher B, Desarbre E, Page M. Efficacy of BAL30376 in a murine model of gram-negative sepsis [abstract F1-315]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
41. Ishii Y, Sugihara S, Tateda K, Yamaguchi K. In vitro synergistic effects of combinations of CP3242, as a novel metallo-β-lactamase inhibitor, and carbapenems against carbapenemase producing organisms [abstract F1-331]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
42. Osaki Y, Morinaka A, Mikuniya K, et al. CP3242, a novel metallo-β-lactamase inhibitor: in vitro and in vivo efficacy against clinically isolated metallo-β-lactamase–producing *P. aeruginosa* [abstract F1-332]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
43. Muto Y, Matsumoto K, Morinaka A, et al. CP3242, a novel metallo-β-lactamase inhibitor: pharmacokinetics and in vivo pharmacodynamic activities against metallo-β-lactamase–producing *P. aeruginosa* in a murine thigh infection model [abstract F1-333]. In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
44. Weems JJ Jr, Steinberg JP, Filler S, et al. Phase II, randomized, double-blind, multicenter study comparing the safety and pharmacokinetics of tefibazumab to placebo for treatment of *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2006**; 50:2751–5.
45. Rupp ME, Holley HP Jr, Lutz J, et al. Phase II, randomized, multicenter, double-blind, placebo-controlled trial of a polyclonal anti–*Staphylococcus aureus* capsular polysaccharide immune globulin in treatment of *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2007**; 51:4249–54.
46. Dejonge M, Burchfield D, Bloom B, et al. Clinical trial of safety and efficacy of IHN-A21 for the prevention of nosocomial staphylococcal bloodstream infection in premature infants. J Pediatr **2007**; 151:260–5.
47. Bloom B, Schelonka R, Kueser T, et al. Multicenter study to assess safety and efficacy of INH-A21, a donor-selected human staphylococcal immunoglobulin, for prevention of nosocomial infections in very low birth weight infants. Pediatr Infect Dis J **2005**; 24:858–66.
48. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis **2004**; 39:309–17.
49. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis **1999**; 29:239–44.
50. Cannon J, Pachucki C, Aneziokoro C, Lentino J. The effectiveness and safety of oral linezolid as primary or secondary treatment of bloodstream infections: a retrospective observational analysis. Infectious Diseases in Clinical Practice **2006**; 14:221–6. Available at: http://www.infectdis.com/pt/re/idcp/toc.00019048-200607000-00000k.htm;jsessionid=JhgLQfQ4phTqnzJ5G0QBf4FycsWPQCQLJhjtyBbsr82tKnp91TGx!-1327505820!181195628!8091!-1. Accessed 13 November 2008.
51. Erlandson KM, Sun J, Iwen PC, Rupp ME. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome measure of patients with vancomycin-resistant *Enterococcus* bacteremia. Clin Infect Dis **2008**; 46:30–6.
52. Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of gram-positive bacteremia and infective endocarditis: a retrospective case series of 31 patients. Pharmacotherapy **2006**; 26:347–52.
53. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **2008**; 46(Suppl 5):S368–77.
54. Liu C, Graber CJ, Karr M, et al. A population-based study of the incidence and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* disease in San Francisco, 2004–2005. Clin Infect Dis **2008**; 46:1637–46.
55. Schlievert PM, Case LC, Strandberg KL, Abrams BB, Leung DY. Superantigen profile of *Staphylococcus aureus* isolates from patients with steroid-resistant atopic dermatitis. Clin Infect Dis **2008**; 46:1562–7.
56. Bishop E, Melvani S, Howden BP, Charles PG, Grayson ML. Good clinical outcomes but high rates of adverse reactions during linezolid

therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. Antimicrob Agents Chemother **2006**; 50: 1599–602.
57. Boucher HW, Sakoulas G. Perspectives on daptomycin resistance, with emphasis on resistance in *Staphylococcus aureus.* Clin Infect Dis **2007**; 45:601–8.
58. Tsiodras S, Gold HS, Sakoulas G, et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus.* Lancet **2001**; 358:207–8.
59. Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis **2008**; 8:159–66.
60. Jacoby GA, Munoz-Price LS. The new β-lactamases. N Engl J Med **2005**; 352:380–91.
61. Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum-β-lactamase–producing *Enterobacteriaceae.* Antimicrob Agents Chemother **2006**; 50:1257–62.
62. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in *Enterobacteriaceae* bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother **2007**; 60:913–20.
63. Gilbert D. "The truth, if it exists, is in the details." Crit Care Med **2008**; 36:1368–9.
64. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med **2005**; 165:1430–5.
65. Nordmann P, Poirel L. Emerging carbapenemases in gram-negative aerobes. Clin Microbiol Infect **2002**; 8:321–31.
66. Tato M, Coque TM, Ruiz-Garbajosa P, et al. Complex clonal and plasmid epidemiology in the first outbreak of Enterobacteriaceae infection involving VIM-1 metallo-β-lactamase in Spain: toward endemicity? Clin Infect Dis **2007**; 45:1171–8.
67. Peleg AY, Franklin C, Bell JM, Spelman DW. Dissemination of the metallo-β-lactamase gene bla_{IMP-4} among gram-negative pathogens in a clinical setting in Australia. Clin Infect Dis **2005**; 41:1549–56.
68. Livermore DM, Woodford N. The β-lactamase threat in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter.* Trends Microbiol **2006**; 14: 413–20.
69. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clin Microbiol Rev **2005**; 18:657–86.
70. Bratu S, Tolaney P, Karumudi U, et al. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. J Antimicrob Chemother **2005**; 56:128–32.
71. Bratu S, Brooks S, Burney S, et al. Detection and spread of *Escherichia coli* possessing the plasmid-borne carbapenemase KPC-2 in Brooklyn, New York. Clin Infect Dis **2007**; 44:972–5.
72. Paterson DL, Doi Y. A step closer to extreme drug resistance (XDR) in gram-negative bacilli. Clin Infect Dis **2007**; 45:1179–81.
73. Munoz-Price LS, Weinstein RA. Acinetobacter infection. N Engl J Med **2008**; 358:1271–81.
74. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii.* Antimicrob Agents Chemother **2007**; 51:3471–84.
75. Maragakis LL, Perl TM. *Acinetobacter baumannii:* epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis **2008**; 46: 1254–63.
76. Noskin GA. Tigecycline: a new glycylcycline for treatment of serious infections. Clin Infect Dis **2005**; 41(Suppl 5):S303–14.
77. Schafer JJ, Goff DA, Stevenson KB, Mangino JE. Early experience with tigecycline for ventilator-associated pneumonia and bacteremia caused by multidrug-resistant *Acinetobacter baumannii.* Pharmacotherapy **2007**; 27:980–7.
78. Peleg AY, Potoski BA, Rea R, et al. *Acinetobacter baumannii* bloodstream infection while receiving tigecycline: a cautionary report. J Antimicrob Chemother **2007**; 59:128–31.
79. Peleg AY, Adams J, Paterson DL. Tigecycline efflux as a mechanism for nonsusceptibility in *Acinetobacter baumannii.* Antimicrob Agents Chemother **2007**; 51:2065–9.
80. Maroko R, Cooper A, Dukart G, Dartois N, Gandjini H. Results of phase 3 study comparing a tigecycline (TGC) regimen with an imipenem/cilastatin (IMI) regimen in treatment of patients (Pts) with hospital-acquired pneumonia (HAP). In: Proceedings of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago, IL). Washington, DC: American Society of Microbiology, **2007**.
81. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA **2003**; 289:885–8.
82. Lepper PM, Grusa E, Reichl H, Hogel J, Trautmann M. Consumption of imipenem correlates with β-lactam resistance in *Pseudomonas aeruginosa.* Antimicrob Agents Chemother **2002**; 46:2920–5.
83. Deshpande LM, Jones RN, Fritsche TR, Sader HS. Occurrence and characterization of carbapenemase-producing Enterobacteriaceae: report from the SENTRY Antimicrobial Surveillance Program (2000–2004). Microb Drug Resist **2006**; 12:223–30.
84. Pfaller MA, Sader HS, Fritsche TR, Jones RN. Antimicrobial activity of cefepime tested against ceftazidime-resistant gram-negative clinical strains from North American hospitals: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Diagn Microbiol Infect Dis **2006**; 56:63–8.
85. Lin YC, Chen TL, Ju HL, et al. Clinical characteristics and risk factors for attributable mortality in *Enterobacter cloacae* bacteremia. J Microbiol Immunol Infect **2006**; 39:67–72.
86. Bratu S, Landman D, Alam M, Tolentino E, Quale J. Detection of KPC carbapenem-hydrolyzing enzymes in *Enterobacter* spp. from Brooklyn, New York. Antimicrob Agents Chemother **2005**; 49:776–8.
87. Fritsche TR, Strabala PA, Sader HS, Dowzicky MJ, Jones RN. Activity of tigecycline tested against a global collection of Enterobacteriaceae, including tetracycline-resistant isolates. Diagn Microbiol Infect Dis **2005**; 52:209–13.
88. Pintado V, San Miguel LG, Grill F, et al. Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. J Infect **2008**; 56:185–90.
89. Taubes G. The bacteria fight back. Science **2008**; 321:356–61.
90. Karlberg JPE. Trends in disease focus of drug development. Nat Rev Drug Discov **2008**; 7:639–40.
91. GlaxoSmithKline and Mpex Pharmaceuticals form alliance to develop novel efflux pump inhibitors for use against serious gram-negative infections. London, and San Diego: GlaxoSmithKline, **2008**.
92. Novexel and Forest Laboratories announce license agreement for NXL104, a novel broad-spectrum beta lactamase inhibitor. Paris: Novexel, **2008**.
93. FDA guidance documents. Rockville, MD: US Food and Drug Administration, **2008**. Available at: http://www.fda.gov/cder/guidance/. Accessed 13 November 2008.
94. Clinical trial design for community-acquired pneumonia: public workshop, January 17–18, 2008. Rockville, MD: US Food and Drug Administration, **2008**. Available at: http://www.fda.gov/CDER/meeting/CAP/presentations.htm. Accessed 13 November 2008.
95. Infectious Diseases Society of America. Position paper: recommended design features of future clinical trials of antibacterial agents for community-acquired pneumonia. Clin Infect Dis **2008**; 47(Suppl 3): S249–65.
96. Spellberg B, Fleming TR, Gilbert DN. Executive summary: workshop on issues in the design and conduct of clinical trials of antibacterial drugs in the treatment of community-acquired pneumonia. Clin Infect Dis **2008**; 47(Suppl 3):S105–7.
97. Wellcome Trust and GlaxoSmithKline announce partnership to target drug-resistant hospital infections. Oxford, UK: Wellcome Trust, **2007**.