Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America

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The Antimicrobial Availability Task Force (AATF) of the Infectious Diseases Society of America (IDSA) has viewed with concern the decreasing investment by major pharmaceutical companies in antimicrobial research and development. Although smaller companies are stepping forward to address this gap, their success is uncertain. The IDSA proposed legislative and other federal solutions to this emerging public health problem in its July 2004 policy report "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews." At this time, the legislative response cannot be predicted. To emphasize further the urgency of the problem for the benefit of legislators and policy makers and to capture the ongoing frustration our clinician colleagues experience in their frequent return to an inadequate medicine cabinet, the AATF has prepared this review to highlight pathogens that are frequently resistant to licensed antimicrobials and for which few, if any, potentially effective drugs are identifiable in the late-stage development pipeline.

Infections caused by multidrug-resistant microbes present daily challenges to infectious diseases physicians and their patients in the United States and throughout the world [1, 2]. Despite an increasing frequency and severity of antimicrobial resistance, the future development of new anti-infective agents is threatened by the cessation of research in this field by many major pharmaceutical companies [3–6]. For these larger companies, discovery and clinical development of novel anti-infective agents incurs substantial financial disincentives largely related to the relatively low return on investment that is intrinsic to anti-infective drug development [7–10]. Smaller companies are attempting to step forward to address the medical need, but it is not yet clear that they will have the financial wherewithal, clinical development infrastructure, or partnering opportunities with large pharmaceutical companies that would allow their products to reach the market [11, 12].

In March 2003, the Antimicrobial Availability Task Force (AATF) of the Infectious Diseases Society of America (IDSA) was constituted by the IDSA Board of Directors. The AATF was charged with evaluating current trends related to the research, development, and manufacture of anti-infective therapies at a time of increasing antimicrobial resistance and, furthermore, with making recommendations to promote the value of these products and ensure their future availability. As a result of such evaluations, the AATF prepared a policy report entitled "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews," which proposed potential solutions to the problem of decreasing antibiotic development by major pharmaceutical companies [13]. Important members of the US Senate and US House of Representatives appear to have taken notice of the issues raised by IDSA, because favorable legislation developed with IDSA's significant input has been introduced in both Houses of Congress [14–17]. In the opinion of the AATF, passage of legislation that includes the major concepts in these initial bills would go far toward establishing the dynamic, well-funded antimicrobial drug discovery infrastructure necessary for the subsequent development and production of drugs.

Although patient lives are at the heart of IDSA's advocacy campaign, the favorable impact of robust programs for discovery and development of antimicrobial agents on health care economics must be mentioned. Passage of transformative leg-

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islation would be a bargain when measured against the toll of antimicrobial resistance: the loss of thousands of lives and the avoidable cost of billions of health care dollars. The AATF believes that its message to legislators and policy makers will be better communicated, and the chances for enactment of helpful legislation strengthened, if a more detailed illustration of the "bad bugs, no drugs" problem were provided. The current article offers such a review.

METHODS

The AATF created a list of high-priority bacterial and fungal pathogens on the basis of ⩾1 of the following characteristics: current clinical and/or public health concern in the United States because of a high incidence of infection and substantial morbidity; infection with high attributable mortality rates, even if the population-based incidence is low (e.g., the majority of infections occur in immunocompromised patients in tertiary care medical centers); and unique virulence or resistance factors that could circumvent the usual therapeutic effect of antimicrobial therapy. An additional criterion was the presence of few or no novel candidates in the late-stage US drug-development pipeline for treatment of infection due to these pathogens. We chose to focus only on compounds in phases 2 or 3 of development (i.e., studies of therapy for specific infections, with well-defined inclusion and exclusion criteria), given the high failure rate of compounds that have not successfully navigated phase 1 studies (i.e., initial single- or multiple-dose studies involving healthy adult volunteers conducted primarily to collect pharmacokinetic and safety data). For each organism proposed for the list, a rationale for inclusion was drafted and the needs for drug development identified. The list of pathogens was not conceived of as exhaustive but rather as illustrative of pathogens considered to be most important.

The following sources were used to identify the drug candidates in the development pipeline: (1) the Pharmaceutical Research and Manufacturers Association survey of medicines in development for treatment of infectious diseases was searched according to relevant infection categories (available at: http://i.phrma.org/newmedicines/); (2) abstracts from the 2002–2004 Interscience Conferences on Antimicrobial Agents and Chemotherapy were searched for late-stage investigational antimicrobials by using the search term "phase" [18]; (3) the Web sites of the 15 major pharmaceutical and the 7 largest biotechnology companies identified by Spellberg et al. [3] were accessed, and data on drugs in development were reviewed; (4) the PubMed database was searched for relevant literature published from January 2003 through August 2005 by using the search terms "antimicrobial drug development," "investigational antimicrobials," and "novel antimicrobials"; and (5) ClinicalTrials.gov (available at: http://www.clinicaltrials.gov) was accessed and searched by Condition, with a Disease Heading of "Bacterial and Fungal Infections." These searches were complemented by reference to recent reviews of the topic [19–22]. Nonabsorbable antimicrobials administered via the gastrointestinal tract (e.g., ramoplanin) or respiratory tract (e.g., aztreonam) were excluded from consideration for this review.

RESULTS

Members of the AATF identified the following particularly problematic pathogens: *Acinetobacter baumannii, Aspergillus* species, extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, vancomycin-resistant *Enterococcus faecium, Pseudomonas aeruginosa,* and methicillin-resistant *Staphylococcus aureus* (MRSA). Compounds, if any, in late-stage development for treatment of infection due to these organisms are shown in tables 1, 2, and 3.

A. baumannii

Rationale for interest. *Acinetobacter* species are gram-negative organisms commonly found in the environment. Although previously considered to be relatively avirulent, the *Acinetobacter calcoaceticus-baumannii* complex is emerging as a problematic, multidrug-resistant, nosocomial and community-acquired pathogen. The incidence of severe infection caused by *Acinetobacter* species has been increasing. For example, National Nosocomial Infection Survey data for US intensive care units indicate that *Acinetobacter* species caused 6.9% of cases of hospital-acquired pneumonia in 2003, compared with 1.4% in 1975; the rates of bloodstream infection, surgical site infection, and urinary tract infection also increased during this period (from 1.8% to 2.4%, 0.5% to 2.1%, and 0.6% to 1.6%, respectively) [23].

Risk factors for development of *A. baumannii* infection include alcoholism, smoking, chronic lung disease, and/or invasive procedures. Although the organism can cause suppurative infection in virtually any organ system, patients receiving mechanical ventilation are at special risk for hospital-acquired pneumonia caused by *Acinetobacter* species. The infection presents as a multilobar infiltrate, often with accompanying cavitation, pleural effusion, and fistula formation. US mortality rates for this infection have been reported to be 19%–54% [23].

The role of *Acinetobacter* species in war-related injuries is now well documented [24]. Soldiers serving in Iraq and Afghanistan have had osteomyelitis and/or wound infection due to these pathogens. Bacteremia may occur 3–5 days after the onset of wound infection. Many of the isolates are multidrug resistant. Similar findings were observed in Vietnam, where *Acinetobacter* species were the most common gram-negative organisms to contaminate extremity injuries and the second most common bloodstream isolates. An additional, unique setting for *Acinetobacter* infection involved survivors of the Asian tsunami in December 2004 [25]. These isolates have

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

Compound (brand name; manufacturer)	Class (mechanism of action)	Novel mechanism of action?	Formulation(s)	Development or approval status	Comments
Anidulafungin (Pfizer)	Echinocandin (cell-wall synthesis inhibitor)	No	Intravenous	Filed for FDA approval	Initial application for esophageal candidiasis rejected by FDA; application resubmitted August 2005 for use against invasive candidiasis and candidemia; acquired by purchase of Vicuron Pharmaceuticals, 2005
BAL-8557 (Basilea)	Azole (cell membrane inhibitor)	No	Intravenous and oral	Phase 3	Phase 2 study conducted in persons with esophageal candidiasis
Mycograb (Neutec)	Human genetically recombinant antibody targeting immunodominant yeast heat shock protein 90	Yes	Intravenous	Phase 3	Therapy for candidiasis; may have potential for therapy of aspergillosis
Posaconazole (Noxafil; Schering-Plough)	Azole (cell membrane inhibitor)	No	Oral	Phase 3	FDA application filed in 2004 for treatment of invasive fungal infections (e.g., aspergillosis, fusariosis, and zygomycosis) in patients with refractory disease or intolerance to other therapy. Approved by FDA in June 2005; intravenous formulation undergoing phase 1 study; likely role for therapy of endemic mycoses
Ravuconazole (Esai)	Azole (cell membrane inhibitor)	No	Intravenous and oral	Unknown	Compound returned by Bristol-Myers Squibb to Esai in 2004

NOTE. FDA, US Food and Drug Administration.

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

Compound name(s) (brand name; manufacturer)	Class (mechanism of action)	Novel mechanism of action?	Formulation	Development or approval status	Comments
Primarily gram-positive aerobic spectrum					
Dalbavancin (Pfizer)	Lipoglycopeptide (cell-wall synthesis inhibitor)	No	Intravenous	Filed for FDA approval	New drug application filed in December 2004 for complicated skin and skin structure infection; active in vitro against staphylococci (including MRSA) and streptococci; long half-life allowing once weekly administration; acquired by purchase of Vicuron Pharmaceuticals
Iclaprim (Arpida)	Diaminopyrimidine (dihydrofolate reductase inhibitor)	No	Intravenous	Phase 3	Primarily active in vitro against MRSA; an oral formulation is in early development
Oritavancin (Targanta)	Glycopeptide (cell-wall synthesis inhibitor)	No	Intravenous	Phase 3	Active in vitro against staphylococci (including MRSA), streptococci, and enterococci; has long half-life; acquired from InterMune, 2006
Telavancin (Theravance)	Lipoglycopeptide (cell-wall synthesis inhibitor; membrane perturbation)	Yes	Intravenous	Phase 3	Active in vitro against staphylococci (including MRSA), streptococci, and enterococci
Topical pleuromutilin, SB-275833 (GlaxoSmithKline)	Pleuromutilin (protein synthesis inhibitor)	Yes	Topical	Phase 3	Active in vitro against staphylococci, including mupirocin-resistant strains, and streptococci
Gram-positive and gram-negative aerobic spectra					
Ceftobiprole (Basilea; Johnson & Johnson)	Cephalosporin (cell-wall synthesis inhibitor)	No	Intravenous	Phase 3	Active in vitro against staphylococci (including MRSA), streptococci, and wild-type enteric gram-negative bacilli; licensed by Johnson & Johnson in 2005
Cethromycin (Advanced Life Sciences)	Ketolide (protein synthesis inhibitor)	No	Oral	Phase 3	Licensed from Abbott; community respiratory tract pathogen spectrum
Doripenem (Johnson & Johnson)	Carbapenem (cell-wall synthesis inhibitor)	No	Intravenous	Phase 3	Acquired with Peninsula Pharmaceuticals, 2005; spectrum similar to that of marketed carbapenems but somewhat more active in vitro against *Pseudomonas aeruginosa*
Faropenem daloxate (Replidyne)	Penem (cell-wall synthesis inhibitor)	No	Oral	Phase 3	Licensed from Daiichi Suntory; community respiratory tract pathogen spectrum, excluding atypical pathogens
Garenoxacin (Schering-Plough)	Quinolone (topoisomerase inhibitor)	No	Oral	Phase 3	Licensed from Toyama in 2004; Schering-Plough has indicated it may sublicense the compound; community respiratory tract pathogen spectrum
PPI-0903, TAK-599 (Cerexa)	Cephalosporin (cell-wall synthesis inhibitor)	No	Intravenous	Phase 2	Active in vitro against staphylococci (including MRSA), streptococci, and wild-type enteric gram-negative bacilli; licensed from Takeda by Peninsula Pharmaceuticals and transferred to Cerexa in 2005
Prulifloxacin (Optimer)	Quinolone (topoisomerase inhibitor)	No	Oral	Phase 3	Licensed from Nippon Shinyaku by Optimer; community respiratory tract pathogen spectrum
RO-4908463, CS-023 (Roche)	Carbapenem (cell-wall synthesis inhibitor)	No	Intravenous	Phase 2	Licensed from Sankyo by Roche; undergoing phase 2 study for pneumonia; spectrum similar to that of marketed carbapenems but somewhat more active in vitro against MRSA and *P. aeruginosa*

NOTE. FDA, US Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*.

been highly resistant to antimicrobial drugs.

Therapy of *Acinetobacter* infection has been complicated by increasing resistance due to aminoglycoside-modifying enzymes, ESBLs, carbapenemases, or changes in outer-membrane proteins and penicillin-binding proteins [26]. In some parts of the United States, many isolates are now resistant to all aminoglycosides, cephalosporins, and fluoroquinolones [27]. The carbapenems and combinations of a β-lactam with a β-lactamase inhibitor, such as ampicillin-sulbactam, retain useful activity, but resistance rates are increasing [28]. Colistin, previously abandoned in clinical use because of an unacceptably high rate of renal toxicity, is currently the most reliably active agent [29, 30]. Therefore, clinicians must resort to empirical combination therapy, which has an unproven utility, and therapeutic failures and relapses can be anticipated.

The needs for drug development. The recent US Food and Drug Administration (FDA) approval of tigecycline for treatment of complicated skin and skin structure infections and complicated intra-abdominal infections in adults may offer clinicians a therapeutic option, because the compound is active in vitro against some current *A. baumannii* isolates [31]; studies are ongoing to assess its efficacy and safety in treatment of *Acinetobacter* infections (Evan Loh, personal communication). Because of the potential toxicities inherent in use of antimicrobials similar to tetracycline to treat children, studies of tigecycline in this age group are not likely to be undertaken.

Unfortunately, we could not find another compound in the pipeline for treatment of multidrug-resistant *Acinetobacter* infection (table 2). With the increasing incidence of *Acinetobacter* infection and increasing rates of multidrug resistance, *A. baumannii* is a prime example of a mismatch between unmet medical needs and the current antimicrobial research and development pipeline.

Aspergillus Species

Rationale for interest. *Aspergillus* species are filamentous fungi that play a predominant role in infections of immunocompromised hosts, especially persons developing neutropenia as a consequence of cytotoxic chemotherapy for cancer or receiving immunosuppressive treatment for organ and stem cell transplants [32–37]. The incidence of invasive *Aspergillus* infections has been increasing and is anticipated to continue to do so as the number of immunocompromised patients increases substantially [38]. Although the incidence of candidiasis in these populations is higher than that of invasive aspergillosis, several reasonable alternatives exist for the treatment of candidal infections.

Aspergillus infections have a high mortality rate (approaching 50%–60%), despite the best treatment with recently approved antifungals [39]. Improvement of these dismal treatment success rates would increase the chance for patients with cancer to have a normal life span and allow organ transplant recipients not only to survive longer but also to avoid repeated transplantations.

Each of the existing agents commonly used for the treatment of aspergillosis has significant limitations. Amphotericin B deoxycholate is highly toxic; the newer lipid formulations of amphotericin B, although somewhat better tolerated than amphotericin B deoxycholate, are not substantially more efficacious. Although the echinocandin caspofungin has received FDA approval as second-line therapy for aspergillosis, it is not approved for primary therapy, and its marketing authorization was based on study of the drug in <80 patients [40]. Studies examining the efficacy of caspofungin, liposomal amphotericin B, and voriconazole (an azole) have shown very low success rates of ~40% [41–43]. Voriconazole is now generally considered to be the drug of choice for the primary treatment of invasive aspergillosis [39]. However, drug-drug interactions with this agent are common. Additionally, there is substantial interpatient pharmacokinetic variability, requiring monitoring of blood concentrations in certain circumstances.

The needs for drug development Currently, once invasive aspergillosis has developed, cure rates are astonishingly low, and mortality rates are very high. Current therapeutic options are characterized by drug-drug interactions, toxicities, and increasing rates of resistance. More-efficacious and better-tolerated therapies are needed. Orally available compounds would be highly useful. In addition, prophylactic and effective empirical treatment strategies are desirable for populations of patients susceptible to aspergillosis.

The status of various antifungal drugs in late-stage development is shown in table 1. Of note, the registration strategy often involves study of candidiasis, as opposed to aspergillosis, because of the greater ease of investigating efficacy and safety in *Candida* infections; data on potential antiaspergillus activity are often limited. Of the 5 drugs listed in table 1, posaconazole and ravuconazole show promise as compounds with activity against *Aspergillus* species. Vaccine development is only in the formative stages. In summary, a substantive breakthrough in the research and development of drugs with antiaspergillus activity is not on the horizon.

ESBL-Producing *E. coli* and *Klebsiella* Species

Rationale for interest. Of all aerobic gram-negative bacilli, *E. coli* and *Klebsiella* species most frequently cause disease in humans, with the most common sites of infection being the urinary tract, biliary tract, gastrointestinal tract, and wounds due to trauma. Bacteremia, hospital-acquired pneumonia, postoperative meningitis, and other nosocomial infections produce life-threatening disease [44–50]. Increasing in vitro resistance of these pathogens to β-lactam antibiotics and to other classes of antimicrobials sig-

Table 3. Antistaphylococcal vaccines and immunoglobulins undergoing development in phase 2 or later clinical studies.

Compound name (brand name; manufacturer)	Mechanism of action	Route of administration	Development status	Comments
Staphylococcus aureus polysaccharide conjugate vaccine (StaphVAX; Nabi Biopharmaceuticals)	Polysaccharide conjugate vaccine comprised of *S. aureus* capsular polysaccharides 5 and 8 conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin	Intramuscular	Terminated	Prevention of *S. aureus* infection in patients with end-stage renal disease undergoing hemodialysis; failed in phase 3
S. aureus immune globulin, intravenous [human formulation] (Altastaph; Nabi Biopharmaceuticals)	Hyperimmune, polyclonal immune globulin raised by vaccination of healthy volunteers with StaphVAX	Intravenous	Phase 2	Prevention of infection in patients undergoing hemodialysis and infants with very low birth weight
			Phase 2	Adjunctive therapy of persistent *S. aureus* bacteremia
Tefibazumab (Aurexis; Inhibitex)	Humanized monoclonal antibody	Intravenous	Phase 2	Therapy of *S. aureus* bacteremia
INH-A21 (Veronate; Inhibitex)	Donor-selected polyclonal human immune globulin enriched in antibody to cell-surface adhesion proteins	Intravenous	Phase 3	Prevention of infection in infants with very low birth weight
BSYX-A110 (MedImmune)	Antilipoteichoic acid monoclonal antibody	Intravenous	Phase 2	Prevention of infection in infants with low birth weight; recently acquired from GlaxoSmithKline
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	Intravenous	Phase 3	Adjunctive therapy of staphylococcal infection

nals the urgent need for new effective drugs.

The spectrum and number of β-lactamases have increased dramatically in recent years [51, 52]. The number of discrete enzymes identified increased from 13 in 1970 to 282 in 1999; by 2004, the total had jumped to 532 (Karen Bush, personal communication). Furthermore, the substrate range of the enzymes has broadened from the aminopenicillins (e.g., ampicillin) to the extended-spectrum cephalosporins (e.g., cefotaxime and ceftriaxone), a monobactam (i.e., aztreonam), the aminopenicillin β-lactamase inhibitor combinations (e.g., ampicillin and sulbactam), the ureidopenicillins (e.g., piperacillin), and, finally, the carbapenems (e.g., imipenem and cilastatin; meropenem; and ertapenem) [52]. In vitro resistance to ceftazidime and/or aztreonam is used as a phenotypic marker of one of these new groups of enzymes, referred to as ESBLs. Unfortunately, the acquisition of new enzymes is not associated with loss of ability to hydrolyze the earlier β-lactams, such as ampicillin.

The prevalence of ESBL production among *E. coli* and *Klebsiella* species varies depending on geography, nature of the institution, age of population, and patient comorbidities. During a 6-year period (1997–2002), *Klebsiella* species with an ESBL phenotype were identified in blood cultures at a rate of 42.7% in Latin America, 21.7% in Europe, and 5.8% in North America [53]. A 2001 North American surveillance study of isolates from intensive care units found that prevalences of the ESBL phenotype were 11.2% for *E. coli* and 16.2% for *Klebsiella* species [54].

A more recent survey of selected antimicrobial-resistant pathogens associated with nosocomial infections in intensive care unit patients highlights the problem [55]. The resistance rates reported for 2003 were compared with data collected from 1998 through 2002. Among 9 resistant pathogens reported, the 47% increase in the prevalence of resistance among *K. pneumoniae* isolates was by far the largest change encountered.

Resistance to other classes of antibacterials is common among ESBL-producing organisms. Of 57 ESBL-producing clinical isolates of *Klebsiella oxytoca* collected from April 2001 through June 2003, a total of 56 were also resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and fluoroquinolones [48]. The latter results were confirmed in a second report: of 91 ESBL–producing *Klebsiella* species, 84% were resistant to gentamicin, 70% were resistant to trimethoprim-sulfamethoxazole, 60% were resistant to piperacillin-tazobactam, and 51% were resistant to ciprofloxacin; none was resistant to imipenem [56]. However, 2 other reports document outbreaks of infection with *Klebsiella* species that produce carbapenem class A β-lactamases [57, 58].

The acquisition of resistance genes has not decreased the pathogenicity or virulence of *Klebsiella* species and *E. coli*. In the United States, outbreaks of infection have increased in frequency since the initial event in 1988 [44–50]. In patients with bacteremia due to ESBL-producing *K. pneumoniae*, the failure to treat with an antibacterial with in vitro activity resulted in a mortality rate of 64%, compared with a mortality rate of 14% among patients who received an active antibacterial [47].

The needs for drug development. The research and development pipeline for agents active against ESBL-producing gram-negative bacilli is spare (table 2). Our search for new, relevant drugs in clinical trials at the phase 2 level or beyond identified only 2 carbapenems under investigation. Doripenem, currently in phase 3 clinical trials, is a carbapenem with a spectrum of activity against gram-negative bacteria that is similar to that of meropenem; RO-4908463 (also known as CS-023) is undergoing phase 2 study. Neither of these compounds will address the medical need created by the emergence of carbapenemases. Tigecycline exhibits in vitro activity against ESBL-producing *E. coli* and *Klebsiella* species and may prove to be a useful agent for infections caused by these pathogens [31]. The need for additional discovery and development efforts for drugs active against ESBL-producing *E. coli* and *Klebsiella* species is evident.

Vancomycin-Resistant *E. faecium*

Rationale for interest. Antibiotic-resistant enterococci have bedeviled infectious diseases clinicians for decades [59]. On the one hand, it is often difficult to ascertain whether a given isolate is causing disease; on the other hand, when treatment is indicated, the therapeutic options are limited, especially when bactericidal activity is desirable. More recently, *E. faecium* has been a particularly problematic pathogen; in contrast to most isolates of *Enterococcus faecalis, E. faecium* has exhibited high rates of glycopeptide resistance in the United States.

Enterococci are now a significant cause of bloodstream infection in hospitalized patients, including patients in and those not in intensive care unit wards (9.0% and 9.8%, respectively) [60]. Other problematic enterococcal infections include endocarditis, catheter-associated bacteremia, meningitis, and intra-abdominal infection [59]. Groups particularly susceptible to infection with this pathogen include patients with neutropenia [59] and/or cancer [61], patients receiving long-term hemodialysis [62], and liver transplant recipients [63]. Rates of vancomycin resistance among *E. faecium* isolates as high as 70% have been reported in high-risk populations [54, 55, 60]; in one recent survey of 494 US hospitals, a mean rate of 10% across all patient care areas was observed [2]. These pathogens are a particular problem in the intensive care unit [55].

Although there has been considerable controversy as to whether vancomycin resistance in cases of enterococcal blood-

stream infection is independently associated with mortality, a recent meta-analysis found a clearly elevated risk (OR, 2.52; 95% CI, 1.9–3.4) [64]. Furthermore, infections due to these organisms incur substantial economic costs [65].

The needs for drug development. In contrast to the situation for some of the other organisms discussed in this article, a variety of treatment options for vancomycin-resistant *E. faecium* infections currently exists (table 2). For example, quinupristin-dalfopristin and linezolid have received FDA-approved labeling for treatment of selected types of vancomycin-resistant enterococcal infections. Although the marketed compounds daptomycin and tigecycline are active in vitro against these organisms, clinical data are not available to confirm their clinical efficacy and safety.

However, the available antimicrobials have various deficiencies. Both quinupristin-dalfopristin and linezolid lack bactericidal activity; in addition, only linezolid is marketed in an oral formulation. A clear need for the antienterococcal armamentarium is an oral, bactericidal compound. No such drug is in phase 2 or phase 3 development (table 2). Other potential approaches to therapy and prevention of enterococcal infections are vaccine-based or antibody-based interventions. Both Nabi Biopharmaceuticals and Inhibitex have preclinical programs in these areas but no products in late-stage development.

P. aeruginosa

Rationale for interest. *P. aeruginosa* is an invasive, gram-negative bacterial pathogen that causes a wide range of severe infections. Life-threatening infection may occur in patients who become immunocompromised after chemotherapy for cancer or immunosuppressive therapy for organ transplantation [66]. Furthermore, *P. aeruginosa* causes serious infections of the lower respiratory tract, the urinary tract, and wounds in younger and older hospitalized ill patients [67, 68]. The organism is also found in the lower respiratory tract airway of children with cystic fibrosis, inciting inflammation that inexorably destroys lung tissue and ultimately leads to respiratory failure and death [69].

As with *Acinetobacter* species and ESBL-producing Enterobacteriaceae, the incidence of *P. aeruginosa* infection among intensive care unit patients is increasing. Whereas *P. aeruginosa* was the etiological agent in 9.6% of cases of hospital-acquired pneumonia in US intensive care units in 1975, in 2003 the percentage had almost doubled to 18.1% [55]. The rate of bloodstream infection with *P. aeruginosa* was relatively stable (4.8% in 1975 vs. 3.4% in 2003), but the rates of surgical site infection and urinary tract infection approximately doubled between 1975 and 2003 (from 4.7% to 9.5% and from 9.3% to 16.3%, respectively).

Moreover, *P. aeruginosa* has a greater ability than most gram-positive and many gram-negative pathogens to develop resistance to virtually any antibiotic to which it is exposed, because of multiple resistance mechanisms that can be present within the pathogen concurrently [70, 71]. In some clinical isolates, resistance occurs to all available FDA-approved antibiotics.

The most common resistance mechanism is production of β-lactamases, including penicillinases, cephalosporinases, and carbapenemases [72]. The development of carbapenemases is especially ominous, because carbapenems constitute the last remaining β-lactam class to which most clinical isolates historically have been susceptible. In addition, various efflux pump systems are capable of actively removing virtually every antibiotic from the intracellular milieu [73]. An additional mechanism of resistance involves mutations that cause changes within the cell wall, leading to a dramatic reduction in the number of porin channels through which antibiotics must travel to reach their target inside the pathogen [71]. This loss of permeability has been an important cause of resistance to imipenem during the past several years. Multiple mechanisms of resistance may be present simultaneously, with each contributing to overall resistance to a given antibiotic. Because increasing resistance is not usually associated with decreased virulence in *P. aeruginosa,* infections are increasingly difficult to treat.

Increasing rates of antimicrobial resistance among *P. aeruginosa* are a problem worldwide [71]. In the United States, 33% of *P. aeruginosa* isolates were resistant to fluoroquinolones in 2002, for an increase of 37% from the period 1997 to 2001; 22% were resistant to imipenem, for an increase of 32%; and 30% were resistant to ceftazidime, for an increase of 22% [74]. These rates remained elevated in the 2004 surveillance report [55]. In US intensive care units, rates of multidrug resistance (defined as resistance to $\geqslant$3 of the following agents: ceftazidime, ciprofloxacin, tobramycin, and imipenem) among *P. aeruginosa* increased from 4% in 1993 to 14% in 2002 [75]. Most importantly, current US data document statistically greater mortality for hospitalized patients who receive inadequate empirical antibiotic therapy for *P. aeruginosa* bloodstream infections (30.7%) than for those who receive appropriate initial therapy (17.8%), highlighting the need for development of effective agents [76].

Patients with cystic fibrosis represent one population that is especially plagued by *P. aeruginosa* infection. Aggressive management of these children with parenteral and/or inhaled antibiotics is now permitting them to live into their second and even third decades [77]. Most children with cystic fibrosis who survive to adolescence are infected with organisms resistant to all known antibiotics, with the possible exception of colistin [29]. Eventually, lung transplantation becomes the only hope for survival in these adolescents and young adults, because anti-

biotic therapy eventually becomes ineffective.

The needs for drug development. There is a clear, unmet need for new antibiotic therapies for *P. aeruginosa* infections. Antibiotic agents in phases 2 or 3 development are limited to the carbapenems, to which resistance is already present (table 2). Novel agents with the ability to inhibit efflux pumps are in preclinical drug development, but they have not entered into human clinical trials. Multiple novel approaches to antipseudomonal drug therapy are desperately needed; these could include new mechanisms of action that have potent antipseudomonal activity, as well as innovative delivery systems [78].

MRSA

Rationale for interest. *S. aureus* causes many types of serious infection, especially in susceptible populations, such as premature infants and individuals who have undergone surgery, are undergoing dialysis, or have prosthetic devices. Nosocomial infection caused by *S. aureus* prolongs hospital stay, leads to increased hospitalization-related costs, and substantially increases the rate of in-hospital death [79].

After the discovery of penicillin and the tetracyclines and their introduction into the clinical setting, *S. aureus* rapidly acquired resistance to these agents. A similar scenario evolved, albeit more slowly, with the penicillinase-resistant penicillins. MRSA is now the etiologic pathogen for the majority of health care–associated infections [80], and it creates a huge burden on the health care system, as evidenced by a rate of 3.95 MRSA infections per 1000 discharges [81]. Nosocomial MRSA infection is associated with higher morbidity, mortality, and medical costs than infection caused by methicillin-susceptible *S. aureus* [82, 83].

The emergence of community-associated MRSA has raised additional concern [84]. Strains of community-associated MRSA, which are readily transmitted from person-to-person when crowding occurs (e.g., in prisons and on athletic teams) or when infants and children play together, cause skin and skin structure infection, osteomyelitis, and pneumonia. Most of these organisms produce Panton-Valentine leukocidin, a virulence factor associated with severe, rapidly progressive infection, even in previously healthy persons. Fortunately, Panton-Valentine leukocidin–producing community-associated MRSA strains contain the relatively short staphylococcal cassette chromosome IV, which thereby limits the number of resistance genes. Therefore, at present, these organisms remain susceptible to a variety of non–β-lactam antibiotics, including orally bioavailable compounds, such as clindamycin, doxycycline, and trimethoprim-sulfamethoxazole.

In the United States, vancomycin has been the mainstay of therapy for MRSA infection, but glycopeptide resistance is emerging, with documented resistant, heteroresistant, and intermediately susceptible isolates recovered from persons with clinical infection [85]. Newer parenteral antibiotic agents for severe MRSA infection include linezolid and daptomycin; rare strains resistant to these newer drugs have been encountered. Tigecycline was recently granted marketing authorization by the FDA, and dalbavancin (a lipoglycopeptide) was submitted to the FDA for review in December 2004. These 2 compounds offer alternatives for therapy of MRSA infection.

Mupirocin has been shown to be effective as topical therapy for cutaneous MRSA infection. However, mupirocin-resistant strains have been isolated and associated with therapeutic failures [86].

The needs for drug development. As can be seen in table 2, multiple anti-MRSA compounds are in late-stage development, and others, such as Paratek's compound PTK 0796, may be forthcoming [80]. However, the apparent plethora of available antibiotics for MRSA infection is somewhat misleading. A critical need is for effective antibiotics that can be taken orally, allowing for effective step-down therapy for nosocomial infection or initial therapy for infections acquired in the community. Some orally available compounds (e.g., DX-619 and iclaprim) are undergoing phase 1 study. Additional parenteral options are needed, because some patients cannot tolerate treatment with 1 or more classes of drugs, because of allergy or other adverse drug reactions.

Topical alternatives to parenteral or oral therapies are useful in the outpatient setting. Among newer topical agents, GlaxoSmithKline's topical pleuromutilin is closest to reaching the clinic (table 2), but others (such as an agent from Replidyne) are in preclinical development.

Because many of the consequences of infection with *S. aureus* are related to toxin production, toxin-targeted or other virulence factor–based interventions to treat infection with this bacterium could be useful; some immune globulin preparations that might impact virulence are under study. In addition, methods to prevent infection before it occurs are also critically important. Several companies are investigating antistaphylococcal immunoglobulin (table 3). Success in this challenging area would be welcome.

DISCUSSION

Ensuring the continued availability of novel antimicrobials to combat existing and emerging pathogens, especially pathogens expressing resistance to currently available therapies, is a critical public health issue. Published inventories of drugs in development have taken a class-specific focus. Although this perspective is useful, the AATF believes that a pathogen-driven analysis better highlights the strengths and weaknesses of the product pipeline.

Our review of the current state of the pipeline reveals some variability in the number of development candidates from organism to organism, with some, such as MRSA, receiving substantial attention

from major pharmaceutical companies and others, such as *A. baumannii, Aspergillus* species, ESBL-producing *E. coli* and *Klebsiella* species, and *P. aeruginosa,* receiving much less. The pipeline reflects active decisions by these companies about where they are investing research dollars on behalf of their shareholders. Unfortunately, many of the problem pathogens we have identified are characterized by commercial markets that are relatively small, as well as unpredictable; these factors have deterred major pharmaceutical companies from investing in these unmet needs. Fortunately, the economic equation for smaller companies differs from that for larger companies, in that compounds associated with lower revenues may be financially attractive. Nonetheless, the question remains as to whether novel, early-stage compounds developed by smaller companies will see the light of day, given the high cost of late-stage (especially phase 3) clinical development.

What can be done to address this problem? The IDSA has proposed a number of solutions that could be implemented by the FDA and other federal agencies, such as the National Institutes of Health [13]. In addition, measures to address current financial disincentives for the development of anti-infective agents could be legislated [13]; indeed, some of the IDSA's proposed remedies have been included in legislation recently introduced into the House of Representatives and the Senate.

The discovery and development of new antimicrobials is an expensive and time-consuming process requiring a long-term commitment to maintaining a substantial and sophisticated infrastructure. Once dismantled, such programs cannot be restarted in weeks or months. Clinicians and public health officials, working in collaboration with the pharmaceutical industry, must act now to ensure a robust pipeline of compounds for the next decade. IDSA's membership, including specifically those clinicians who serve on the front line caring for patients with nosocomial infection due to multidrug-resistant pathogens, can make their needs known via IDSA's advocacy efforts, as found on the IDSA Web site (available at: http://www.idsociety.org).

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An article in the 1 March 2006 issue of the journal (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) contained 2 errors. First, in table 1, the text in the "Comments" column for posaconazole should read "Approvable letter from FDA June 2005" (*not* "Approved by FDA in June 2005"). The journal regrets this error.

Second, the Acknowledgments section incorrectly listed Cubist as an affiliation for Helen Boucher. Dr. Boucher is not affiliated with Cubist Pharmaceuticals; her only affiliation is with Tufts–New England Medical Center. The authors regret this error.

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