The Antibiotic Resistance Crisis

Part 2: Management Strategies and New Agents

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This is the second part of a two-part series about the antibiotic resistance crisis. Causes and threats were discussed in the April 2015 issue of P&T.

INTRODUCTION

The rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics.[1–6] Implementation of recommended steps, such as the adoption of antibiotic stewardship programs; improving diagnosis, tracking and prescribing practices; optimizing therapeutic regimens; and preventing infection transmission, are expected to be effective in managing this crisis.[2,5,7–11] Increasing collaboration among concerned stakeholders to establish policies, initiatives, and investments in new agents to battle the antibiotic resistance crisis is also promising.[4,5,8,12–16] Recently approved antibiotic compounds are expected to help stem this crisis, as are the novel approaches to the treatment of bacterial infections that are currently being studied.[2]

MANAGING THE ANTIBIOTIC RESISTANCE CRISIS

Recommended Steps to Reduce Antibiotic Resistance

The Centers for Disease Control and Prevention (CDC), as well as other organizations and experts, recommends various steps that health care practitioners (HCPs) and facilities can pursue to reduce antibiotic resistance, such as adopting an antibiotic stewardship program; improving diagnosis, tracking and prescribing practices; optimizing therapeutic regimens; and preventing infection transmission.[5,7] A discussion of each of these measures follows.

Adopt Antibiotic Stewardship Programs

Antibiotic stewardship programs guide all prescribers in administering antibiotics correctly.[7] Antibiotic stewardship involves making a commitment to use antibiotics only when needed, choose the proper drug, and administer the medication at the appropriate dose and duration in every case.[5] Successful implementation of an antibiotic stewardship program requires an interdisciplinary team, system innovation, educational intervention, and feedback provided to health care workers.[11]

Antibiotic stewardship programs have been shown to improve patient care, shorten hospital stays, and reduce health care facilities' pharmacy costs.[5,7] A review of 24 studies published from 1996 to 2010 demonstrated that antibiotic stewardship programs achieved an 11% to 38% reduction in defined daily dose (DDD) per 1,000 patient-days.[8] This result included significant reductions in total antibiotic consumption, duration, and inappropriate use.[8]

Another study involved regular interaction between an infectious disease specialist and the medical intensive care unit (ICU) team to assess guideline compliance, as well as antibiotic and health care costs.[11] The results of this prospective study showed that this intervention significantly reduced use of extended-spectrum penicillins, carbapenems, vancomycin, and metronidazole.[11] The intervention group also demonstrated a significantly lower rate of treatments that did not comply with hospital guidelines, shorter patient stays, and lower in-hospital mortality.[11] In addition, $89,944 was saved from early antibiotic discontinuation alone.[11] Results of a study conducted in Maryland demonstrated that an antibiotic stewardship program saved $17 million over eight years.[5]

It has been recommended that the ICU should be a focus of attention for antibiotic stewardship.[8] A review of 2,000 ICU patients in a large academic center showed that 655 patients (33%) had acquired a nosocomial infection; 169 of them (26%) received inappropriate antibiotics and experienced a 4.26-fold increase in mortality.[8] Another recent report illustrated the central role of the ICU in a hospital-wide outbreak of a carbapenemase-producing *Klebsiella pneumoniae*.[8]

Improve Prescribing Practices

Incorrect prescribing practices, such as the unnecessary use or wrong choice of an antibiotic agent, have been shown to be prevalent in both inpatient and outpatient settings.[1] A post-prescription review of multiple hospitals in 10 U.S. states identified opportunities to improve antibiotic prescribing in 37% of the scenarios, often through the use of diagnostic tests, improved documentation of symptoms, and optimization of antimicrobial therapy.[10] Data have also shown that as often as 50% of the time, HCPs prescribed antibiotics unnecessarily or incorrectly.[1] In some cases, for example, doctors might not order laboratory tests to confirm that bacteria are causing the infection; as a result, an antibiotic might be prescribed unnecessarily.[5]

In other cases, patients may demand treatment for conditions, such as colds, when antibiotics are not needed and will not help, since viruses cause most colds.[5,8] Data suggest that HCPs may be too willing to satisfy such patients' expectations for an antibiotic prescription.[5] Surveys have shown that 40% to 75% of adults and children who sought care for viral respiratory tract infections were given a prescription for an antibacterial agent.[8] Prescribing antibiotics when they aren't needed not only fails to help patients but can harm them, since adverse reactions and drug interactions can occur.[5] The inappropriate use of antibiotics also unnecessarily promotes antibiotic resistance.[5]

A 2005 Cochrane Review of 39 relevant publications suggested an intervention that might have a sufficient effect in counteracting the problem of patient demand: "delayed prescription."[8] This practice involves instructing patients to fill an antibiotic prescription a few days later if symptoms do not improve.[8] This tactic promotes patient satisfaction but also prevents abuse, since viral respiratory tract infections will usually improve within this period.[8]

Educational campaigns regarding antibiotic resistance have been implemented among medical professionals and organi-

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zations.[9] Such campaigns have raised HCPs' awareness of the need to combat antibiotic resistance through improved prescribing practices.[9] However, while informative, these measures have not been effective in alleviating the overall overuse of antibiotics.[9]

Optimize Therapeutic Regimens

Antibiotics are generally prescribed according to a fixed regimen that involves a specific dose, dosage frequency, and length of treatment.[9] Such regimens typically last five to seven days, although many last 14 days or longer.[9] However, recent evidence indicates that extended regimens may be unnecessary, since many clinical trials have shown that shorter courses of therapy are often just as effective as longer ones.[11,12]

One study showed that patients with hospital-acquired infections, including ventilator-associated pneumonia (VAP), who had received appropriate antimicrobial therapy had good clinical responses within the first six days.[11] Results from a multicenter, randomized controlled trial of 401 patients also indicated that clinical outcomes for patients receiving appropriate empiric therapy for microscopically proven VAP for eight days were similar to those for patients who had received treatment for 15 days.[11] These observations have been confirmed in additional controlled clinical trials.[11] Four Cochrane Reviews also showed that a shorter course was uniformly equivalent to other "standard" durations of treatment—seven days for pyelonephritis, 10 days for septic arthritis, and three days for community-acquired pneumonia (CAP).[8]

The assumption behind extended regimens is that administering a high dosage over a longer period will eradicate the infecting pathogen from the body.[9] However, prolonged antibiotic therapy may be detrimental because it facilitates colonization with antibiotic-resistant bacteria, which could cause recurrent episodes of infection.[11] By prescribing a limited antibiotic dose and course of treatment, the selective pressure on bacterial organisms and the development of resistance may be reduced.[9] Interestingly, some studies have demonstrated that relapse rates are not significantly higher in patients in whom treatment is discontinued when symptoms diminish compared with patients who receive the full course of treatment.[9]

Despite the evidence that a shorter course of antibiotic administration may be just as effective, most guidelines still recommend relatively prolonged or imprecise treatment durations.[11] Another disadvantage to prescribing antibiotics for longer-than-needed durations is that some patients who discontinue treatment when their symptoms improve, rather than finishing the entire course, may "hoard" the balance of the medication for future use, increasing the likelihood of the medication's misuse to "treat" nonsusceptible organisms.[9]

Some investigators have hypothesized that using biological markers—for example, C-reactive protein, soluble-triggering receptor expressed on myeloid cells-1, or procalcitonin (PCT)—might better facilitate therapeutic decisions regarding antibiotic treatment regimens.[11] PCT levels reflect bacterial replication and have been tested extensively to aid decisions on when to initiate or stop antibacterials.[8] A meta-analysis of seven randomized controlled trials with 1,458 patients showed that when treatment decisions were guided by PCT levels, total antibiotic use was reduced by 51% without altering treatment outcomes.[8] Although PCT is a good marker for community-acquired infections (CAIs), there is some question as to whether it is useful for health care–associated infections (HAIs).[11] This is because blood PCT concentrations can rise in nonseptic conditions, such as major trauma, surgery, acute respiratory distress syndrome, multiorgan failure, post-transplantation rejection, cardiogenic shock, severe burns, and heat stroke.[11]

Improve Diagnosis and Diagnostic Tools

Perhaps the most effective way to reduce inappropriate antibiotic use is to eliminate diagnostic uncertainty.[12] Identifying antibiotic-resistant infections can be challenging, so selection of antibiotic treatments is often empiric.[7,9] In the U.S., a recent report showed that a microbiological diagnosis was made in only 7.6% of 17,435 patients who were hospitalized with CAP.[13] Multiple antimicrobials are often administered simultaneously in the hope that one will be useful in controlling an unidentified pathogen.[9] More commonly, general practitioners may prescribe successive courses of antibiotics until an effective treatment is found.[9] This approach can be harmful because it subjects the patient's microbiota to intense and repeated selective pressure, which encourages the development of antibiotic resistance.[9]

Empiric use of antibiotics could be reduced through the implementation of more rapid, accurate diagnostic methods.[9] In the past, accurate diagnosis of infectious diseases using traditional methods required multiple laboratory-based tests that take days or weeks to complete.[9] However, within the past decade, slow, traditional methods based on phenotypic characteristics (e.g., growth on defined media, colony morphology, gram staining, and biochemical reactions) have started to give way to newer diagnostic techniques, such as real-time multiplex polymerase chain reaction (PCR) and matrix-assisted, laser desorption/ionization, time-of-flight mass spectrometry.[11] Such molecular diagnostic techniques detect the unique nucleic acid or biochemical composition of the microbe at the point of care, enabling rapid pathogen-specific identification and treatment.[5,8] Using PCR techniques, investigators at the Karolinska Institute in Sweden were able to identify probable viral and bacterial pathogens in 89% of the cases that were studied.[8]

Multiple instruments utilizing molecular diagnostic platforms are now being marketed by well-established manufacturers and are beginning to displace or complement conventional automatic phenotyping tools.[11] These instruments can provide more rapid and accurate microbial identification from blood cultures within one to two hours.[11] Instruments such as the PLEX-ID, which was used to detect and follow the evolution of the H1N1 influenza virus strain in 2009, can detect and identify more than 5,400 unique microbes within hours.[8] Such advanced technologies enabling the rapid identification of pathogens, and in some cases their antimicrobial resistance patterns, could undoubtedly promote the earlier and more accurate treatment of bacterial infections.[11]

Although increasingly advocated, these advanced molecular detection technologies are not yet being applied as widely as necessary in the U.S.[5,8,9] In the absence of these advanced techniques, ensuring that appropriate diagnostic tests are ordered is a critical step toward determining that the proper antibiotic is prescribed.[7] Re-evaluating the choice of antibiotic

after diagnostic test results are available should also be routine in all prescribing scenarios.[7]

Improve Tracking Methodologies

The capabilities of federal and state governments to detect and respond to urgent or emerging antibiotic-resistant threats is currently limited.[5] A complete picture of the domestic incidence, prevalence, mortality, and cost of resistant bacterial infections is not yet available, even for those that pose a serious or urgent threat.[5] This is because data regarding the use of antibiotics in both health care and agriculture have not been collected systematically.[5]

However, the CDC has recently implemented the National Healthcare Safety Network (NHSN) for use by health care facilities to electronically report infections, antibiotic use, and resistance.[5] These data allow regions, states, and facilities to identify and track antibiotic-resistant bacteria that are responsible for many HAIs.[5] As more hospitals submit data to the NHSN database, they will be able to track antibiotic usage and bacterial resistance, enabling areas of concern to be addressed, needed improvements to be made, and successes to be shared.[5] With this information, experts can also develop specific strategies to prevent infections and the spread of resistant bacteria.[5] The CDC also sponsors other tracking programs, such as the Active Bacterial Core surveillance (ABCs), the Gonococcal Isolate Surveillance Project (GISP), the National Tuberculosis Surveillance System (NTSS), and the Healthcare-Associated Infections—Community Interface (HAIC).[5]

In addition, through a collaborative effort among the CDC, the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state and local public health departments, the National Antimicrobial Resistance Monitoring System (NARMS) was established.[5] This public health surveillance system tracks antibiotic infections and resistance in humans and animals that are commonly transmitted through foods, such as *Salmonella, Campylobacter,* and other bacteria.[5] The NARMS program also distributes information, conducts research on antibiotic resistance, and provides data to the FDA to assist the agency in decisions regarding the use of antibiotics in livestock.[5] More details regarding these and other CDC-sponsored tracking networks are presented in Table 1.

Prevent Transmission of Bacterial Infections

Prevention of infection can significantly decrease resistance by eliminating the need for antibiotics in the first place.[5] Patients are placed at risk for antibiotic-resistant infections when pathogens are transferred from one patient to another via the hands of HCPs or objects used in health care.[7] Therefore, HCPs must understand the importance of eliminating cross-transmission of antibiotic-resistant bacteria, especially those with adverse consequences or high potential to spread, such as *Clostridium difficile* or carbapenem-resistant Enterobacteriaceae.[7]

To accomplish this goal, compliance with infection-control guidelines established by the health care facility is essential.[7] Diligent hand hygiene before and after all patient interactions that take place during the delivery of health care is critical to reduce the risk of transmitting both antibiotic-susceptible and antibiotic-resistant bacterial pathogens.[7] Disinfection of the health care environment and patient-care equipment should also be required.[7] Modernization of infection-prevention approaches, through utilization of robotic and automated disinfection technologies, would help with these efforts.[12] Automated hand-washing disinfection technology improves hand-washing rates, and self-cleaning hospital rooms can reduce the risk of HAIs.[12]

The CDC provides infection-control guidelines and tools and conducts research to find new ways of preventing the transmission of infections.[5] The CDC also conducts contact tracing, a prevention strategy that tracks individuals who are infected and their contacts to whom the infection may have been transmitted.[5] Contact tracing is used to ensure that appropriate interventions, such as treatment, prophylaxis, or temporary isolation from the public, are identified, administered, and managed appropriately.[5] Contact tracing is resource-intensive, but it has successfully limited transmission of bacterial infections such as tuberculosis, gonorrhea, and meningococcus, as well as the recent threat posed by the Ebola virus in the U.S.[5]

Lastly, the *Streptococcus pneumoniae* vaccine has provided evidence that vaccines can be effective in limiting the transmission of resistant bacterial infections.[5] The first version of this vaccine, which was introduced in 2000, reduced the frequency of infection but did not protect against a particular strain of *S. pneumoniae* called serotype 19A.[5] This strain became increasingly resistant to antibiotics and therefore was responsible for causing more infections.[5] However, a newer version of the vaccine that provides protection against serotype 19A became available in 2010.[5] As a result, the rate of this antibiotic-resistant pneumococcal infection has been decreasing, proving that vaccines can help prevent the spread of resistant bacterial infections.[5]

Growing Concern Spurs Public and Private Initiatives, Policies, and Investments

In addition to adopting the recommended steps, a clearly defined, comprehensive, national action plan needs to be established to manage the antibiotic resistance crisis.[5,8,12] Such a plan would ideally address the use of antibiotics in both inpatients and outpatients to reduce antibiotic resistance threats, improve patient outcomes, and save health care dollars.[5] It would include measures to collect data to inform decisions, reduce antibiotic abuse in medicine and agriculture, foster antibiotic stewardship, optimize the use of newer molecular diagnostic techniques, support resistance-related research, and promote the development of new antibiotics.[8] Toward this end, President Barack Obama issued an executive order in September 2014 regarding a plan for fighting the antibiotic resistance crisis. It calls for a national strategy for improving diagnostic tests, research on alternative agents, and tracking antibiotic use and infection outbreaks. More recently, in March 2015, the President urged Congress to double funding for measures that will confront the antibiotic resistance crisis.[17] A discussion of some of the initiatives, policies, and investments that are currently being pursued follows.

Government Initiatives

The CDC distributes public health messages and resources that strive to improve antibiotic use.[5] The CDC is also working with a variety of partners to improve the use of antibiotics in health care settings.[5] Current CDC efforts focus on four core

Table 1 CDC's Antibiotic Resistance and Antibiotic-Resistant Infections Tracking Platform[5]

Tracking Networks	Data Collected	Resistant Bacteria/Fungi*
Emerging Infections Program (EIP), which has three main elements: • **ABCs:** Active Bacterial Core surveillance • **HAIC:** Healthcare-Associated Infections—Community Interface • **FoodNet:** Foodborne Diseases Active Surveillance Network	A network of public health/academic/hospital collaborations in 10 states. It provides access to bacterial and fungal samples for testing and detailed clinical case data. The three main EIP programs collect different types of resistance data: • **ABCs** provides clinical information and resistance data for bacteria that cause infections predominantly in the community. • **HAIC** provides clinical information and resistance data for bacteria and fungi that cause infections at the intersection of health care and the general community. • **FoodNet** supplies clinical and epidemiologic data on some human isolates in the National Antimicrobial Resistance Monitoring System (NARMS).	**ABCs** • *Streptococcus pneumoniae* • Groups A and B *Streptococcus* • Methicillin-resistant *Staphylococcus aureus* **HAIC** • *Clostridium difficile* • *Candida* (a fungus) • Carbapenem-resistant Enterobacteriaceae • Multiple-drug-resistant *Acinetobacter* **FoodNet:** (see NARMS list below)
National Antimicrobial Resistance Monitoring System (NARMS)	A national public health surveillance system that tracks changes in the susceptibility of foodborne and other enteric bacteria to antibiotics of human and veterinary medical importance, NARMS is a collaboration among the CDC, FDA, USDA, and state and local health departments. CDC tests bacterial isolates from humans, while FDA and USDA test isolates from retail meats and food animals.	• *Salmonella* • Campylobacter • Shigella
National Healthcare Safety Network (NHSN)	A system that collects and provides data on infections and drug resistance in health care settings. Since NHSN collects data directly from health care facilities, it can provide facility-level information on health care-associated infections and antibiotic resistance (and, in the future, on antibiotic use).	• *S. aureus* • *Enterococcus* • Enterobacteriaceae • *Acinetobacter* • *Pseudomonas aeruginosa* • *Candida*
Gonococcal Isolate Surveillance Program (GISP)	A program to track antibiotic resistance data for gonococcal isolates. Isolates are collected from sexually transmitted disease clinics in approximately 28 cities.	*Neisseria gonorrhoeae*
National Tuberculosis Surveillance System (NTSS)	National Electronic Disease Surveillance System–based reporting of tuberculosis cases, including resistance data. Public health departments from 50 states and the U.S. territories contribute data.	*Mycobacterium tuberculosis*

* ABCs also includes surveillance for *Neisseria meningitidis* and *Haemophilus influenzae.* NARMS also includes surveillance for *E. coli O157* and *Vibrio* (non-*V. cholerae).*

CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; USDA = U.S. Department of Agriculture

actions to fight antibiotic resistance: 1) preventing infections and the spread of resistant bacteria; 2) tracking resistant bacteria; 3) improving antibiotic use; and 4) promoting the use of new diagnostic tools and the development of new antibiotics.[5]

Initiatives managed by the CDC include the "Get Smart" program and the "Antibiotic Stewardship Drivers and Change Package," which are national campaigns that provide health care facilities with suggestions for interventions to improve antibiotic prescribing and use.[5] More information regarding these initiatives can be found at http://www.cdc.gov/getsmart and http://www.cdc.gov/getsmart/healthcare/implementation.html, respectively.[5]

International Initiatives

The World Health Organization (WHO) has adopted several resolutions over the past two decades that call for international measures to diminish the emergence and spread of antimicrobial resistance.[4] In addition, in 2009, the "Antibiotic Resistance" initiative (ReAct) helped organize a conference that included participants from 45 countries representing public, academic, pharmaceutical industry, governmental, and international organizations.[14] The British Society for Antimicrobial Chemotherapy has also launched a global initiative, "Antibiotic Action," which is a worldwide alliance of groups including the Infectious Diseases Society of America (IDSA), ReAct, charities, and not-for-profit agencies.[14] The goal of Antibiotic

Action is to apply pressure to and raise the profile of the antibiotic resistance threat with policy-makers around the world.[4] In addition, a Transatlantic Taskforce on Antibiotic Resistance (TATFAR) has been established by the European Union and the U.S.[14] TATFAR recently published a report that recommends five strategies for improving the antibiotic drug pipeline (http://www.cdc.gov/drugresistance/pdf/TATFAR-Progress_report_2014.pdf).[14]

Public–Private Partnerships

Public–private partnerships (PPPs) are a potentially important resource to address the lack of development of new antibiotics.[8,12,14] PPPs may involve government grants, contracts, and/or investments in for-profit drug development, similar to the model by which the U.S. Department of Defense offsets research and development costs for new military technologies.[8,12] Ideally, private industry and federal systems will work together to devise novel legislative and economic initiatives that align societal and corporate interests to ensure that new antibiotics become available.[7,12]

The U.S. government has participated in PPP initiatives for antibiotic research through the Biomedical Advanced Research and Development Authority (BARDA).[8] BARDA has awarded more than $150 million in contracts to facilitate the development of antibiotics such as TP 434 (eravacycline) and GSK 225152, which have activity against highly resistant gram-negative bacilli.[8] Another example is the establishment of the Clinical Research Network on Antibacterial Resistance in 2014 by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health.[8] This network of collaborating clinical centers was formed to conduct research regarding antibiotic resistance, usage, and stewardship; infection diagnosis and prevention; and antibiotic clinical trials.[8]

PPPs have also taken the form of nonprofit corporations funded by both public and private revenues.[8] One such example is the Global Alliance for TB Drug Development, which is a partnership between Novartis, academia, and the NIAID that successfully developed a novel drug to treat tuberculosis (PA-824, a nitroimidazole), which has been studied in phase 2 clinical trials.[8] In addition, Wellcome Trust, a global charitable organization, has established a Seeding Drug Discovery program to help strengthen public–private and academic–industrial partnerships engaging in antibiotic drug research.[14] The IDSA has established the "10 x '20" initiative, which supports the development of 10 new antibiotics by 2020.[14] The IDSA has also actively lobbied the U.S. government to take action to restimulate the development of new antibiotics.[14]

Payer Incentives

Incentives involving the Joint Commission, the Centers for Medicare and Medicaid Services, and other payers can also be effective.[8] One example is the broadscale implementation and endorsement of preventive measures that had been proven effective in a well-validated clinical trial.[8] The controlled trial in 103 Michigan ICUs found that a bundle of five steps to prevent central-line bacteremia reduced infection rates from 7.7 to 1.4 per 1,000 catheter-days.[8] The CDC declared that if this bundle of steps was implemented across the U.S., it would potentially save 18,000 lives and $1.8 billion annually.[8] The steps were then adopted by the Department of Health and Human Services (HHS) and endorsed by the Joint Commission.[8] The HHS partnered with Blue Cross/Blue Shield, which provided financial rewards for using the bundle.[8]

Government Legislation

Legislation to address challenges encountered by the pharmaceutical industry with respect to antibiotic development has been signed into law or is under consideration.[2,7] Incentives have been proposed to encourage pharmaceutical companies to re-enter the field of antibiotic drug development; these include measures to streamline regulatory approval, improve economic viability, or provide alternative or supplemental funding for efforts in this area.[2,14]

In July 2012, the GAIN Act, which aims to improve the net present value (NPV) of antibiotics, was signed into law as part of the FDA Safety and Innovation Act. The NPV is a calculation that includes development costs and the operating profits a drug will generate.[8] This legislation extends patent protection for new antibiotics that treat serious or life-threatening infections by five years.[16] These antibiotics will also be eligible for fast-track and priority review status to expedite FDA approval.[16] The GAIN Act is an important first step, but these incentives may not be enough to substantively increase the NPV of antibiotics—additional action may be needed.[8]

Regarding measures to curtail the application of antibiotics in agriculture, many state and federal legislative efforts have been thwarted by opposition from the pharmaceutical and agricultural industries.[18,19] Nonetheless, in 2012, the FDA was successful in banning the use of cephalosporins for growth promotion in certain livestock.[8] A wider ban on antibiotic use for animal-growth promotion is included in proposed legislation known as the Preservation of Antibiotics for Medical Treatment Act (PAMTA).[8] Other new legislation has also been proposed—the Delivering Antibiotic Transparency in Animals (DATA) Act would require public reporting of the types and amounts of antibiotics administered to feed animals.[8]

NEW AGENTS FOR THE TREATMENT OF BACTERIAL INFECTIONS

Recently Approved Antibiotics

Increasing awareness of the antibiotic resistance crisis has prompted the pharmaceutical industry to revamp its antibiotic discovery and development programs.[10] While the decade between 2000 and 2010 saw only five new antibiotics approved for clinical use, this pace has accelerated, with four new antibiotics approved in 2014 alone and one approved so far in 2015.[5,20] Information regarding antibiotics that received FDA approval from 2005 to the present follows and appears in Table 2.

Tigecycline

Tigecycline is a broad-spectrum glycylcycline (i.e., a third-generation tetracycline) approved for clinical use in 2005.[2,5] Tigecycline is active against methicillin-resistant *Staphylococcus aureus* (MRSA) and is useful in the treatment of mixed infections, except for those caused by *Pseudomonas*.[2,10] The role of tigecycline in the treatment of vancomycin-resistant

Table 2 Antibiotics Approved Since 2005[5,20–23]

Drug Name	Year Approved	Drug Class	Indications*
Tigecycline (Tygacil, Pfizer)	2005	Tetracycline	Patients 18 years of age and older with: • cSSSIs • cIAIs • CABP
Doripenem (Doribax. Shionogi)	2007	Carbapenem	Adult patients with: • cIAIs • cUTIs, including pyelonephritis
Telavancin (Vibativ, Theravance Biopharma)	2008	Glycopeptide	Adult patients with: • Hospital-acquired and ventilator-associated bacterial pneumonia • cSSSIs
Ceftaroline (Teflaro, Cerexa)	2010	Cephalosporin	Patients with:† • CABP • ABSSSIs
Tedizolid (Sivextro, Cubist Pharmaceuticals)	2014	Oxazolidinone	Adult patients with ABSSSIs
Dalbavancin (Dalvance, Durata Therapeutics)	2014	Glycopeptide	Adult patients with ABSSSIs
Oritavancin (Orbactiv, Medicines Company)	2014	Glycopeptide	Adult patients with ABSSSIs
Ceftolozane/tazobactam (Zerbaxa, Cubist Pharmaceuticals)	2014	Cephalosporin/beta-lactamase inhibitor	Adult patients with: • cIAIs, in combination with metronidazole • cUTIs, including pyelonephritis
Ceftazidime/avibactam (Avycaz, Cerexa Inc.)	2015	Cephalosporin/beta-lactamase inhibitor	Adult patients with: • cIAIs, in combination with metronidazole • cUTIs, including pyelonephritis

ABSSSIs = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; cIAIs = complicated intra-abdominal infections; cSSSIs = complicated skin and skin structure infections; cUTIs = complicated urinary tract infections

* Caused by designated susceptible bacteria. See prescribing information for these and other important details.

† Safety and effectiveness in pediatric patients have not been established.

Enterococcus (VRE) and severe *Acinetobacter* infections is uncertain, although it has notable *in vitro* activity against carbapenem-resistant *Acinetobacter* (CRA).[10] Tigecycline is often one of the only active agents for carbapenem-resistant gram-negative infections, but resistance is emerging.[5]

Doripenem

Doripenem, approved by the FDA in 2007, is a carbapenem that is most commonly used to treat serious gram-negative infections.[5] However, dissemination of resistant pathogens such as carbapenem-resistant Enterobacteriaceae (CRE) is reducing the overall effectiveness of this drug.[5] In retrospective surveys, combination therapy with doripenem was shown to be superior to monotherapy for treatment of CRE infections.[10] In addition, *in vitro* synergy against CRE has been documented for polymyxin B–doripenem; however, this finding has not yet been confirmed by clinical studies.[10]

Telavancin

Telavancin is a glycopeptide that received FDA approval in 2008 for the treatment of gram-positive skin and soft tissue infections.[2,5] The use of telavancin is limited because it is administered intravenously and is therefore difficult to use in an outpatient setting.[5] In addition, it should not be used in a woman of childbearing age without a pregnancy test.[5] Combined data from the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia (ATTAIN) trials showed that the cure rate with telavancin was 58.9% compared with 59.5% for vancomycin (95% confidence interval [CI] for the difference, –5.6% to 4.3%).[2] In a subset analysis, cure rates were higher with telavancin in patients with monomicrobial *S. aureus* infection, although patients with MRSA infection had similar results.[2]

Ceftaroline

Ceftaroline is a fifth-generation cephalosporin that was approved in 2010.[5] Unlike other cephalosporins, it is active against MRSA.[5,10] Ceftaroline is also active against vancomycin-resistant *S. aureus* (VRSA) and is well tolerated.[2,5] Extended-spectrum beta-lactamase (ESBL)-producing and CRE-resistant isolates are resistant to ceftaroline.[5] Phase 3 clinical trials have found that ceftaroline is noninferior to ceftriaxone for the treatment of CAP and noninferior to vancomycin and aztreonam for the treatment of complicated skin and skin structure infections (cSSSIs).[2]

Tedizolid

Tedizolid is a new oxazolidinone, approved by the FDA in 2014, that offers improvements over linezolid.[2,20] The minimum inhibitory concentrations (MICs) of tedizolid are lower than linezolid for staphylococci, streptococci, and enterococci.[2] Close to 80% of linezolid-resistant strains were inhibited by tedizolid at a concentration of less than or equal to 4 mcg/mL.[2] Tedizolid is active against MRSA that possesses the plasmid-mediated *cfr* (chloramphenicol florfenicol resistance) gene, which causes resistance to linezolid, chloramphenicol, florfenicol, and clindamycin.[2]

In a double-blind phase 2 investigation, patients with cSSSIs that were suspected or confirmed to be due to gram-positive bacteria (most had *S. aureus* and more than 80% had MRSA) were given oral 200-mg, 300-mg, or 400-mg doses of tedizolid once daily for five to seven days.[2] All three dosage groups exhibited clinical cure rates in excess of 95% for MRSA as well as for methicillin-sensitive *S. aureus* infections.[2]

Dalbavancin

Dalbavancin, a glycopeptide that is active against gram-positive bacteria, was approved by the FDA in 2014.[20] Dalbavancin MICs for *Staphylococcus* species are significantly lower than those for vancomycin.[21] Similar to other glycopeptides, dalbavancin is poorly absorbed when administered orally, so it must be given intravenously.[21] Phase 3 randomized clinical studies have demonstrated that dalbavancin was noninferior when compared to vancomycin and linezolid in the treatment of skin and soft tissue infections.[21]

Oritavancin

Oritavancin is a glycopeptide that was approved in 2014.[2] It is active against gram-positive bacteria, including MRSA, VRE, and VRSA.[2,11,21,22] Oritavancin is administered by intravenous (IV) infusion. It is not metabolized following IV dosing and is excreted unchanged, which means that dosage adjustment is not required for age, gender, race, weight, and mild-to-severe renal or mild-to-moderate hepatic dysfunction.[21] Oritavancin was demonstrated to be noninferior to IV vancomycin for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in two randomized, double-blind, multicenter clinical trials.[21]

Ceftolozane/Tazobactam

Ceftolozane/tazobactam, a novel combination of a cephalosporin and a beta-lactamase inhibitor, received FDA approval in 2014.[21] It is mostly active against infections caused by gram-negative bacteria.[21,22] Ceftolozane/tazobactam has demonstrated good-to-excellent *in vitro* activity against *P. aeruginosa*, *Escherichia coli*, and *K. pneumoniae*.[21] In a multinational, randomized, double-blind study, ceftolozane/tazobactam plus metronidazole was found to be noninferior to meropenem in the treatment of complicated intra-abdominal infections (cIAIs).[23] In another multinational, randomized, double-blind study, the clinical cure rates for ceftolozane/tazobactam were shown to be comparable to levofloxacin in the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, caused by susceptible organisms.[23]

Ceftazidime/Avibactam

Ceftazidime/avibactam, another novel cephalosporin and beta-lactamase inhibitor combination, was approved by the FDA in February 2015.[20] It is active against gram-negative bacteria, such as *P. aeruginosa* and Enterobacteriaceae, excluding metallo-beta-lactamases.[21,24] The addition of avibactam to ceftazidime protects ceftazidime from breakdown by pathogens that produce ESBL, *K. pneumoniae* carbapenemase (KPC), and AmpC.[24]

Antibiotics in the Development Pipeline

Antibiotics in the research pipeline include new-generation aminoglycosides, beta-lactamase inhibitors, quinolones, ketolides, tetracyclines, and oxazolidinones.[2] As of December 2014, approximately 37 new antibiotics for the treatment of serious bacterial infections were in clinical development.[22] However, the success rate for drug development is low (one in five), and even if these agents are proven safe and effective in clinical trials, they likely will not be available for clinical use for three to five years.[10,22]

Aminoglycosides are broad-spectrum antibiotics that are used as monotherapy, as well as synergistically with other antibiotics such as beta-lactams.[2] However, although these agents have been in use for more than 60 years, they are associated with significant toxicity.[2] Plazomicin is the first of the new-generation aminoglycosides, known as neoglycosides.[2] Plazomicin exhibits dose-dependent bactericidal activity and inhibits bacterial protein synthesis.[2] It is resistant to enzymatic inhibition, so bacterial enzymes that inactivate gentamicin do not act on plazomicin.[2]

Plazomicin retains the broad-spectrum activity of aminoglycosides, including activity against gram-negative and gram-positive bacteria.[2] It acts synergistically with daptomycin and ceftobiprole against MRSA, as well as against *Pseudomonas* when combined with cefepime, doripenem, and piperacillin/tazobactam.[2] In addition, plazomicin was found to have a lower MIC for *Acinetobacter* when compared with currently FDA-approved aminoglycosides.[2] Plazomicin is in phase 3 clinical trials.[2,22] Potential indications for plazomicin include catheter-related bloodstream infections, hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia, cIAIs, and cUTIs.[22]

New beta-lactamase-inhibiting compounds are also being developed.[2] Avibactam has a broad spectrum, including activity against KPC-producing bacteria.[2] Combination therapy with avibactam and ceftaroline has been investigated.[2] Ceftaroline/avibactam has been shown to have a very broad spectrum, including activity against MRSA, and is in phase 2 clinical trials.[2,22]

Broad-spectrum quinolones to combat bacterial strains that are resistant to existing quinolone compounds are also in development.[2] Two new quinolone compounds, nemonoxacin and delafloxacin, are in phase 2 and 3 clinical trials, respectively.[2,22] Nemonoxacin has shown broad-spectrum antibacterial activity against gram-negative and gram-positive isolates.[21] It has also displayed potent antibacterial activity against MRSA and VRE.[21] Oral nemonoxacin has demonstrated a clinical and bacteriological response, similar to levofloxacin, in the treatment of CAP.[21] Potential indications for nemonoxacin include community-acquired bacterial pneumonia (CABP), diabetic foot infection,

and ABSSSIs.[22] Delafloxacin is an oral and parenteral drug that is active against a variety of gram-positive bacteria, including MRSA.[2,21] It also has activity against quinolone-resistant strains of *P. aeruginosa* and *K. pneumoniae*.[21] Potential indications for delafloxacin include ABSSSIs, CABP, uncomplicated gonorrhea, HABP, cUTIs, and cIAIs.[22]

Solithromycin is a new ketolide compound that is in development.[2] It is highly active against gram-positive and modestly active against gram-negative bacteria.[2] On the basis of *in vitro* studies comparing the MIC of solithromycin for various pathogens, its main indication is expected to be for CAP and skin and soft tissue infections.[2] Other potential indications for solithromycin include uncomplicated urogenital gonorrhea and urethritis.[22] Solithromycin is in phase 3 clinical trials.[22]

Omadacycline is a tetracycline that is similar to tigecycline in its spectrum, but unlike tigecycline it is absorbed orally.[2] Omadacycline is in phase 2 clinical trials.[22] Potential indications for omadacycline include CAP, ABSSSI, and cUTIs.[22] Eravacycline is a new tetracycline compound that shares several properties with omadacycline.[2] It has broad-spectrum activity against gram-negative and gram-positive bacteria.[22] Eravacycline is in phase 3 clinical trials.[22] Potential indications for eravacycline include cUTIs, cIAIs, and HABP.[22]

Radezolid is an oxazolidinone that shares some properties with tedizolid, such as activity against linezolid-resistant strains.[2] However, it achieves 11-times-higher levels inside macrophages and neutrophils, a property that might be useful when applied to persistent infections with intracellular organisms.[2] Radezolid is in phase 2 clinical trials.[22] Potential indications for radezolid include CAP and ABSSSIs.[22]

New Approaches to Treating Bacterial Infections

Antibiotics in current clinical use have been derived mostly from natural substances produced by bacteria and fungi to defend against microbial attack.[3,9] These substances are then often modified by scientists to create additional or amplified antimicrobial activity.[3,4] However, although 20 new classes of antibiotics derived from natural substances were identified from 1940 to 1980, this pace could not be sustained.[19] Since then, most of the new antibiotics that have been introduced have been variants that are members of known classes.[4,19] Other issues that make natural antibiotic compounds unattractive for drug development include chemical complexity and stability, abundance, and purification.[3] In addition, about 99% of the microorganisms that are a potential source of new antibiotics cannot be grown in a laboratory environment and therefore remain uncultured.[25] Because of these difficulties, the pharmaceutical industry has instead favored screening large libraries of synthetic molecules for antibiotic activity.[3]

New strategies in antibiotic discovery, such as resistance and virulence inhibition, new targets, new culturing techniques, and novel drug combinations, are expected to preserve natural products as a continued source of new antibiotics.[3]

New sources of natural antibiotics, such as samples from marine bacteria, tropical rain forests, myxobacteria, and extremophilic bacteria, are actively being investigated.[4] Notably, the discovery of teixobactin, the first of a new class of antibiotics, was reported in January 2015.[25] Key to this discovery was the use of a new technique (the isolation chip, or "iChip") to grow the previously impossible-to-culture microbe that produces teixobactin, *Eleftheria terrae*.[25] Use of the iChip allowed this microbe to be grown in the laboratory in soil, its natural environment.[25] Teixobactin has been reported to have excellent activity against gram-positive bacteria, including resistant strains.[25]

New approaches to treating infections that do not require killing the microbe are also being investigated.[12] These include disarming pathogens so that they do not cause disease (e.g., inhibiting production of endotoxin by the bacteria), starving microbes of nutrients (e.g., iron) so they cannot proliferate in the host, modulating host response to pathogens, and using probiotics to protect the host microbiota.[12]

Discoveries using molecular genomics have provided the means to understand antibiotic-producing organisms and pathogens, and the transmission of antibiotic-resistance genes among bacteria.[4,14] Genomes of organisms that produce natural antibiotics, such as *Streptomyces* species from soil, marine organisms, and plants, have been examined and biosynthetic pathways identified.[14] Genetic manipulation of such pathways has produced new metabolites with antibiotic activity.[14] Genetic experiments have also shown that a substantial number of potential new bacterial target sites exist, including those that could reduce virulence.[14] Genes that are critical to the survival of pathogens are also potential new targets.[4] Antimicrobials with activity against bacterial molecules that have not been targeted previously, such as bacteria DNA polymerase III, the cell-division protein FtsZ, or fibronectin binding proteins, are also being considered.[4] In another strategy, molecular techniques are being used to clone genes responsible for antibiotic biosynthesis into a different strain, to yield a hybrid molecule with antibiotic activity.[4]

Advances in analytical chemistry, synthetic biology, and bioinformatics are also making it possible to overcome barriers to antibiotic drug discovery.[3,4] Using new techniques, a large number of new compounds can be synthesized on a solid support and then screened for activity using combinatorial chemistry.[4] These strategies are expected to generate new compounds with novel antimicrobial activities.[4]

CONCLUSION

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics.[14] Despite the alarming and increasing threat posed by emerging antibiotic-resistant bacteria worldwide, the implementation of recommended steps, new policies to manage the crisis, and renewed research efforts to find novel agents and approaches to treating bacterial infections could dramatically reduce these risks.[2,7] HCPs, researchers, policy-makers, and representatives of the pharmaceutical industries have begun to come together in these ways to fight the antibiotic resistance crisis.[10] Although success will require a considerable investment of human and financial resources, the cost of not acting would likely be much greater.[10]

REFERENCES

1. Golkar Z, Bagazra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. *Infect Dev Ctries* 2014;8(2):129–136.

2. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can overcome microbial resistance. *Virulence* 2013;4(2):185–191.
3. Wright GD. Something new: revisiting natural products in antibiotic drug discovery. *Can J Microbiol* 2014;60(3):147–154.
4. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. *Front Microbiol* 2013;4:47.
5. Centers for Disease Control and Prevention, Office of Infectious Disease. Antibiotic resistance threats in the United States, 2013. April 2013. Available at: http://www.cdc.gov/drugresistance/threat-report-2013. Accessed February 20, 2015.
6. Congressional Research Service Report. Life expectancy in the United States. March 2005. Available at: http://www.cnie.org/nle/crsreports/05mar/RL32792.pdf. Accessed January 5, 2015.
7. Lushniak BD. Antibiotic resistance: a public health crisis. *Public Health Rep* 2014;129(4):314–316.
8. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis* 2013;56(10):1445–1450.
9. Michael CA, Dominey-Howes D, Labbate M. The antibiotic resistance crisis: causes, consequences, and management. *Front Public Health* 2014;2:145.
10. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. *Clin Opin Pharmacol* 2014;18C;58–60.
11. Luyt CE, Brechot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. *Crit Care* 2014;18(5):480.
12. Spellberg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. *Clin Infect Dis* 2014;59 suppl 2:S71–S75.
13. The antibiotic alarm. *Nature* 2013;495(7440):141.
14. Piddock LJ. The crisis of no new antibiotics—what is the way forward? *Lancet Infect Dis* 2012;12(3):249–253.
15. Gelles D. Merck in $8.4 billion deal for Cubist, big maker of antibiotics. *The New York Times.* December 8, 2014. Available at: http://dealbook.nytimes.com/2014/12/08/merck-agrees-to-acquire-drug-maker-cubist-for-9-5-billion. Accessed January 5, 2015.
16. The Pew Charitable Trust. GAIN: How a new law is stimulating the development of antibiotics. November 7, 2013. Available at: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics. Accessed January 5, 2015.
17. Tavernise S, Shear M. Obama seeks to double funding to fight antibiotic resistance. *The New York Times.* March 27, 2015. Available at: http://www.nytimes.com/2015/03/28/us/politics/obama-seeks-to-double-funding-to-fight-antibiotic-resistance.html?_r=0. Accessed April 4, 2015.
18. Viswanathan VK. Off-label abuse of antibiotics by bacteria. *Gut Microbes* 2014;5(1):3–4.
19. Gross M. Antibiotics in crisis. *Curr Biol* 2013;23(24):R1063–R1065.
20. Centerwatch. FDA approved drugs for infections and infectious disease. Available at: https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/25/infections-and-infectious-diseases. Accessed February 27, 2015.
21. Bassetti M, Merelli M, Temperoni C, Astilean A. New antibiotics for bad bugs: where are we? *Ann Clin Microbial Antimicrob* 2013;12:22.
22. The Pew Charitable Trust. Antibiotics currently in clinical development. December 31, 2014. Available at: http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development. Accessed February 28, 2015.
23. Zerbaxa (ceftozolane/tazobactam) prescribing information. December 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf. Accessed February 28, 2015.
24. Mendes C, Antunes A. Pipeline of known chemical classes of antibiotics. *Antibiotics* 2013;2(4):500–534.
25. Ling LL, Schneider T, Peoples AJ, et al. A new antibiotic kills pathogens without detectable resistances. *Nature* 2015;517:455–459. ■