Seven Ways to Preserve the Miracle of Antibiotics

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Antibiotic resistance is a well-acknowledged crisis with no clearly defined comprehensive, national corrective plan. We propose a number of interventions that, collectively, could make a large difference. These include collection of data to inform decisions, efforts to reduce antibiotic abuse in people and animals, great emphasis on antibiotic stewardship, performance incentives, optimal use of newer diagnostics, better support for clinical and basic resistance-related research, and novel methods to foster new antibiotic development.

Keywords. antibody resistance; antibiotic salvage; European Union, stewardship; molecular diagnostics.

Antibiotics are a true miracle of modern medicine. However, in reference to penicillin, the drug he discovered, Fleming gave warning in 1946 [1] that

the public will demand [the drug and] … then will begin an era … of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted.

Unfortunately, Fleming’s warning was unheeded, so this miracle of antibiotics is now endangered owing to the rapid escalation of antibiotic resistance combined with the equally rapid decline in discovery and development of new antibiotics.

This is now considered a global health crisis [2], and the reason is not difficult to understand.

Resistance within all microbial classes continues to grow by natural evolution driven by massive use of agents that apply selective antimicrobial pressure. Pharmaceutical development that previously kept us ahead of resistance is now stalled due to economic and regulatory barriers. Fifteen of 18 large pharmaceutical companies have totally left the antibiotic field, and there has been no new class of antibiotics for gram-negative bacilli in 4 decades; only 2 drugs with new microbial targets (linezolid and daptomycin) have been introduced since 1998 [3]. The pipeline is sparse, the problem is global, and the prognosis is poor.

It is our impression that the potential for antibiotic abuse and resistance in the United States is potentially catastrophic. But it also seems clear that we could do much better with a bundled program with interventions that have established merit. These are particularly attractive in the era of healthcare reform, which prioritizes saving lives and saving money, as the cost and consequences of antibiotic resistance are enormous. What follows is not an in-depth review, but rather a summary of some major, sometimes humbling, relevant observations (Table 1) [4–17], with 7 major interventions that collectively address the multitude of contributing factors.

Our proposed “antibiotic salvage bundle” would include the following steps:

1. Establish a US database for antibiotic use and resistance comparable to that of the European Union;
2. Restrict use of antibiotics in agriculture;
The US accounts for 4.6% of the global population and 46% of the global antibiotics market [5]. It is estimated that the cost of antibiotic resistance adjusted for population is 41-fold greater in the US because of greater frequency of resistance as compared to the EU [6]. A pathogen is defined in about 7.6% of US patients hospitalized with community-acquired pneumonia [7], compared to up to 89% in other systems using advanced diagnostic methods [7, 8]. It is estimated that the use of the “bundle” to prevent central line bacteremia could save approximately 18,000 lives and $1.8 billion annually in the US [9]. There is a need for more effective consumer education to counter widespread misconceptions such as “Finally, over that cold. Thank God for Z-Pak” (Twitter—850,375 followers) [10]. An analysis by the Office of Health Economics in London calculated that, based on the cost of development and anticipated return, the current net value of new antibiotics is $50 million compared to +$1 billion for a neuromuscular disease [11]. Review of controlled trials for 8 bacterial infections showed that “short” courses were therapeutically equivalent to “standard” courses [12–15]. The risk of nosocomial MRSA bacteremia is approximately 49 times greater with admission to a hospital in the US compared to hospitals in the Netherlands [16]. A Cochrane meta-analysis suggests that use of procalciotonin could reduce antibiotic consumption in hospitalized patients with bacterial infections at diverse anatomical sites by 51% [17]. There have been no new antimicrobial classes for gram-negative bacilli in the past 40 years, and 15 of the 18 major pharmaceutical suppliers of antibiotics have now left the field [3].

**Abbreviations:** EU, European Union; MRSA, methicillin-resistant *Staphylococcus aureus*; US, United States.

**LESSONS FROM THE EUROPEAN UNION TO DEFINE AND IMPLEMENT PRIORITIES**

The European Union (EU) recognized the impending crisis of antibiotic resistance and established methods for surveillance on antibiotic use and resistance more than 15 years ago. Antibiotic use is reported as daily drug dose (DDD) per 1000 inhabitants per day according to pharmacy records, and resistance data are reported by sentinel laboratories using standard methods. The result is a living record of country-specific data for antibiotic consumption and resistance profiles by microbial species, drug, and date for 26 countries [18]. The United States has no comparable data system, but the European Union record suggests we should.

The correlation between antibiotic consumption and resistance is illustrated by comparing data for methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenemase-producing *Klebsiella* for the Netherlands versus Greece, 2 countries that are at the low versus high end, respectively, of per capita antibiotic use in the EU database (Table 2) [19, 20]. The difference is expected, but the magnitude is dramatic. The obvious result is the relative safety and limited need for new antibiotics in hospitals in the Netherlands, presumably reflecting policies and practices that foster prudent antibiotic use and infection control [16, 19].

An example of the use of EU data is France, which had high rates of multidrug-resistant *Streptococcus pneumoniae* in 2002 and also had the highest rate of antibiotic use in the European Union (36.5 DDD/1000 inhabitants) [21]. This led to an ambitious nationwide program directed to both providers and consumers. The results showed a 26% nationwide decrease in antibiotic prescriptions during the study period [21], and a follow-up report of the global antibiotic market showed that France is the country with the greatest reduction in antibiotic prescriptions in the world—a decrease of 21% from 2000 to 2009 [5].

The European Union systematically assesses antibiotic usage and resistance data to guide interventions to effect systematic change [11, 18, 19] and accomplishes this despite great diversity in resources, language, and politics (http://www.ema.
The United States has a number of surveillance systems in place that provide relevant data, but nothing that is nearly as comprehensive or effective as the EU system. The Centers for Disease Control and Prevention (CDC) has initiated a plan that addresses some of these issues, but the lack of incentives from credentialing agencies such as The Joint Commission (a nonprofit organization that accredits and certifies healthcare organizations and programs in the United States) or funding agencies such as the Centers for Medicare and Medicaid Services are likely to limit use. It seems unacceptable and embarrassing that the United States at present does not have the necessary support to implement this plan. The Strategies to Address Antimicrobial Resistance Act was introduced to Congress nearly 6 years ago to address this need but has never come to a vote. It should be passed.

**ADDRESSING ANTIBIOTIC ABUSE IN FARM ANIMALS**

An astonishing 80% of all antibiotics sold in the United States are administered to food animals, primarily for growth promotion and infection prophylaxis [4, 22]. There is good evidence that this practice has consequences to human health and has no clear benefit to farmers, although quantitation of this effect is not possible due to the enormity of the dispersal area from run-off and other sources of environmental contamination. [23]. The direct effect was noted >35 years ago, with high rates of antibiotic resistance in the intestinal flora of farm animals and farmers [18], and more recently with molecular methods that show that resistant bacteria in farm animals do reach consumers in meat products [24]. The indirect impact is supported by observations that up to 90% of antibiotics given to animals are excreted in urine and stool and then widely dispersed through fertilizer, surface runoff, and groundwater, with a profound impact on the environmental microbiome [24]. Country-specific bans on antibiotic abuse in farm animals in the European Union have been accompanied by significant declines in antibiotic resistance in humans and animals without documented harm to humans or animals [23]. The European Union has recently asked all member states to require antibiotic prescriptions for all antibiotic use in farm animals [11]. Similar restrictions are proposed by the Institute of Medicine in the United States and by the World Health Organization [2]. The FDA has recently announced a ban on cephalosporins for growth promotion in certain livestock. A more expansive ban of nearly all antibiotic use for growth promotion is included in the proposed legislation known as the Preservation of Antibiotics for Medical Treatment Act (PAMTA; http://waxman.house.gov/press-release/rep-waxman-introduce-legislation-monitor-antibiotic-use-animals) would require public reporting of types and amounts of antibiotics administered to feed animals, including via feed mills. Both DATA and PAMTA should be passed.

**METHODS TO IMPLEMENT PREVENTION OF NOSOCOMIAL INFECTIONS**

The term *implementation* as used here refers to the transfer of scientific advances into practice. The sequence of events for reducing the frequency of central line bacteremia (CLB) illustrates the concept: National data for CLB in US hospitals in 2002 showed approximately 80 000 cases per year with 28 000 deaths and $45 000 per case in healthcare costs [25]. A 5-step bundle to prevent CLB was developed and pilot tested to establish efficacy, then tested in a controlled trial in 103 intensive care units in Michigan; the Michigan CLB rates fell from 7.7 to 1.4 per 1000 catheter-days [25]. The CLB prevention bundle was then adopted as a priority by the US Department of Health and Human Services (HHS). Blue Cross/Blue Shield provided financial rewards for adoption of the bundle; LeapFrog allocated credit; and the Joint Commission on Hospital Accreditation endorsed the bundle. The CDC then showed the CLB bundle to be effective in its sentinel hospital network, leading Dr Arjun Srinivasan, Director of Antibiotic Resistance at the CDC, to state that if all hospitals in the United States used the CLB bundle, it would potentially save 18 000 lives and $1.8 billion annually [9].

The unique feature of this sequence is the efficient transition from a well-validated clinical trial data to broad-scale implementation [26]. The key issue was not the publication to validate the science, but the endorsement by organizations that fund and regulate medicine, leading to a policy of financial penalties to hospitals for failure to reduce CLB rates by 50% [27]. Note that there is now new emphasis to reduce rates of multiple common nosocomial infections including *Clostridium difficile*-associated diarrhea, ventilator-associated pneumonia, catheter-associated urinary tract infects, selected surgical site infections, and MRSA bacteremia [27].

**STEWARDSHIP TO IMPROVE HOSPITAL-BASED ANTIBIOTIC USE**

Hospitals are a centerpiece for resistance, reflecting the clustering of highly vulnerable patients, extensive use of invasive procedures, and high rates of antibiotic use. In the United States, the result is a nosocomial “environmental resistome” that is implicated in an estimated excess cost of $18 000–$29 000 per infected patient [28]. The ability to better control this paradoxical tragedy of the healthcare system is well
illustrated by the strong correlation between antibiotic use and resistance, reflecting the need for stewardship and infection control measures, as shown by the dramatic differences within the European Union [19, 20] (Table 2).

Hospital-based antibiotic stewardship programs are critical to improve antibiotic decisions. A review of 24 reports considered to be of high quality (1996–2010) showed that stewardship programs achieved significant reductions in antibiotic use (11%–38% reduction in DDD/1000 patient-days), including significant reductions in total antibiotic consumption, duration, and inappropriate use [29]. Hospital-based interventions with substantial potential or documented benefits include the following:

- The intravenous to oral switch that reduces vascular line sepsis risk and hastens discharge with agents appropriate for oral use, including fluoroquinolones, metronidazole, clindamycin, linezolid, fluconazole, and azithromycin, will be facilitated.
- Intensive care units (ICUs) need to be an area of focused effort, as shown by a review of 2000 consecutive ICU patients from a large academic center in which 655 patients (33%) had a nosocomial infection including 169 (26%) who received inappropriate antibiotics with a 4.26-fold increase in mortality [29]. A recent report illustrates the central role of the ICU in a hospital-wide outbreak of a carbapenemase-producing Klebsiella pneumoniae [30].
- A potentially important method to reduce unnecessary antibiotic exposure is short courses. Multiple controlled trials including 4 Cochrane Library reviews showed that a short course was uniformly equivalent to “standard” duration including 8 days for ventilator-associated pneumonia [12], 7 days for pyelonephritis [13], 10 days for septic arthritis [14], and 3 days for community-acquired pneumonia (CAP) [15].
- Procalcitonin levels reflect bacterial replication [17] and have been extensively tested to facilitate decisions of when to use or stop antibacterials. A meta-analysis of 7 randomized controlled trials with 1458 patients showed that procalcitonin-guided decisions reduced total antibiotic use by 51% without altering outcome [17].
- Optimal dosing of antibiotics includes tactics that are uncommon in practice but improve outcome such as once-daily aminoglycosides and fluoroquinolones or by prolonged intravenous infusions of β-lactams [31]. Increased minimum inhibitory concentrations of MRSA has forced new dosing recommendations that target trough levels and require broad-scale reeducation on use of the most frequently used antibiotic in US hospitals. Colistin is an example of a drug now in relatively common use despite limited modern pharmacologic data; recent reviews show substantial erroneous dosing directions in the package insert [32].

Hence, there is a compelling need for antibiotic stewardship programs to preserve and properly use existing antibiotics. Antibiotic stewardship is the common denominator for these diverse and complex interventions that have established merit, but implementation of effective stewardship programs is unlikely without incentives from credentialing agencies or funding agencies, which are currently lacking.

**AVOID INAPPROPRIATE ANTIBACTERIAL USE FOR VIRAL INFECTIONS**

Surveys indicate that 40%–75% of adults and children who seek care for viral respiratory tract infections are treated with antibacterial agents. Consumer demand is cited as an important factor, suggesting that this a combined consumer and provider education challenge. A 2005 Cochrane review [33] of 39 relevant publications concluded that the only intervention with effect size sufficient to impact bacterial resistance was “delayed prescription,” meaning that antibiotic prescriptions are to be filled a few days later if symptoms do not improve. This tactic achieves patient satisfaction and prevents abuse because viral respiratory tract infections usually improve in the designated time frame. The Cochrane review noted that lectures, meetings, and printed materials for either consumers or providers had minimal impact [33], although some combinations have been successful, such as the previously described campaign directed to both consumers and providers in France [21].

**DIAGNOSTIC METHODS THAT CAN TRANSFORM THE MANAGEMENT OF INFECTIOUS DISEASES**

Contemporary clinical microbiology is based on a 150-year-old standard with culture of organisms on seaweed extract (ie, agar). We are in the midst of a transformation where microbiology diagnostics are based on the detection of the pathogen’s unique nucleic acid or biochemical composition. Recently introduced methods can be target-specific, such as polymerase chain reaction (PCR) methods to detect a single microbe such as MRSA or to detect 17 respiratory tract viruses or a resistance mechanism [34]. Applications anticipated in the near future include the PLEX-ID instrument that can detect and identify >5400 unique microbes within hours and was used to detect and then follow evolution of the 2009 pandemic H1N1 influenza strain [35].

Most antibiotic orders are empiric, but molecular diagnostics offer the promise of rapid, even point-of-care, detection of specific microbes to permit more immediate pathogen-specific
treatment. This will require substantial prescriber training, but the need is transparent. In the United States, a recent report showed that a microbiologic diagnosis was made in only 7.6% of 17,435 hospitalized patients with CAP [7]. In contrast, investigators at the Karolinska Institutet (Sweden) used PCR to detect viruses, and semiquantitative PCR for relevant bacteria, in CAP patients and detected a probable pathogen for 89% of patients [8]. Another benefit of molecular diagnostics is detection of the nucleic acid of heretofore unknown pathogens. The contents of brain abscesses from 39 patients using 16S ribosomal DNA analysis yielded 76 bacterial species including 23 species that could not be cultured, suggesting potentially important nuances of infectious diseases that have yet to be explored [36]. These data emphasize the need for more research on the pathogenic role of these uncultivable organisms, as well as the need for research on what drives resistance.

METHODS TO PROMOTE ANTIBIOTIC DEVELOPMENT

In the United States, the lack of clear, feasible clinical trial pathways for the regulatory evaluation of candidate antibiotics has greatly exacerbated the antibiotic market failure. Meanwhile, the European Medicines Agency has recently released a broad regulatory guidance document that facilitates the feasibility of antibiotic clinical trials [11]. The Infectious Diseases Society of America has recently proposed a new regulatory pathway, limited-population antibiotic drug mechanism, to facilitate the development and availability of critically needed antibiotics, and FDA officials have spoken publicly about the merits of the idea [37]. This would enable substantially smaller clinical trials, which would be less expensive, take less time, and address a critical need. In return for approval based on efficacy in small clinical trials, the antibiotic would receive a very narrow indication focused only on the high-risk patients for whom benefits were shown to outweigh risks.

The FDA may address the regulatory issues that have intimidated antibiotic development, but there is also the reality that antibiotic development is no longer an economically wise investment. The financial challenges for antibiotic development are illustrated by an analysis by the London School of Economics; at discovery, an antibiotic has a net present value are illustrated by an analysis by the London School of Economics; at discovery, an antibiotic has a net present value (NPV) of $25 million compared to a $1 billion estimated NPV for a new musculoskeletal drug [6]. Contributing factors are the facts that antibiotics are the only drugs that lose benefit by extensive use, are given in short courses, and are generally priced at a peak charge of $1,000–$3,000 per course compared to, for example, cancer chemotherapy at sometimes >$80,000 or atorvastatin that is often given for decades. In July 2012, legislation to improve the NPV of antibiotics, called the Generating Antibiotic Incentives Now (GAIN) Act, was signed into law as part of the FDA Safety and Innovation Act. GAIN is an important first step, but careful analyses concluded that these incentives are not strong enough to substantially alter the NPV of antibiotics, so more is needed [38].

Public–private partnerships (PPPs) are an alternative potentially important resource to address the antibiotic market failure. US HHS Secretary Kathleen Sebelius has written that PPPs are considered critical to overcome the “chokepoints in our medical pipelines” [39]. PPPs may consist of nonprofit corporations funded by both public and private revenues, such as the Global Alliance for TB Drug Development. The Global Alliance recently successfully developed a novel drug for tuberculosis (PA-824, a nitrimidazole) through phase II clinical trials in partnership with Novartis, academic centers, and the National Institute for Allergy and Infectious Diseases (NIAID).

PPPs may also consist of government grants, contracts, or investments in for-profit drug development, akin to the model by which the Department of Defense offsets research and development costs for new military technologies. The US government has established such PPP programs, for example, at the Biomedical Advanced Research and Development Authority (BARDA). BARDA has already awarded contracts totaling well over $150 million to facilitate development of candidate antibiotics such as PT 434 and GSK 225152 that have activity against highly resistant gram-negative bacilli. Another example is the development by the NIAID of a Clinical Research Network on Antibacterial Resistance slated to start in 2014 [40]. This network of collaborating clinical centers modeled after the AIDS Clinical Trial Group could be the foundation of national data for antibiotic resistance, antibiotic usage, antibiotic stewardship, and infection prevention, as well as antibiotic trials. This new program is welcome, although, given the magnitude of the resistance problem, the level of National Institutes of Health funding for this network and the related resistance issues are concerning.

In summary, bacterial resistance now threatens the extraordinary health benefits achieved with antibiotics. Resistance is a global crisis reflecting the extensive use of these drugs and the failure of pharmaceutical companies to address the challenge. This review presents a bundle of methods to address the antibiotic resistance issue with 3 emphasis areas: to identify priorities, reduce antibiotic consumption, and stimulate new product development. Nearly all recommendations have a scientific foundation, precedent, and demonstrated impact.

Note

Potential conflicts of interest. J. G. B. has received payment for consultation or honoraria from Epocrates, Medscape, and Medicine. B. S. has received institutional grant support from Cubist, Pfizer, Eisai, and Bristol-Myers Squibb, and has received payment for consultation or honoraria from GlaxoSmithKline, Pfizer, Basilea, The Medicines Company, Achaogen, Eisai, Meiji, Polymedix, Cardes, Affinium, and Adenium. D. G. reports no potential conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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