Antibiotic Resistance: Treatment and Drug Development Challenges Addressed

Written by Mary Mosley

The resistance of infectious organisms to currently available antibiotics is a major medical challenge. The prevalence and mechanisms of multidrug-resistant pathogens vary widely worldwide. In the United States and Europe, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) appears to have stabilized, while it is increasing in other regions [Dantes R et al. *JAMA Intern Med* 2013]. Key factors contributing to the magnitude of disease from resistant organisms are biological fitness of the organism, virulence, control techniques, and antibiotic stewardship. Antibiotic resistance to gram-negative bacteria (GNB) continues to increase and represents one of the biggest challenges, according to Mark L. Metersky, MD, University of Connecticut School of Medicine, Farmington, Connecticut, USA [Braykov NP et al. *Infect Control Hosp Epidemiol* 2013].

The intensive control techniques required by the Danish government have led to a MRSA prevalence of only 1.4% [AgersØ Y et al. *DANMAP* 2011; Danish National Board of Health, 2008]. Health care facilities are required to report all MRSA infections (even colonization), practice strict isolation in all settings, perform widespread testing of at-risk patients and exposed staff, and treat all colonized patients aggressively (mupirocin nasal ointment, chlorhexidine soap). Antibiotic stewardship should include determining the infecting organism, the appropriate initial antibiotic drug choice, the appropriate dosing, and the shorter duration of treatment.

ADDRESSING THE DEVELOPMENT CHALLENGE

The drought of antibiotics in the investigational pipeline resulted from regulatory, scientific, and economic issues, with current United States Food and Drug Administration (FDA) regulations being the predominant issue hampering drug development and making costs prohibitive, with low to negative return on investment.

Brad Spellberg, MD, Harbor–University of California Los Angeles Medical Center, Los Angeles, California, USA, proposed approaches to address these issues:

- Targeted therapies focused on unmet need
- Smaller antibiotic development programs
- Narrowing and restricting labeling and high pricing
- Shorter course of therapy
- Treating infections without killing organisms

The era of broad-spectrum agents (eg, quinolones) to treat narrow-spectrum infections (skin infections, pneumococcal community-acquired pneumonia) should be over, said Dr. Spellberg. Recent guidance from the FDA has led to some development programs for unmet need. The FDA has stated a willingness to approve a new antibiotic drug with 2 indications from the conduct of 2 studies, rather than the previously required 4 studies, making this a more attractive proposition for drug companies. The targeted approach for unmet need will likely be more facile and less expensive and require less time than programs focused on large markets that can drive inappropriate use.

Off-label use represents the majority of inappropriate antibiotic use in the United States, said Dr. Spellberg, which requires changes in labeling and pricing. The duration of treatment should be short—only until the patient is better, as opposed to the current practice of complete prescription consumption, which lacks evidence of benefit and contributes to drug resistance.

Killing bacteria promotes resistance; thus, there must be a shift to nonlethal methods, such as disarming bacteria, passively starving host nutrients, outcompeting with probiotics, and targeting the microbe—not the host.

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Dr. Spellberg argued that the economic model for antibiotic drug development must change. In the United States, this may mean a public-private partnership model akin to defense contractors, where the government defrays much of the initial costs in the interest of public health with specification of industry profits.

EFFECTIVE AND CONSERVATIVE ANTIMICROBIAL THERAPY

The agents currently used for antimicrobial therapy (AMT) must be used wisely to conserve them for the future, stated Jean Chastre, MD, Universite Pierre and Marie Curie, Paris, France. There are 3 approaches for this objective: using their pharmacokinetics (PK) and pharmacodynamics (PD) to improve outcomes, utilizing aerosolization for in situ delivery, and adjusting treatment for extensively drug-resistant (XDR) pathogens, which are primarily susceptible only to colistin.

Of the difficult-to-treat pathogens, a small fraction of isolates are totally resistant; thus, the PK/PD must be optimized to reach the available susceptibility. The time above the minimal inhibitory concentration (MIC) must be maintained for 80% to 100% of the dosing interval for time-dependent antibiotics such as penicillin and carbapenem for severe infections. Achieving this in patients in the intensive care unit (ICU) may be complicated by organ dysfunction and increased cardiac output secondary to sepsis, among other factors that may modify drug clearance [Roberts JA et al. *Lancet Infect Dis* 2014]. Thus, dose adjustment is required to avoid levels that are toxic or too low—but with great caution because PK is altered in these patients. One study showed that achieving the MIC target for 100% of the dose was achieved in only 60.4% of ICU patients [Roberts JA et al. *Clin Infect Dis* 2014]. Strategies to improve PK/PD parameters, including time above MIC, include use of a loading dose, prolonged duration of drug infusion to >4 hours (without underdosing), and continuous infusion, which was shown to improve survival in a Phase 2 trial [Dulhunty JM et al. *Clin Infect Dis* 2013]. Steps to optimize AMT in ICU patients are highlighted in Table 1 [Roberts JA et al. *Lancet Infect Dis* 2014].

Colistin and possibly tigecycline are treatments for XDR GNB. Caution must be used with colistin because of nephro- and neurotoxicity and because of the different prescribing conventions (international units [IU]; number of milligrams of colistin base activity [CBA]) that can lead to dosing errors. One million IU is equivalent to 30-mg CBA and 80 mg of colistin methanesulfonate, which is the inactive prodrug form in which it is administered.

The PK of colistin makes its use in ICU patients difficult because of renal clearance that affects blood concentration. A loading dose must be used to achieve required colistin concentrations [Plachouras D et al. *Antimicrob Agents Chemother* 2009]. Combination therapy with colistin and a carbapenamase may be needed in some settings. Such a combination was strongly associated with survival (HR, 2.08; 95% CI, 1.23 to 3.51; p=0.006 vs monotherapy) in carbapenamase-producing *Klebsiella pneumoniae* bloodstream infections in an observational study from Greece [Daikos GL et al. *Antimicrob Agents Chemother* 2014].

Table 1. Recommendations to Optimize Antimicrobial Treatment in the Intensive Care Unit

Fully diagnose the infection (site, severity, responsible pathogen)
Select initial treatment (based on local epidemiology and individual data)
Establish the patient's physiologic characteristics (eg, weight, sex, creatinine clearance, urine output, serum albumin, fluid overload status, presence of extracorporeal circuits)
Determine the first dose of antibiotic (based on patient's characteristics and local bacterial susceptibility)
Give the first dose as soon as possible
Take blood samples to determine antibiotic pharmacokinetics and get the results in a timely manner
Get the support of an infectious disease specialist and a pharmacist to deliver pharmacokinetic/pharmacodynamic-optimized therapy

Tigecycline is a new and worthwhile treatment option, with activity against a variety of GNB, but it has minimal activity against *Pseudomonas aeruginosa*, *Pseudomonas mirabilis*, and indole-positive Proteaceae [Doan TL et al. *Clin Thea* 2006; Rose WE et al. *Pharmacotherapy* 2006]. Tigecycline should never be used for *P aeruginosa* infection, stated Prof. Chastre, or for β-lactam-susceptible GNB.

Aerosolized delivery of AMT as an adjunct to intravenous administration may address the low levels of lung penetration (<1/3 of dose) obtained with conventional delivery, thus increasing drug concentration at the site of infection. Furthermore, direct delivery limits systemic exposure and allows the use of AMT with higher systemic toxicity, such as aminoglycosides or polymyxins [Luyt CE et al. *Curr Opin Infect Dis* 2009]. Vibrating-mesh nebulizers are being developed to improve the efficiency of delivering the total aerosolized dose; current systems lose a majority of the dose in the device chamber.

In summary, antibiotic resistance is a major medical challenge. Tackling this problem will likely require implementation of several strategies, including a policy of careful selection of antibiotic, route of administration and dosing schedule (shorter duration of effectively dosed therapy), and ongoing development of new agents, possibly supported by government programs.