Antibiotic Use and Emerging Resistance

How Can Resource-Limited Countries Turn the Tide?

Lisa M. Bebell*,†, Anthony N. Muiru‡

Boston, MA, USA

ABSTRACT

Antibiotic resistance is a global crisis driven by appropriate and inappropriate antibiotic use to treat human illness and promote animal growth. The antimicrobial resistance epidemic continues to spread due to the triple threat of unfettered access, minimal product regulation and oversight of antibiotic prescription, and lack of clinical diagnostic tools to support antibiotic de-escalation in low-resource settings. In high-resource settings, evidence-based strategies have improved the appropriateness of antibiotic use, limiting the spread of drug-resistant organisms and reducing hospital-associated infections, strategies which may also be effective to stop the spread of resistance in resource-poor countries. Current research and surveillance efforts on antimicrobial resistance and hospital-associated infections in low-resource settings are extremely limited and largely focused on intensive care units. Many challenges exist to improving antibiotic use and infection control in resource-limited settings, and turning the tide requires intensifying research and surveillance, antimicrobial stewardship, and developing new bedside diagnostic tools for bacterial infections and antimicrobial susceptibility.

Since the discovery of penicillin in 1928 by Alexander Fleming, societies have relied on antibiotics in everyday clinical practice. Healthcare providers prescribe these "miracle drugs" to our patients more than any other class of medications, with impressive clinical results and improved patient outcomes [1]. Clinicians and patients rely on antibiotics and are accustomed to having effective antibiotics to cure nearly any bacterial infection.

Though antibiotics are prescribed for an individual patient's condition, unlike other medications, antibiotics have effects that reach far beyond the individual [2]. Even when used appropriately and as prescribed, antibiotics and bacteria resistant to antibiotics seep into our local drinking water sources [3—5] after human, agricultural, and animal use [6] and wastewater treatment [7]. They are also common contaminants of locally produced and imported meat and poultry for human consumption [8—13] acting as direct conduits for causing human illness or colonization. Resistant bacteria have the potential to affect the natural bacterial flora of any person, regardless of who first swallowed the pill or received the injection. Indeed, substantial evidence demonstrates a causal link between widespread appropriate and inappropriate antimicrobial use and the emergence of antimicrobial resistance [14—19].

Antibiotic resistance is defined 1) as the ability of a specific bacterium to survive in the presence of an antibiotic that was originally effective to treat infections caused by the bacterium or 2) as the acquisition of a specific antibiotic resistance mechanism [20,21]. There are 4 major mechanisms of bacterial antibiotic resistance: production of enzymes that inactivate the drug; production of modified targets against which the antibiotic has a reduced effect; reduction of permeability to the drug; and active export of antibiotics using various pumps [22]. Bacteria may be intrinsically resistant to antimicrobial agents or may acquire resistance to $\geq$1 class of antibiotics by de novo mutation or exchange of resistance genes from other organisms. Acquired resistance genes may enable a bacterium to produce enzymes that cleave and destroy the antibiotic, to express efflux pumps preventing the drug from reaching a bacterial intracellular target, to modify the drug's target site and thwart binding of drug to target, or to produce alternative metabolic pathways bypassing the drug's target pathway (Table 1) [22—26]. Antibiotic-susceptible bacteria may acquire new genetic material from antibiotic-resistant strains through conjugation, transformation, or transduction, with simple transposons often facilitating the incorporation of the multiple resistance genes into the genome or plasmids [22].

Though dozens of "superbugs" resistant to antibiotics have made headlines over the last quarter century, clinical microbiologists increasingly agree that multidrug-resistant gram-negative bacteria pose the greatest risk to public health [27]. Resistance in gram-positive bacteria, especially *Staphylococcus aureus* and Enterococcus, also continues to rise, with broad implications for loss of effective treatments for skin and soft tissue infections, urinary tract infections, and pneumonias [28,29], all of which are common healthcare-associated infections (HCAI). Antibiotic resistance is common in HCAI, which are localized or systemic infections that are not present at admission to a healthcare facility but occur while patients are receiving treatment for another condition in the facility [30]. Common HCAI include central line—associated blood stream infections,

Dr. Bebell is supported through a T32 training grant from the National Institutes of Health (#NIAID AI 007433).
The authors report no relationships that could be construed as a conflict of interest.
From the *Department of Infectious Diseases, Massachusetts General Hospital, Boston, MA, USA; †Massachusetts General Hospital Center for Global Health, Boston, MA, USA; and the ‡Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. Correspondence: L. M. Bebell (lbebell@mgh.harvard.edu).

GLOBAL HEART

VOL. 9, NO. 3, 2014
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2014.08.009

TABLE 1. Common antibacterial drug targets and selected mechanisms of resistance, by antibiotic class

Antibiotic Class	Antibiotic Mechanism of Action	Mechanism(s) of Antibiotic Resistance
Beta-lactams Penicillins Cephalosporins Carbapenems Monobactams	Interference with bacterial cell wall synthesis	1. Production of beta-lactamases or extended-spectrum beta-lactamases, which hydrolyze and inactivate drug 2. Change/down-regulation of porins (access points through bacterial cell membrane), prohibiting drug entry 3. Change in configuration of penicillin binding site (such as encoded by *mecA* gene in MRSA)
Glycopeptides Vancomycin Teicoplanin	Interference with bacterial cell wall synthesis	1. MRSA: accumulation of cell wall fragments that thicken the wall and are capable of binding vancomycin extracellularly; change to several metabolic pathways 2. *Enterococcus* and MRSA: acquisition of genes that alter peptide synthesis, reducing glycopeptide affinity
Macrolides Chloramphenicol Clindamycin Quinupristin-dalfopristin Linezolid	Inhibition of protein synthesis—bind to 50S ribosomal subunit	1. Multidrug efflux pump systems that pump the drug out of the cell 2. Prevention of leader single amino acid substitutions in the chromosomal dihydrofolate reductase peptide synthesis, stopping transcriptional or translational attenuation
Aminoglycosides, tetracyclines	Inhibition of protein synthesis—bind to 30S ribosomal subunit	1. Expression of aminoglycoside-modifying enzymes 2. Prevention of leader peptide synthesis, stopping transcriptional or translational attenuation
Fluoroquinolones	Interference with bacterial DNA synthesis	1. Up-regulating production of enzymes inactivating the antimicrobial agent 2. Mutations in DNA gyrase and topoisomerase enzymes involved in RNA production 3. Drug efflux pump systems that pump the drug out of the cells
Rifampin	Interference with bacterial RNA synthesis	Mutation or duplication of drug target, modification cell permeability
Trimethoprim-sulfamethoxazole	Inhibition of metabolism (bacterial folate synthesis)	Single amino acid substitutions in the chromosomal dihydrofolate reductase (as in *S. pneumoniae*) leading to decreased binding of drug
Polymixins Daptomycin	Disruption of bacterial membrane structure	Mutations altering cell surface charge

DNA, deoxyribonucleic acid; MRSA, methicillin-resistant *Staphylococcus aureus*; RNA, ribonucleic acid.
Adapted, with permission, from Tenover [22], with supplemental information from other sources [20,23—26].

catheter-associated urinary tract infections, and surgical site infections [30]. Preventing and treating HCAI should be considered as part of the infection control package when considering solutions to stem the tide of antimicrobial resistance worldwide.

As antibiotic resistance becomes increasingly prevalent and recognized, health providers are in danger of losing effective antibiotics to treat both routine infections and infections caused by antibiotic-resistant organisms. To most effectively address this public health crisis, it is