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The clinical consequences of antimicrobial resistance

Louis B Rice[1,2]

The continued evolution of antimicrobial resistance in the hospital and more recently in the community threatens to seriously compromise our ability to treat serious infections. The major success of the seven-valent *Streptococcus pneumoniae* vaccine at reducing both infection and resistance has been followed by the emergence of previously minor serotypes that express multiresistance. The almost universal activity of cephalosporins and fluoroquinolones against community *Escherichia coli* strains has been compromised by the spread of CTX-M β-lactamase-producing, fluoroquinolone-resistant strains, and the emergence of community-onset methicillin-resistant *Staphylococcus aureus*, particularly in the United States, has forced us to re-think our empirical treatment guidelines for skin and soft-tissue infections. Finally, our most potent and reliable class of antibiotics, the carbapenems, is compromised by the growth, primarily in intensive care units, of multiresistant *Klebsiella pneumoniae*, *Acinetobacter baumanni*, and *Pseudomonas aeruginosa*. The lack of a robust pipeline of new agents, particularly against resistant Gram-negative bacteria, emphasizes the importance of optimizing our use of current antimicrobials and promoting strict adherence to established infection control practices.

Addresses
[1] Medical Service 111(W), Louis Stokes Cleveland VA Medical Center, 10701 East Blvd., Cleveland, OH 44106, United States
[2] Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, United States

Corresponding author: Rice, Louis B (louis.rice@va.gov)

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Introduction

The emergence and spread of antimicrobial resistance in pathogenic bacteria takes many forms, but always represents a process of evolution in response to selective antimicrobial pressure. This selective pressure is most commonly generated by human production and use of antimicrobial agents. The clinical impact of antimicrobial resistance may be great or insignificant, depending on the level of resistance, the site of infection, and the availability of effective, nontoxic therapeutic alternatives.

The past decade has witnessed some changes in the antimicrobial susceptibility landscape that have the potential to dramatically impact our effectiveness in treating community-acquired and hospital-acquired infections and alter the ways in which we practice medicine. In this article, I will focus on a few examples of evolving resistance that impact our treatment of patients in both the community and hospital setting: the fall and rise of resistant *Streptococcus pneumoniae*; the emergence and spread of community-acquired methicillin-resistant *Staphylococcus aureus*; the emergence and spread of cephalosporin-resistant and now fluoroquinolone-resistant *Escherichia coli*; the clonal spread of multiresistant *Enterococcus faecium*; the emergence and spread of carbapenem-resistant *Klebsiella pneumoniae* in the hospital setting and the continued evolution of extensively drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumanni* (Table 1).

Multiresistant *S. pneumoniae*

The extraordinary success of the *Haemophilus influenzae* B Hib vaccine at virtually eliminating *H. influenzae* meningitis in young children in the industrialized world led to concerted efforts by the pharmaceutical industry to develop protein conjugated vaccines against *S. pneumoniae*, which along with *Neisseria meningitides* replaced *H. influenzae* as the major cause of meningitis in that age group [1]. In comparison to the relative simplicity of the Hib vaccine, the development of an effective pneumococcal vaccine was complicated by the multitude of different serotypes that caused human infection. The rapid emergence and spread of multiresistant pneumococci during the 1980s and 1990s amplified the need for an effective vaccine. With these issues in mind, developers of the vaccine focused on including pneumococcal serotypes that were frequent causes of invasive disease and which were most likely to be resistant [2]. The seven-valent pneumococcal conjugate vaccine was introduced in the United States in 1999 and within a short period of time dramatically altered both the occurrence of invasive pneumococcal disease in the vaccine recipients and their contacts and the susceptibility patterns of the pneumococci that were isolated [3]. The decrease in the number of infections caused by resistant strains and the marked shift in the serotypes causing disease indicated a gratifying success in preventing infection by the vaccine serotypes that extended beyond vaccinated children to the community at large [3].

Between 2000 and 2006, the number of cases of invasive pneumococcal disease in the U.S. was reduced by roughly

Table 1

Selected pathogens, resistance phenotypes and underlying mechanisms.

Species	Resistance phenotype	Mechanism(s)
Streptococcus pneumoniae	β-Lactam	Low affinity Pbps
	Fluoroquinolone	Mutant topoisomerases
CA-MRSA	Penicillin	β-Lactamase
	Oxacillin	Low affinity Pbp
	Clindamycin	Constitutive erm expression
	Vancomycin	Mechanism unclear
Enterococcus faecium	Ampicillin	Low affinity Pbp
	Vancomycin	Altered peptidoglycan precursor
	Linezolid	Mutant ribosomal RNA genes
	Daptomycin	Mechanism unclear
Escherichia coli	Cephalosporins	CTX-M β-lactamases
	Fluoroquinolones	Mutant topoisomerases
		Qnr enzymes
		Modifying enzyme (Ciprofloxacin)
		Efflux pumps (intrinsic and acquired)
Klebsiella pneumoniae	Cephalosporins	ESBLs (variety)
	Carbapenems	KPC-type β-lactamases
	Fluoroquinolones	Mutant topoisomerases
		Qnr enzymes
		Modifying enzyme (Ciprofloxacin)
		Efflux pumps (intrinsic and acquired)
Acinetobacter baumanni	Carbapenems	OXA-type β-lactamases
	Amikacin	Ribosomal methylase
Pseudomonas aeruginosa	Carbapenems	Metallo-β-lactamases
		AmpC/porin reduction combinations
	Aminoglycosides	Modifying enzymes
	Fluoroquinolones	Mutant topoisomerases
		Efflux pumps (intrinsic and acquired)

one-third (from 60 000 to 41 400) (http://www.cdc.gov/ncidod/dbmd/Diseaseinfo/drugresisstreppneum_t.htm). The percentage of infections caused by resistant strains reduced only slightly (from 40 to 38%) over that time span. The only serotype for which both prevalence and resistance increased was serotype 19A [4•], which is not included in the seven-valent vaccine. While this may reflect the expansion of serotype 19A pneumococci into a niche abandoned by the vaccine susceptible strains, data from populations unexposed to the vaccine have also shown a shift to more infections owing to resistant 19A strains [5•], suggesting that the reductions in serotype strains and the expansion of 19A strains may be occurring in parallel, without necessarily being cause and effect. In regions where vaccine has yet to be introduced, the emergence of resistant 19A strains appears to be associated with the increasing use of antibiotics [5•], emphasizing the importance of judicious use of antimicrobial agents even in settings where the seven-valent vaccine has reduced invasive pneumococcal disease. So while the introduction of the seven-valent vaccine was an unqualified success, the remarkable ability of *S. pneumoniae* to evolve to both antibiotic resistance and to serotype challenges suggests that staying ahead of resistance in this species will be a continuing challenge.

Community-associated methicillin-resistant *S. aureus*

The introduction of penicillin into clinical use in the 1940s led to a dramatic reduction in the morbidity and mortality associated with *S. aureus* infections [6]. The clinical use of penicillin was soon associated with the emergence and rapid spread of *S. aureus* strains resistant by virtue of production of β-lactamase, first in the hospital and shortly thereafter in the community. Although data on the genotypes of those original strains are sparse, common wisdom holds that β-lactamase production in *S. aureus* spread primarily through the transmission of β-lactamase-producing plasmids from strain to strain (probably via the many *S. aureus* bacteriophages) [7]. Shortly after the introduction of methicillin in 1961, which is resistant to hydrolysis by the *S. aureus* β-lactamase, methicillin-resistant strains appeared [8]. Resistance to methicillin was conferred by the expression of low affinity penicillin-binding protein Pbp2a, which was chromosomally encoded and not readily transferable. Spread of these strains throughout the world's hospitals has been largely clonal and promoted by poor hygiene practices in the hospitals. As a consequence of this epidemiology, strict infection control practices have been shown to reduce rates of methicillin resistance in all countries [9•].