Pathogens Resistant to Antibacterial Agents

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KEYWORDS

- Drug resistance • Methicillin-resistant *Staphylococcus aureus*
- Vancomycin-resistant *Enterococcus*
- Vancomycin intermediate-susceptible *Staphylococcus aureus*
- Extended-spectrum β-lactamase
- Penicillin-resistant *Streptococcus pneumoniae*
- *Klebsiella pneumoniae* carbapenemase
- *Acinetobacter baumanii*

Multidrug-resistant pathogens historically were limited to the hospital setting. In the 1990s, multidrug-resistant pathogens were described to be affecting outpatients in health care–associated settings (nursing homes, dialysis centers, infusion centers, among patients recently hospitalized). More recently, multidrug-resistant pathogens have become major issues in the community, affecting persons with limited or in many cases no contact with health care. This article reviews the molecular mechanisms by which resistance traits are conferred and disseminated and the epidemiology of such bacterial resistance.

MECHANISMS OF RESISTANCE

It is important to distinguish the many ways by which an organism may demonstrate resistance. Intrinsic resistance to an antimicrobial agent characterizes resistance that is an inherent attribute of a particular species; all organisms of the species may lack the appropriate drug-susceptible target or possess natural barriers that prevent an antimicrobial agent from reaching its target. Some examples are the natural resistance of gram-negative bacteria to vancomycin because the drug cannot penetrate the

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gram-negative outer membrane, or the intrinsic resistance of the penicillin-binding proteins (PBPs) of enterococci to the effects of the cephalosporins.

Acquired resistance, the primary focus of this article, reflects a change in the genetic composition of a bacterium so that a drug that once was effective is no longer active, resulting in clinical resistance. Sometimes genetic change results in diminished antimicrobial activity, but not complete loss of drug effectiveness.

The major strategies used by bacteria to avoid the actions of antimicrobial agents are outlined in **Table 1**. These include limiting the intracellular concentration of an antimicrobial agent by decreased influx or increased efflux, neutralization of the antimicrobial agent by enzymes, alteration of the target so that the agent no longer interferes with it, and elimination of the target altogether by the creation of new metabolic pathways.[1] Bacteria may use one or multiple mechanisms against a single agent or class of agents or a single change may result in resistance to several different agents or even multiple unrelated drug classes.

Gram-positive and gram-negative bacteria possess different structural characteristics and these differences determine the mechanisms for primary resistance. The targets of most antimicrobial agents are located either in the cell wall, cytoplasmic membrane, or within the cytoplasm. In gram-negative bacteria, the outer membrane may provide an additional intrinsic barrier that prevents drugs from reaching these targets. Additionally, modifications in outer membrane permeability by both alterations in porin channels and by upregulation of multidrug efflux pumps may contribute to resistance in many gram-negative organisms. Moreover, inactivating enzymes released across the cytoplasmic membrane can function more efficiently within the confines of the periplasmic space.

The mechanisms by which intracellular concentrations of drugs are limited include decreased outer membrane permeability, decreased uptake through the cytoplasmic

Table 1
General mechanisms of resistance to antimicrobial agents

Resistance Mechanism	Specific Examples	References
Diminished intracellular drug concentration		
Decreased outer membrane permeability	β-Lactams (eg, OmpF, OprD)	2
Decreased cytoplasmic membrane transport	Quinolones (eg, OmpF)	1
	Aminoglycosides (decreased energy)	3
Increased efflux	Tetracyclines (eg, tetA)	195
	Quinolones (eg, norA)	196
	Macrolides (eg, mefA)	196
	Multiple drugs (eg, mexAB-OprF)	2
Drug inactivation (reversible or irreversible)	β-Lactams (β-lactamases)	95
	Carbapenemases (carbapenems)	105,96
	Aminoglycosides (modifying enzymes)	3
	Chloramphenicol (inactivating enzymes)	1
Target modification	Quinolones (gyrase modifications)	6
	Rifampin (DNA polymerase binding)	6
	β-Lactams (PBP changes)	6
	Macrolides (rRNA methylation)	5
	Linezolid (23srRNA modifications)	58
Target bypass	Glycopeptides (vanA, vanB)	7
	Trimethoprim (thymidine-deficient strains)	—