Microbiology

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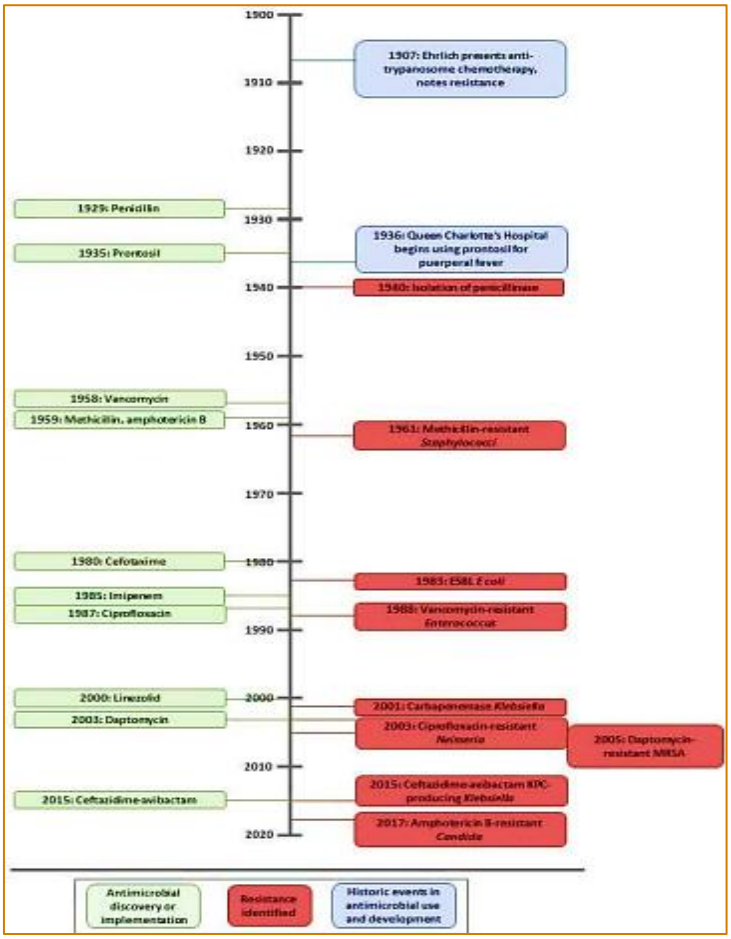
Antimicrobial resistance mechanisms of bacteria

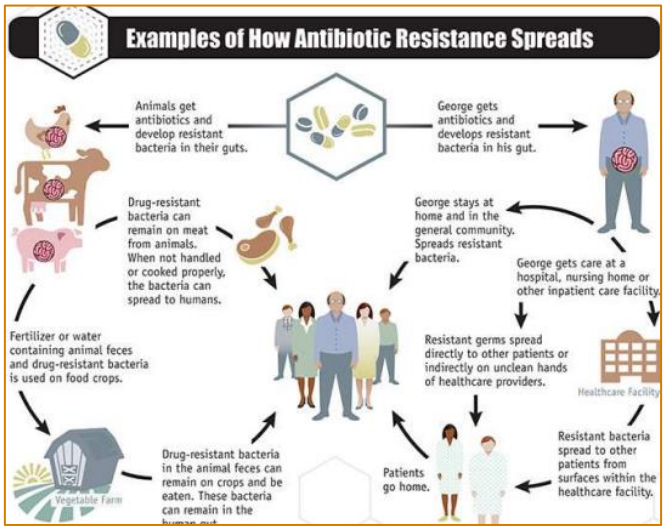
- **Antimicrobial Resistance Mechanisms of Bacteria**
  - Antibiotics originated from the evolutionary conflict between microbes and ecological competitors.
  - Resistance to antibiotics is predictable as microbes can develop resistance to some agents.
  - Antimicrobial resistance has worsened the impact of infectious diseases, increasing infections and healthcare costs.
  - Antimicrobial agents are classified based on their mechanisms of action.
  - Susceptibility and resistance are measured by minimum inhibitory concentration (MIC), which is the lowest drug concentration that inhibits bacterial growth.
  - If the average MIC for a species falls in the resistant range, the species is considered intrinsically resistant to that drug.
  - Bacteria can acquire resistance genes from related organisms, and the level of resistance varies depending on the species and acquired genes.



- ***Mechanism of antimicrobial:***

Mechanism of Action	Antimicrobial Groups
Inhibit Cell Wall Synthesis	β-Lactams
	Carbapenems
	Cephalosporins
	Monobactams
	Penicillins
	Glycopeptides
Depolarize Cell Membrane	Lipopeptides

Inhibit Protein Synthesis	Bind to 30S Ribosomal Subunit
	Aminoglycosides
	Tetracyclines
	Bind to 50S Ribosomal Subunit
	Chloramphenicol
	Lincosamides
	Macrolides
	Oxazolidinones
	Streptogramins
Inhibit Nucleic Acid Synthesis	Quinolones
	Fluoroquinolones
Inhibit Metabolic Pathways	Sulfonamides
	Trimethoprim



- Emergence and Spread of Antibiotic-Resistant Bacteria
  - ✓ Natural Resistance:
    - *Intrinsic resistance* is a trait shared universally within a bacterial species, independent of previous antibiotic exposure, and not related to horizontal gene transfer.
    - Common mechanisms of intrinsic resistance include reduced permeability of the outer membrane (especially LPS in Gram-negative bacteria) and natural activity of efflux pumps.
- Acquired Resistance:
  - ✓ Methods of Acquiring Resistance:
    - Horizontal gene transfer (transformation, transposition, and conjugation).
    - Resistance may be temporary or permanent.
    - Plasmid-mediated transmission of resistance genes is the most common method of acquiring external genetic material.

- **Mechanisms of Resistance**
  - Main Mechanisms of Resistance:

1. Limiting Drug Uptake:
   - ✓ LPS structure in Gram-negative bacteria blocks the entry of large antimicrobial agents [innate resistance]
   - ✓ Mycobacteria have a lipid-rich outer membrane, facilitating access for hydrophobic drugs such as rifampicin and the fluoroquinolones but limiting access for hydrophilic drugs.
   - ✓ Bacteria lacking a cell wall (e.g., Mycoplasma) are naturally resistant to drugs targeting the cell wall (e.g., β-lactams, glycopeptides) [innate resistance].
   - ✓ **Biofilm:**
     - The biofilm matrix is thick and sticky, containing polysaccharides, proteins, and DNA from bacteria.
     - This consistency makes it difficult for antimicrobial agents to reach the bacteria.
     - Higher concentrations of drugs are needed to be effective against bacteria in biofilms.

2. Modification of Drug Targets:
   - ✓ Alterations in penicillin-binding proteins (PBPs) mediate resistance to β-lactam drugs.
   - ✓ Mutations in ribosomal subunits or methylation of ribosomal subunits lead to resistance against ribosome-targeting drugs.
   - ✓ Modifications in DNA gyrase or topoisomerase IV result in resistance to nucleic acid synthesis-targeting drugs.

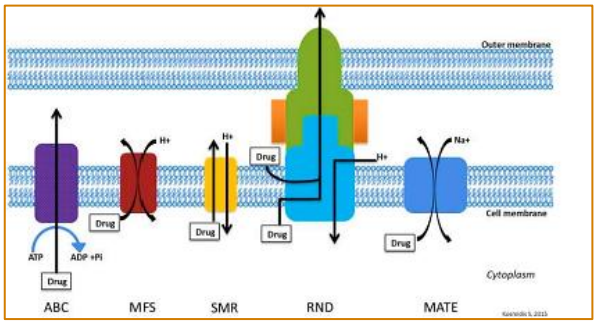
3. Drug Inactivation:
   - ✓ Bacteria can degrade drugs or transfer chemical groups to drugs, like the β-lactamases (originally called penicillinases and cephalosporinases), which hydrolyze the β-lactam ring structure, preventing it from binding to PBPs.
     - **Beta-lactam Resistance as an Example**
       - Mechanisms of Resistance to Beta-lactam Drugs:
         1. Preventing the interaction between PBPs and the drug (via modifications to PBPs or acquisition of new PBPs).
         2. Efflux pumps that expel β-lactam drugs.
         3. Hydrolysis of the drug by β-lactamase enzymes.

     - Beta-lactamase inhibitors are antibiotics that are co-administered with beta-lactam antibiotics.
     - Their purpose is to prevent bacteria from disabling beta-lactam antibiotics using their enzymes.

Table 3. Antimicrobial resistance mechanisms.

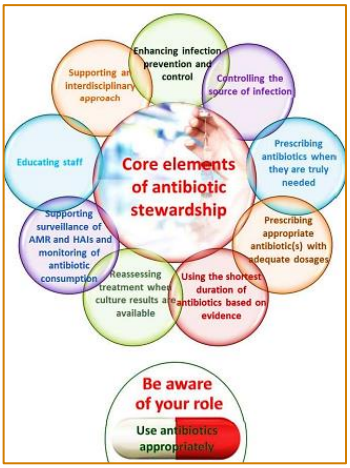
Drug	Drug Uptake Limitation	Drug Target Modification	Drug Inactivation	Efflux Pumps
β-Lactams	Decreased numbers of porins, no outer cell wall	Gram pos—alterations in PBPs	Gram pos, gram neg—β-lactamases	RND
Carbapenems	Changed selectivity of porin			
Cephalosporins	Changed selectivity of porin			
Monobactams				
Penicillins				
Glycopeptides	Thickened cell wall, no outer cell wall	Modified peptidoglycan		
Lipopeptides		Modified net cell surface charge		
Aminoglycosides	Cell wall polarity	Ribosomal mutation, methylation	Aminoglycoside modifying enzymes, acetylation, phosphorylation, adenylation	RND
Tetracyclines	Decreased numbers of porins	Ribosomal protection	Antibiotic modification, oxidation	MFS, RND
Chloramphenicol		Ribosomal methylation	Acetylation of drug	MFS, RND
Lincosamides		Gram pos—ribosomal methylation		ABC, RND
Macrolides		Ribosomal mutation, methylation		ABC, MFS, RND
Oxazolidinones		Ribosomal methylation		RND
Streptogramins				ABC
Fluoroquinolones		Gram neg—DNA gyrase modification Gram pos—topoisomerase IV	Acetylation of drug	MATE, MFS, RND
Sulfonamides		DHPS reduced binding, overproduction of resistant DHPS		RND
Trimethoprim		DHFR reduced binding, overproduction of DHFR		RND

4. Active Drug Efflux:
   - ✓ Efflux pumps in bacteria transport toxic substances out of the cell, often leading to multidrug resistance (MDR).
   - ✓ High-level resistance is often due to mutations modifying the transport channels of these pumps.



- **Important Acronyms in Antimicrobial Resistance**
  - AMR: Antimicrobial Resistance.
  - MDR: Multidrug-Resistant.
  - XDR: Extensively Drug-Resistant.
  - ESKAPE: Refers to six highly virulent and antibiotic-resistant bacteria: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.*
  - ESBL(Extended spectrum β-lactamase) : are enzymes that confer resistance to most betalactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam.
    - ✓ The gastrointestinal tract is the main reservoir for ESBL-producing Enterobacteriaceae.
    - ✓ Colonization with these organisms increases the risk of subsequent infection.
    - ✓ Healthcare-related factors like hospitalization, long-term care facility residence, hemodialysis use, and intravascular catheter presence are strongly associated with colonization and infection.

- **The Global Situation of Antimicrobial Resistance**
  - AMR: Global threat causing 700,000 deaths annually.
  - Projected Impact by 2050: AMR could lead to 10 million deaths and $100 trillion in economic losses.
  - Multidrug Resistance (MDR) is common, especially in hospitals, with the risk of entering a "post-antibiotic era."
  - Consequences: Longer hospital stays, higher medical costs, and increased mortality.
  - Antibiotic Resistance is a natural occurrence but is accelerating due to misuse in humans and animals.
  - WHO Efforts: WHO coordinates a global campaign to raise awareness and promote best practices among the public and professionals.



- **WHO's Efforts to Combat AMR**
  - WHO released a priority list of antibiotic-resistant pathogens in 2017.
  - AWaRe Classification: Antibiotics categorized into three groups (Access, Watch, Reserve) to guide appropriate use and reduce resistance.

- **The Situation in Low- and Middle-Income Countries (LMICs)**
  - Economic Factors:
    - ✓ LMICs lack resources (healthcare infrastructure, functional facilities) for large populations, especially in rural areas.
    - ✓ Limited access to qualified healthcare workers.
    - ✓ Antibiotics sold over the counter (OTC) without prescriptions, even for viral infections.
  - Sociological Factors:
    - ✓ Lack of education and awareness about proper antibiotic use.
    - ✓ Cultural myths and practices lead to the inappropriate use of antibiotics.
    - ✓ Patients demand antibiotics, even when unnecessary, leading to misuse.
  - Industrial Factors:
    - ✓ Decreased focus on infectious disease research and development (R&D) for antibiotics.
    - ✓ Remaining antibiotics are increasingly expensive and unaffordable in many LMICs.
    - ✓ Pharmaceutical companies' incentives further promote unnecessary antibiotic use.
  - Ecological Factors:
    - ✓ AMR requires an ecological approach and the concept of "One Health."
    - ✓ Overuse of antibiotics in food-producing animals, contributing to resistance.
  - Technological Factors:
    - ✓ Limited availability of rapid diagnostic technologies for infections and AMR.
    - ✓ Lack of real-time data and surveillance for better decision-making.

- **Tackling Antimicrobial Resistance**
  - Prevention Strategies:
    - ✓ Promote rational drug use and better prescription practices.
    - ✓ Encourage awareness programs and policy changes to reduce misuse.
    - ✓ Improve research and development for new antibiotics.

- **The Situation in Jordan**
  - Antibiotic Use Without Prescription: 40.4% of the population in Jordan reported using antibiotics without a prescription.
  - Need for Data: There is a need for better data collection to understand the scale of AMR.
  - Proposal for AMR in Jordan:
    1. Reduction of the evolution of antimicrobial resistance.
    2. Synchronization with published clinical practice guidelines for the management of common and/ or serious infections.
    3. Integration of cost parameters.
    4. Encouragement of responsible prescription practices among physicians and dispensing among pharmacists.
    5. Assignment of multi-level prescription responsibility.

Questions

1. **What is the role of efflux pumps in bacterial resistance?**
   A. Enzymatically degrade antibiotics
   B. Prevent antibiotic entry into the cell
   C. Actively transport antibiotics out of the cell
   D. Modify antibiotic binding sites

2. **A young child presents with meningitis caused by *Streptococcus pneumoniae*. The strain is resistant to penicillin. What is the most likely resistance mechanism?**
   A. Alteration of the 30S ribosomal subunit
   B. Beta-lactamase production
   C. Modification of penicillin-binding proteins
   D. Decreased membrane permeability

3. **Which of the following strategies is most effective in reducing the development of antimicrobial resistance?**
   A. Using broad-spectrum antibiotics for all infections
   B. Encouraging over-the-counter antibiotic access
   C. Completing prescribed antibiotic courses and limiting unnecessary use
   D. Relying solely on vaccines to control bacterial infections

4. **What is the primary mechanism of resistance to fluoroquinolones in bacteria?**
   A. Production of efflux pumps
   B. Modification of topoisomerase and DNA gyrase enzymes
   C. Enzymatic inactivation of the antibiotic
   D. Alteration of the 30S ribosomal subunit

5. **Which of the following bacteria is commonly associated with extended-spectrum beta-lactamase (ESBL) production?**
   A. *Escherichia coli*
   B. *Streptococcus pneumoniae*
   C. *Mycobacterium tuberculosis*
   D. *Clostridium difficile*

6. **Which of the following is NOT part of the ESKAPEE group of pathogens?**
   A. *Enterococcus faecium*
   B. *Escherichia coli*
   C. *Klebsiella pneumonia*
   D. *Salmonella Typhi*

7. **Why is the burden of antimicrobial resistance disproportionately higher in low-income and middle-income countries (LMICs)?**

Answers

1. **C.** Actively transport antibiotics out of the cell
2. **C.** Modification of penicillin-binding proteins
3. **C.** Completing prescribed antibiotic courses and limiting unnecessary use
4. **B.** Modification of topoisomerase and DNA gyrase enzymes
5. **A.** *Escherichia coli*: *Escherichia coli* is commonly associated with the production of extended-spectrum beta-lactamases (ESBLs), which provide resistance to many beta-lactam antibiotics.
6. **D.** *Salmonella Typhi: Salmonella Typhi* is not part of the ESKAPEE group, which includes pathogens like *Enterococcus faecium*, *Escherichia coli*, and *Klebsiella pneumoniae*, known for their multidrug resistance.
7. Antimicrobial resistance (AMR) is a global issue, but its impact is especially severe in low-income and middle-income countries (LMICs). Several factors contribute to this disparity:
   1) Limited Healthcare Access**:** Poor infrastructure and inadequate healthcare access lead to improper antibiotic use.
   2) Overuse and Misuse**:** Antibiotics are often available over-the-counter, contributing to misuse and overuse.
   3) Lack of Regulation**:** Weak regulatory systems lead to unmonitored antibiotic distribution and use.
   4) Poor Infection Control**:** Insufficient hygiene and sanitation practices in healthcare settings contribute to the spread of resistant bacteria.
   5) Inadequate Sanitation**:** Lack of clean water and proper sanitation increases infection rates and the need for antibiotics.
   6) Limited Diagnostics**:** A lack of diagnostic tools results in unnecessary broad-spectrum antibiotic prescriptions.
   7) Higher Disease Burden**:** Increased rates of infectious diseases lead to more antibiotic use, fostering resistance.
   8) Resource Limitations**:** Fewer resources for prevention, treatment, and new antibiotics exacerbate the problem.

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