Confronting the global threat of antimicrobial resistance

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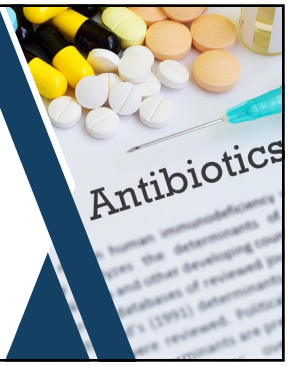
1

Objectives

1. Describe a variety of mechanisms that cause antibiotic resistance.
2. Explore the impact of antimicrobial resistance on public health.
3. Discuss current initiatives to combat antimicrobial resistance.



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The discovery of antibiotics...

...won the battle against infectious diseases

Unfortunately, that is not the case because many bacteria have become resistant to multiple antibiotics

3

Infectious Disease

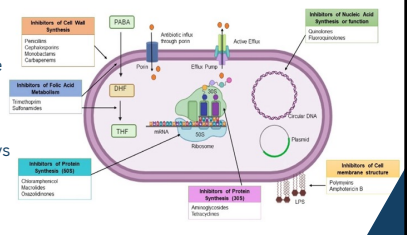
Major cause of morbidity and mortality worldwide

Included in Top 10 contributors to morbidity & mortality → Lower respiratory infection, Diarrheal disease, HIV/AIDS, Malaria

4

Antimicrobial Activity

- Inhibit cell wall synthesis
- Depolarize cell membrane
- Inhibit protein synthesis
- Inhibit nucleic acid synthesis
- Inhibit metabolic pathways in bacteria



5

Antimicrobial Activity

Antibiotics treat infections by influencing bacterial growth or viability

Bacterostatic

- **Inhibits growth**
- Antimicrobial removed → multiplication
- Successful if patient has effective immune system
- MIC performed in lab

Bactericidal

- **Kills bacteria**
- Preferred in serious infections (endocarditis, meningitis, osteomyelitis)
- Neutropenic patients

6

Antibiotic Pharmacodynamic Parameters

Antibiotic Class	Cidal or Static
Penicillins	Bactericidal
Cephalosporins	
Carbapenems	
Monobactams	
Vancomycin	Bactericidal (slowly)

Antibiotic Class	Cidal or Static
Fluoroquinolones	Bactericidal
Aminoglycosides	
Metronidazole	
Daptomycin	
Macrolides	Bacteriostatic
Tetracyclines	

7

Antimicrobial resistance caused by:

- Overuse of antibiotics
- Inappropriate prescriptions
- Agricultural practices

8

Impact on Public Health

Over 2 million people in U.S. have antimicrobial resistant infection

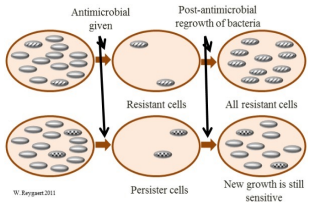
Increased morbidity & mortality
Emergence of resistant infections lead to fewer treatment options, higher rates of hospitalization, complications, and fatalities ~ Estimated 1.27 million deaths worldwide

Healthcare costs
Infections caused by resistant organisms may require extended hospitalization & more extensive treatment
Costs range from $7000 to more than $29,000 per patient

Challenges in treatment
Difficulties in effective treatment options, often resort to older, less effective medications with potentially more severe side effects

9

Persistence versus Resistance



If bacteria are **RESISTANT** to certain agent, then all daughter cells will be resistant

PERSISTANCE describes bacteria that are not susceptible to the agent, but do not possess resistant genes

2018 Jun 26;4(3):482–501. doi: 10.3934/microbiol.2018.3.482

10

Origins of Resistance

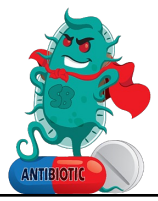
- Bacteria are not necessarily uniformly susceptible or resistant to a specific agent
- Levels of antimicrobial resistance vary within related bacterial groups
- Perform MIC (minimum inhibitory concentration) to determine susceptibility or resistance
- Bacteria may exhibit **natural resistance** or **acquired resistance**

11

Natural Resistance

May be intrinsic or induced

- **Intrinsic**
  - Trait shared universally within species
  - Always expressed in the species
  - Independent of previous exposure to antibiotic
- **Induced**
  - Genes are naturally in the bacteria, but only expressed after exposure to antibiotic



12

Examples of bacteria with intrinsic resistance

Organism	Intrinsic resistance
Bacteroides (anaerobes)	aminoglycosides, many β-lactams, quinolones
All gram positives	aztreonam
Enterococci	aminoglycosides, cephalosporins, lincosamides
Listeria monocytogenes	cephalosporins
All gram negatives	glycopeptides, lipopeptides
Escherichia coli	macrolides
Klebsiella spp.	ampicillin
Serratia marcescens	macrolides
Pseudomonas aeruginosa	sulfonamides, ampicillin, 1st and 2nd generation cephalosporins, chloramphenicol, tetracycline
Stenotrophomonas maltophilia	aminoglycosides, β-lactams, carbapenems, quinolones
Acinetobacter spp.	ampicillin, glycopeptides

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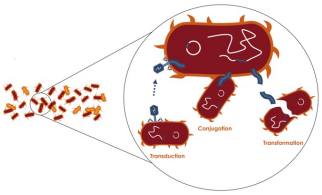
13

Acquired Resistance



- Acquisition of genetic material that confers resistance through transformation, transduction, or conjugation
- Bacteria may experience mutations to its own chromosomal DNA

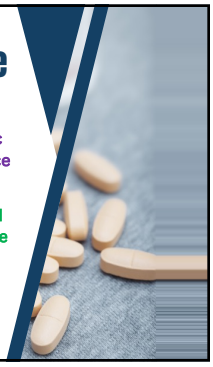
14

Mechanisms of Resistance

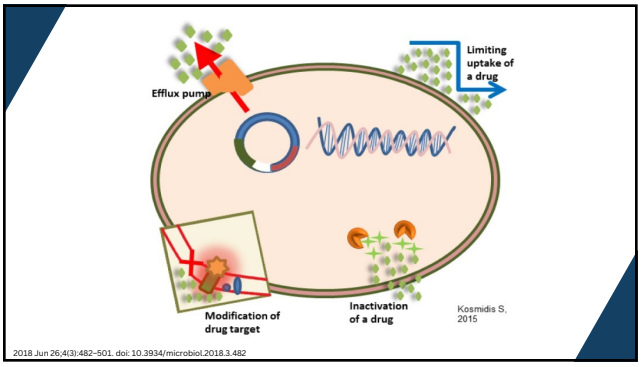
- Limiting drug uptake
- Modification of drug target
- Inactivation of drug
- Active drug efflux

Intrinsic resistance

Acquired resistance



15



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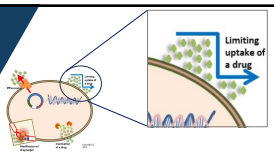
16



Limiting Drug Uptake

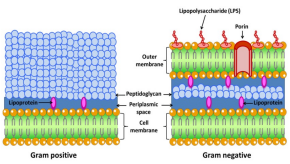
Outer membrane of bacterial cell affects uptake of antimicrobials

- **Gram negatives:** Lipopolysaccharide layer provides barrier
  - Innate resistance to certain antimicrobials
- **Mycobacteria:** High lipid content of outer membrane
  - Hyrdrophobic drugs can access the cell (rifampin, fluorquinolones)
- ***Mycoplasma:*** Lacks cell wall
  - Intrinsic resistance to all drugs that target cell wall (*B*-lactams, glycopeptides)

17

Limiting Drug Uptake

Gram positive organisms



- Enterococci
  - Difficult for polar molecules (aminoglycosides) to penetrate cell wall
- *Staphylococcus aureus*
  - Unexplained mechanism causes a thickened cell wall leading to resistance to vancomycin

Nanomaterials, 12(2), 288. https://doi.org/10.3390/nano12020288

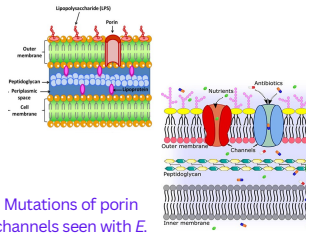
18

Limiting Drug Uptake

Gram negative organisms

Changes in porin channels
- Decrease in number of porins present
- Mutation of porin channel

Enterobacteriaceae reduce porin number causing resistance to carbapenems



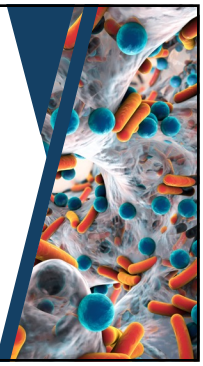
Mutations of porin channels seen with *E. aerogenes* (imipenem & cephalosporins) and *N. gonorrohoeae* (b-lactams and tetracycline)

Nanomaterials, 12(2), 288. https://doi.org/10.3390/nano12020288
Chem. Rev. 2021, 121, 9, 5158–5192

19

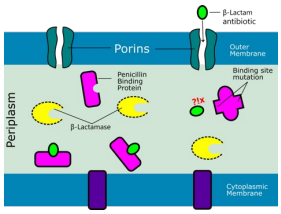
Limiting Drug Uptake ~ Biofilms

- Biofilms protect bacteria from immune response and antimicrobial agents
- Matrix contains polysaccharides, proteins, and DNA of bacteria
- Higher concentrations of the drug is necessary to be effective
- Bacteria in the biofilm have slow metabolism and slow cell division, so drugs that target active, dividing cells have little effect



20

Modification of Drug Target



- Alteration of structure and/or number of PBPs (penicllin-binding protein)
  - Affects drug binding to target
  - One mechanism of resistance to *B*-lactam drugs

21

Modification of Drug Target

- Gram negatives have intrinsic resistance to glycopeptides and lipopeptides
  - Glycopeptides (e.g. vancomycin) inhibit cell wall synthesis
  - Lipopeptides (e.g. daptomycin) depolarize cell membrane
- Vancomycin resistance in enterococci
  - Due to *van* gene that cause change in structure of peptidoglycan precursor - leads to inability of vancomycin to bind
- Daptomycin requires calcium for binding
  - Gene mutation may change charge of cell membrane, inhibiting binding of calcium, and therefore daptomycin

22

Modification of Drug Target

- Ribosomal mutations interfere with ability of drugs that bind to the ribosome
  - e.g. aminoglycosides, macrolides, tetracyclines
- Modification in DNA gyrase or topoisomerase IV affect binding ability of drugs that target nucleic acid synthesis
  - Fluoroquinolones
- Mutations of enzymes interfere with drugs that inhibit metabolic pathways
  - Sulfonamides
  - Trimethoprim

23

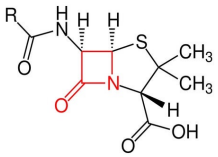
Drug Inactivation

- Degradation of drug
  - Bacteria produce hydrolyzing enzymes, like *B*-lactamase, inactivate *B*-lactam drugs
- Transfer of chemical group to drug
  - Acetyl group, causes acetylation to inactivate aminoglycosides and chloramphenicol
  - Phosphoryl group, causes phosphorylation to inactivate aminoglycosides

24

B-lactam drugs

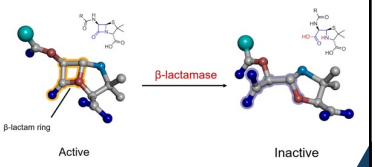
- *B*-lactam ring is a core structure in all *B*-lactam drugs
- Resistance to *B*-lactam drugs:
  - Inability of drug to bind to target PBP
  - Efflux pumps that force out *B*-lactam drugs
  - Hydrolysis of drug by ***B*-lactamase** enzymes



25

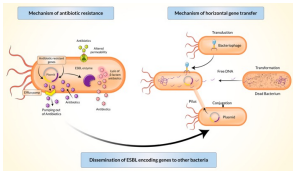
B-lactamase

- Enzyme that hydrolyzes the *B*-lactam ring
  - Drug unable to bind to target, therefore making it inactive
  - Variety of *B*-lactamase enzymes
  - May be acquired via a plasmid or innately in the bacterial chromosome



26

B-lactamase



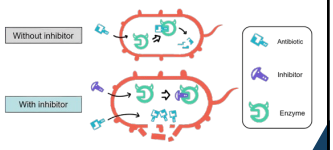
- Vital resistance mechanism against penicillin and cephalosporins
- Most common resistant mechanisms in gram negatives
  - *E. coli* - Overexpression of the *ampC* gene
  - *bla* gene - resistance to later generation cephalosporins - **ESBL**
    - Resistant to multiple drug classes

Biomedicines 2023, 11(1), 2937; https://doi.org/10.3390/biomedicines11112937

27

B-lactamase inhibitor

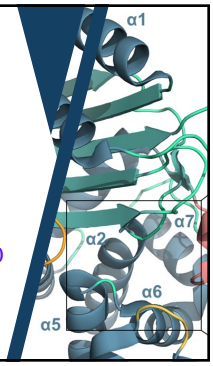
- Structurally similar to B-lactamase
- Very weak antimicrobial activity independently
- **Synergistic with *B*-lactam drug**
- Common pairings:
  - Amoxicillin/clavulinic acid
  - Ampicillin/sulbactam
  - Pipercillin/tazobactam



28

Carbapenemase

- *B*-lactamases that are active against carbapenems
- ***Klebsiella pneumoniae* carbapenemase (KPC)**
  - Resistant to all *B*-lactam drugs, but may be sensitive to *B*-lactamase inhibitors
- **Carbapenem-Resistant Enterobacterales (CRE)**
  - Resistant to all *B*-lactam drugs and not inactivated by *B*-lactamase inhibitors
  - Up to 71% mortality rate



29

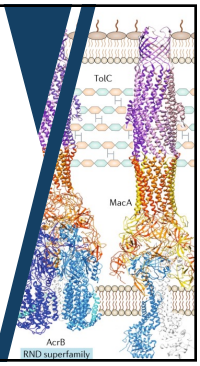
Development of new *B*-lactamase inhibitors

- Trying to battle CRE
- Ceftolozane/tazobactam
  - *P. aeruginosa*
  - Possible ESBL producing strains of gram-negative organisms
- Avibactam
  - Being tested for use with aztreonam against CREs
- Vaborbactam
  - Used with meropenem

30

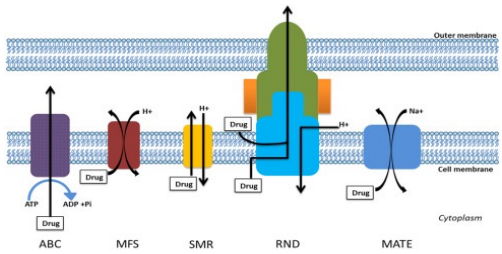
Active Drug Efflux

- Efflux pumps present on most bacteria
  - Primary function: Rid toxins from bacterial cell, transporting them across cytoplasmic membrane
- Efflux mechanisms can confer resistance to specific drugs, resulting in MDR
- Intrinsic efflux mechanism of resistance is activated by environmental signals or genetic mutation
- *P. aeruginosa* and *E. faecalis*



31

Drug Efflux



AIMS Microbiol. 2018 Jun 26;4(3):482–501. doi: 10.3934/microbiol.2018.3.482

32

CDC's Antimicrobial Resistance Laboratory Network

ARLabNetwork

- First network in U.S. to provide thorough antimicrobial resistance testing
- Collective effort
  - Includes 7 reference labs, the National Tuberculosis Molecular Surveillance Center, and labs across all 50 states
- Identify, track, and respond to antimicrobial resistant threats

33

ARLabNetwork

- Carbapenem-resistant Enterobacterales
- MBL-producing Enterobacterales
- Carbapenem-resistant *P. aeruginosa*
- Carbapenem-resistant *A. baumannii*
- Azole-resistant *Aspergillus fumigatus*
- Antifungal-resistant *Candida*
- Drug-resistant *N. gonorrhoeae*
- Drug-resistant *M. tuberculosis*
- Drug-resistant *S. pneumoniae*
- *Clostridium difficile*

34

2017-2023

ARLabNetwork

362,009 Total carbapenem-producing and carbapenem-resistant isolates

- 120,752 Carbapenem-resistant isolates
- 88,384 Carbapenem-resistant *Pseudomonas aeruginosa* isolates
- 25,370 Carbapenem-resistant *Acinetobacter baumannii* isolates
- 127,503 Carbapenem-producing organism screenings

https://www.cdc.gov/antimicrobial-resistance-laboratory-networks/php/about/domestic.html

35

- CDC and FDA have a collection of isolates gathered from national reference labs
- Accomplishments of the AR Isolate Bank:
  - Validate laboratory testing
  - Research and development of drugs and diagnostic tests
  - Testing for drug efficacy
  - Study pathogenic mechanisms and genotypic basis of resistance
  - Detect public health threats and rapidly recommend infection control measures

AR ISOLATE BANK

https://www.cdc.gov/antimicrobial-resistance/php/public-health-strategy/index.html

36

Public Awareness & Education

Importance of Awareness Campaigns
Public awareness campaigns serve as a vital tool in educating the population about the significance of antimicrobial resistance and the importance of taking antibiotics responsibly

Community Engagement
Fostering community engagement through local initiatives encourages collective responsibility for antimicrobial stewardship, enhancing adherence to guidelines

Role of Media
The media plays a significant role in shaping public perception of antimicrobial resistance and can amplify messages about prevention and the importance of proper antibiotic use

37

CDC
Fighting Antimicrobial Resistance
TAKES ALL OF US
November 18-24, 2024

Raise awareness of the importance of appropriate antibiotic and antifungal use and the growing threat of antimicrobial resistance

Antimicrobial resistance may affect anyone and can spread rapidly within healthcare facilities and the community

38

World Health Organization

World Health Organization (WHO) launched a Global Action Plan on antimicrobial resistance

Emphasizes the importance of surveillance, infection prevention, and responsible antibiotic use

39

Role of Healthcare Professionals

Prescribing practices: Adhere to evidence-based guidelines when prescribing antibiotics

Patient education: Educate patients about appropriate use of antibiotics and the risks associated with antimicrobial resistance

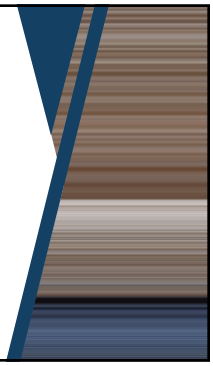
Infection control measures: Implementing rigorous infection control protocols in healthcare settings to minimize the spread of resistant pathogens

40

Role of the Consumers

Wash your hands: The best way to prevent infections is keeping your hands clean

Use antimicrobial agents appropriately: Take them as prescribed; do not share antibiotics with others; do not save them for later; antibiotics do not work on viruses



41

"Preventing infections in the first place is our first line of defense against antimicrobial resistance. Access to clean water and adequate sanitation, vaccination coverage, and access to quality health care can prevent infections and the spread of antimicrobial resistance worldwide. Improving appropriate antibiotic and antifungal use is also critical. Appropriate use of antibiotic and antifungal drugs helps improve patient outcomes by optimizing the treatment of infections, avoiding drug-related side effects, and slowing the development of antimicrobial resistance"

https://www.cdc.gov/antimicrobial-resistance/communication-resources/usaaw.html

42

Thank you!

43

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44