Management of Antibiotic Resistant Pathogens

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Conflicts of Interest

• None
Goals of Lecture

• Current anti-infectives
  » Antibiotic development
• Antimicrobial Resistance
  » Factors impacting development and spread of resistance
  » Mechanisms of Action
  » Mechanisms of Resistance
  » Methods for Testing Resistance
• Practical classification of microbes for choosing an antibiotic
  » Diagnosis
  » Choosing an appropriate antibiotic therapy
• Methods for Testing Resistance
• Summary of Dealing with Resistant Pathogens

TRENDS IN ANTIMICROBIAL DEVELOPMENT

• Fewer companies producing antibiotics and few antibiotics introduced

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

*Intervals from 1982-2010 are 5-year intervals. 2010-2017 is a 3-year interval. Drugs are limited to systemic agents.
*Data courtesy of FDACS Center for Drug Evaluation and Research (2019).
TRENDS IN ANTIMICROBIAL DEVELOPMENT

- Broader spectrum
- Reduced dosing frequency
- Novel mechanisms of action and coverage
- Modifications based on understanding structure-function relation
- Newly introduced agents focused on coverage of resistant *S. aureus* and *Enterococcus*, HIV, and fungi (especially uncommon *Candida* spp. and zygomycetes)

Antibiotics Approved Since 2010

<table>
<thead>
<tr>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftarolene</td>
<td>Telavancin*</td>
<td>Tedizolid</td>
<td>Dalbavancin</td>
<td>Oritavancin</td>
<td>Ceftolozane Tazobactam</td>
</tr>
</tbody>
</table>
Support the development of 10 new systemic antibacterial drugs through the discovery of new drug classes as well as exploring possible new drugs from existing classes of antibiotics.

Support the concurrent advancement of improved diagnostic tests specific to multidrug-resistant infections


Goals

Goal 1: Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections

Goal 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance

Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics and Vaccines

Goal 5: Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control and Antibiotic Research and Development
Key Terms

- Antibiotic = A drug that kills or inhibits the growth of microorganisms

- Resistant = Somewhat arbitrary designation that implies that an antimicrobial will not inhibit bacterial growth at clinically achievable concentrations

- Susceptible = Somewhat arbitrary designation that implies that an antimicrobial will inhibit bacterial growth at clinically achievable concentrations

Key Terms

- MIC = Minimal inhibitory concentration. Lowest concentration of antimicrobial that inhibits growth of bacteria. Commonly used in clinical lab

- MBC = Minimal bactericidal concentration. Concentration of an antimicrobial that kills bacteria. Used clinically only in special circumstances

- Breakpoint = The MIC that is used to designate between susceptible and resistant. Arbitrarily set by a committee
PRINCIPLES OF ANTIBIOTIC RESISTANCE
(Levy SB. NEJM, 1998)

1. Given sufficient time and drug use, antibiotic resistance will emerge
2. Resistance is progressive, evolving from low levels through intermediate to high levels
3. Organisms resistant to one antibiotic are likely to become resistant to other antibiotics
4. Once resistance appears, it is likely to decline slowly, if at all
5. The use of antibiotics by any one person affects others in the extended as well as the immediate environment

Selective Pressures: Antimicrobial Use and Resistance

The figure summarizes the current goals (purple boxes) in trying to minimize the emergence and spread of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB) in the environment and their transmission into the clinic. The current needs and limitations that must be resolved to achieve these goals are also shown (yellow boxes).

Antibiotic Use Leads to Antibiotic Resistance

- Resistant bacteria or their genetic determinates are selected when colonizing or infecting bacteria are exposed to antibiotics
- Resistant bacteria can then be transmitted between patients
- Highest risk patients:
  - Immunocompromised
  - Hospitalized
  - Invasive devices
    (central venous catheters)
Chart 1: Resistant Strains Spread Rapidly

Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant Pseudomonas aeruginosa (FQR). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

IDSA. Bad Bugs No Drugs. 2004
MDRO Organisms Are a Growing Threat

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:
At least 2,049,442 illnesses, 23,000 deaths
*bacteria and fungus included in this report

EMERGING RESISTANT PATHOGENS: COMMUNITY

- HIV:
  » Multiple antivirals
- *Pneumococcus*:
  » Multiple drugs (including penicillins/cephalosporins, macrolides)
- *Staphylococcus aureus*:
  » Multiple drugs (including oxacillin)
- Gram negative enterics:
  » Cephalosporins, carbapenems
- Group A streptococcus:
  » Macrolides, tetracyclines
- *Neisseria gonorrhoeae*:
  » Penicillin, tetracycline, quinolones
- *Salmonella typhimurium*:
  » Multidrug (amp-, TMP-SMX, +/-quinolones)
- *Mycobacterium tuberculosis*:
  » MDR (INH, rifampin), XDR (INH, rifampin, others)
ANTIBIOTIC RESISTANCE: FACTORS CONTRIBUTING TO SPREAD IN COMMUNITIES

- Increase in “high-risk” (immunodeficient) population
- Prolonged survival of persons with chronic diseases
- Congregate facilities (e.g., jails, day care centers)
- Lack of rapid, accurate diagnostic tests to distinguish between viral and bacterial infections
- Increased use of antibiotics in animals & agriculture

Reasons for Antibiotic Overuse:
Conclusions from 8 Focus Groups

Patient Concerns
- Want clear explanation
- Green nasal discharge
- Need to return to work

Physician Concerns
- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure

Antibiotic Prescription


EMERGING RESISTANT PATHOGENS: HEALTH CARE FACILITIES

- Staphylococcus aureus:
  » Oxacillin, vancomycin, linezolid
- Enterococcus:
  » Penicillin, aminoglycosides, vancomycin, linezolid, dalfopristin-quinupristin
- Enterobacteriaceae:
  » ESBL producers, carbapenems
- P. aeruginosa, Acinetobacter spp:
  » β-lactams including carbapenems
- Candida spp.:
  » Fluconazole
- Mycobacterium tuberculosis:
  » MDR (INH, rifampin); XDR (multiple)

ANTIBIOTIC RESISTANCE IN HOSPITALS: FACTORS CONTRIBUTING TO SPREAD IN HOSPITALS

- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community
- Ineffective infection control & isolation practices (esp. compliance)
- Increased use of antimicrobial prophylaxis
- Increased use of polymicrobial antimicrobial therapy
- High antimicrobial use in intensive care units

ESKAPE Pathogens

Enterococcus faecium (VRE)
Staphylococcus aureus (MRSA)
Klebsiella and Escherichia coli producing ESBL
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacteriaceae
MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile
Carbapenem-resistant Enterobacteriaceae
Drug-resistant Neisseria gonorrhoeae

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS

CARBAPENEM-RESISTANT ENTEROCOCCUS DRG.
7,900
1,400

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS

MICROORGANISMS WITH A THREAT LEVEL OF SERIOUS

Multidrug-resistant Acinetobacter
Drug-resistant Campylobacter
Fluconazole-resistant Candida (a fungus)
Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
Vancomycin-resistant Enterococcus (VRE)
Multidrug-resistant Pseudomonas aeruginosa
Drug-resistant non-typhoidal Salmonella
Drug-resistant Salmonella Typhi
Drug-resistant Shigella
Methicillin-resistant Staphylococcus aureus (MRSA)
Drug-resistant Streptococcus pneumoniae
Drug-resistant tuberculosis
**Mechanisms of Action of Antibiotics**

- **DNA replication**
- **Nucleotide biosynthesis**
- **Protein synthesis**
- **Topoisomerase**
- **mRNA transcription**
- **Protein synthesis**
- **Cell wall synthesis**

**β-lactams**
- Cephalosporins
- Carbapenems

**Fluoroquinolones**

**Sulfonamides**
- TMP-SMX

**Metronidazole**

**Peptide antibiotics**
- Cytoplasmic membrane integrity
- Rifampin

**Glycylcyclines**
- Aminoglycosides
- Macrolides
- Oxazolidinones
- Streptogramins
- Lincosamides
- Tetracyclines

**ANTIBACTERIALS: MECHANISMS**

- Interference with cell wall synthesis (bactericidal)
  - Penicillins: Oxacillin, ampicillin, piperacillin
  - Cephalosporins: $1^\circ$, $2^\circ$, $3^\circ$, $4^\circ$, $5^\circ$ cephalosporins
  - Carbapenems: Imipenem, meropenem, ertapenem, doripenem
  - Monobactams: Aztreonam
  - Glycopeptides: Vancomycin, Dalbavancin, Oritavancin, Telavancin

ANTIBACTERIALS: MECHANISMS

• Inhibition of DNA gyrase (bactericidal)
  » Quinolones: Ciprofloxacin, levofloxacin, moxifloxacin

• Interference with ribosomal function
  » Aminoglycosides (bactericidal): Gentamicin, tobramycin, amikacin
  » Tetracyclines: Tetracycline, minocycline, doxycycline
  » Glycylcyclines: Tigecycline
  » Macrolides: Erythromycin, azithromycin, clarithromycin
  » Chloramphenicol
  » Lincosamines: Clindamycin
  » Oxazolidinone: Linezolid
  » Streptogramin: Dalfopristin-quinupristin
ANTIBACTERIALS: MECHANISMS

- Antimetabolites
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole

- Inhibition of DNA-directed RNA polymerase
  - Rifampin, rifapentine, rifabutin

- Degradation of DNA
  - Metronidazole

- Cyclic lipopeptide (effects calcium transport)
  - Daptomycin

Mechanisms of Resistance

Antibiotic Degrading Enzymes

- Sulfonation, phosphorylation, or esterification
  - Especially a problem for aminoglycosides

- β-lactamases
  - Simple, extended spectrum β-lactamases (ESBL), cephalosporinases, carbapenemases
  - Confer resistance to some, many, or all beta-lactam antibiotics
  - May be encoded on chromosome or plasmid
  - More potent in gram-negative bacteria
Mechanisms of Resistance

Antibiotic Degrading Enzymes

• Extended spectrum β-lactamases
  » Can hydrolyse extended spectrum cephalosporins, penicillins, and aztreonam
  » Most often associated with *E. coli* and *Klebsiella pneumoniae* but spreading to other bacteria
  » Usually plasmid mediated
  » Multiple resistance genes (often Aminoglycoside, ciprofloxacin and trimethoprim-sulfamethoxazole) encoded on same plasmid

• Class A Carbapenemase
  » Most common in *Klebsiella pneumoniae* (KPC)
  » Also seen in *E. coli, Enterobacter, Citrobacter, Salmonella, Serratia, Pseudomonas* and *Proteus spp.*
  » Very often with multiple other drug resistance mechanisms, resistance profile similar to ESBL but also carbapenem resistant
  » Spreading across species to other gram-negatives and enterobacteriaceae

Mechanisms of Resistance

Decreased Permeability

• Affects many antibiotics including carbapenems

Efflux Pumps

• Tetracyclines
• Macrolides
Mechanisms of Resistance

Target Alteration

- DNA gyrase
  - Fluoroquinolones
- Penicillin-binding protein
  - Methacillin/penicillin
- Gram positive cell wall
  - Vancomycin
- Ribosome
  - Tetracyclines
  - Macrolides

Principles of Antibiotic Therapy

Empiric Therapy (85%)
- Infection not well defined ("best guess")
- Broad spectrum
- Multiple drugs
- Evidence usually only 2 randomized controlled trials
- More adverse reactions
- More expensive

Directed Therapy (15%)
- Infection well defined
- Narrow spectrum
- One, seldom two drugs
- Evidence usually stronger
- Less adverse reactions
- Less expensive
IMPACT OF ANTIMICROBIALS

![Bar chart showing hospital mortality percentages for all cause and infection-related cases with inadequate and adequate therapy](image)

Kollef Chest 115:462, 1999

DIAGNOSIS

- Gram stain
  - Often provide clues to etiology (may allow presumptive diagnosis in some cases)

- Gram Stain
  - Gram Positive
  - Gram Negative
  - Non-staining

- Shape
  - Cocci
  - Rods
GRAM POSITIVE ORGANISMS

- Gram positive cocci
  » *Staphylococcus aureus*
  » Coagulase negative staphylococcus
  » *Pneumococcus* sp.
  » *Streptococcus* sp.
  » *Enterococcus* sp.

- Gram positive rods
  » *Bacillus* sp. (aerobes)
  » *Clostridial* sp. (anaerobes)

GRAM NEGATIVE ORGANISMS

- Gram negative cocci
  » *Neisseria meningitidis*
  » *Neisseria gonorrhoeae*

- Gram negative rods (non-enteric)
  » *Pseudomonas aeruginosa*
  » *Stenotrophomonas maltophilia*
  » *Acinetobacter* sp.
  » *E. coli*
  » *Klebsiella* sp.
  » *Enterobacter* sp.
  » *Proteus* sp.
  » *Serratia* sp.
NON-STAINING PATHOGENS

• Not stained by Gram’s method
  » Legionella sp.
  » Chlamydia
  » Rickettsia
  » Mycobacteria
    • M. tuberculosis
    • Non-tuberculous mycobacteria

DIAGNOSIS

• Culture
  » “Gold standard”
  » Requires sampling of site of infection prior to therapy
  » Allows determination of antimicrobial susceptibility
Evidence for Efficacy

• *In vitro* activity (discussed later)
• Clinical trials
  » Gold standard = randomized clinical trial
  » Should be comparative (best available alternative)
  » Should use appropriate population
  » Small number precludes discovery of rare adverse reactions

Patient Safety

• Drug interactions
• Age
• Pregnancy, breast feeding
• Toxicity (idiosyncratic reactions)
• Dose adjustment for renal dysfunction
• Dose adjustment for hepatic dysfunction
• Ability to absorb an oral antibiotic
Adherence/compliance

- Frequency of administration
- Duration of therapy
- Multiple drug therapy
- Adverse effects
- Reduction of symptoms
- Taste
- Cost

COMPLIANCE RELATED TO DOSING

Cockburn J BMJ 1987
## Antibiotics with Gram (+) Activity

<table>
<thead>
<tr>
<th></th>
<th>S. aureus</th>
<th>MRSA</th>
<th>VRE</th>
<th>E. faecalis</th>
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</thead>
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<tr>
<td>Nafcillin/Oxacillin</td>
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<td>Amp/Sulb, Pip/Tazo</td>
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<td>Ceftaroline (only)</td>
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<tr>
<td>Carbapenems</td>
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<tr>
<td>Fluoroquinolones</td>
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<td>Vancomycin</td>
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<td>Vancomycin</td>
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<tr>
<td>Clindamycin</td>
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<td>Clindamycin +/-</td>
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<td>Quin/Dalf</td>
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<td>Daptomycin</td>
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<td>Daptomycin</td>
<td>Daptomycin</td>
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<tr>
<td>TMP-SMX</td>
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<td>TMP-SMX</td>
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</tr>
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</table>

## Antibiotics with Gram (-) Activity

<table>
<thead>
<tr>
<th></th>
<th>E. coli</th>
<th>K. pneumoniae</th>
<th>Enterobacter</th>
<th>P. aeruginosa</th>
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</thead>
<tbody>
<tr>
<td>Ampicillin</td>
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<td></td>
</tr>
<tr>
<td>Amp/sulb</td>
<td>Amp/sulb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>Piperacillin</td>
<td>Piperacillin</td>
<td>Pipacillin</td>
<td>Pipacillin</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>Pip/Tazo</td>
<td>Pip/Tazo</td>
<td>Pip/Tazo</td>
<td>Ceftaz/CEFPEM</td>
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<td>Cephalosporins</td>
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<td>3rd, 4th, 5th gen.</td>
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<tr>
<td>Carbapenems</td>
<td>Carbapenems</td>
<td>Carbapenems</td>
<td></td>
<td>Imip, Mero, Dori</td>
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<td>Aztreonam</td>
<td>Aztreonam</td>
<td>Aztreonam</td>
<td>Aztreonam</td>
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<tr>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
<td>Aminoglycosides</td>
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<tr>
<td>Fluoroquinolone</td>
<td>Fluoroquinolone</td>
<td>Fluoroquinolone</td>
<td>Fluoroquinolone</td>
<td>Cipro and Levo</td>
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<td>Trimeth/Sulf</td>
<td>Trimeth/Sulf</td>
<td>Trimeth/Sulf</td>
<td>Trimeth/Sulf</td>
<td></td>
</tr>
</tbody>
</table>
Antibiotics with Anti-anaerobic Activity

- β-lactams
  - Ampicillin/Sulbactam*, Piperacillin/Tazobactam*
  - Carbapenems (imipenem, meropenem, doripenem, ertapenem)*
  - Cefoxitin
  - Cefotetan

- Chloramphenicol
- Metronidazole*
- Clindamycin
- Tigecycline*  * Highly active

<table>
<thead>
<tr>
<th>Organism</th>
<th>Vancomycin</th>
<th>Daptomycin</th>
<th>Linezolid</th>
<th>Ceftaroline</th>
<th>Telavancin</th>
<th>Tedizolid</th>
<th>Oritavancin</th>
<th>Dalbavancin</th>
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</thead>
<tbody>
<tr>
<td><em>Streptococcus</em> Grp A,B,C,G</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Enterococcus faecalis</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Enterococcus faecium</td>
<td>±</td>
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<td>-</td>
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<td>+</td>
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</tr>
<tr>
<td>MSSA</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Coagulase-negative Staph.</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>VRE</td>
<td>-</td>
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<td>+</td>
<td>±3</td>
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<tr>
<td>VISA</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</tr>
<tr>
<td>VRSA</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant Enterococcus; VRSA, vancomycin-resistant *S. aureus*

1: Cefozolam/tazobactam has activity against some *Streptococcus* species, but not *Staphylococcus* species and is not included.
2: Not appropriate for respiratory tract infections (e.g., pneumonia); 3: Not active against *E. faecium*
### Comparison of Antimicrobials

<table>
<thead>
<tr>
<th>Organism</th>
<th>Meropenem</th>
<th>Piperacillin/tazobactam</th>
<th>Ceftriaxone</th>
<th>Cefepime</th>
<th>Ceftaroline</th>
<th>Cefozolane/tazobactam</th>
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</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>H. influenzae</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Klebsiella sp.</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Enterobacter sp.</td>
<td>+</td>
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<tr>
<td>Proteus mirabilis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Acinetobacter sp.</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>±</td>
<td>-</td>
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</tr>
<tr>
<td>ESBL-GNR</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>CRE</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

- CRE, carbapenemase resistant Enterobacteriaceae
- ESBL, extended β-lactamase producing Gram negative rods (E. coli, Klebsiella spp., Enterobacter spp.)
- GNR, Gram negative rods

### Methods for Testing Resistance and Efficacy
Methods for Testing Resistance: Minimal Inhibitory Concentration

Known quantity of bacteria placed into each tube

- 0.25 µg/mL
- 0.5 µg/mL
- 1.0 µg/mL
- 2.0 µg/mL
- 4.0 µg/mL
- 8.0 µg/mL
- 16 µg/mL

Increasing antibiotic concentration

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism


Methods for Testing Resistance: Automated Minimal Inhibitory Concentration

Well Plate for MIC Testing

Many Labs Use Automated Testing
**MIC**$_{90}$: Lowest Concentration That Inhibits Growth of 90% of Isolates

![Graph showing MIC values and MIC$_{90}$](image)

**Methods for Testing Resistance: Kirby-Bauer Disc Diffusion Test**

1. Add test bacteria to small amount of melted agar.
2. Pour over surface of nutrient agar plate, let gel.
3. Add paper disks with known dose of antibiotic to surface.
4. Incubate: antibiotic will diffuse into medium as cells grow.
5. Examine plate: look for clear zones around disk where growth is inhibited.
6. Measure diameter of clear zones.
Methods for Testing Resistance: E-test Strip

E-test®

Concept of Breakpoint to Determine Susceptibility

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>Breakpoint</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>&gt;16</td>
<td>8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
<td>4</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>&gt;16</td>
<td>N/A</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefepime</td>
<td>8</td>
<td>32</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>16</td>
<td>16/32</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2</td>
<td>32</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>4</td>
<td>16</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2</td>
<td>2</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amp/Sulbactam</td>
<td>&gt;16</td>
<td>8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>4</td>
<td>4/8</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Pip/tazo</td>
<td>8</td>
<td>32-64/128</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

EXAMPLE: Susceptibility testing for a single isolate of *Pseudomonas aeruginosa*

-Breakpoint for intermediate resistance for meropenem is 4 and for piperacillin/tazobactam (pip/tazo) 32

-Pip/tazo is the better choice between the two

-Ciprofloxacin is a poor choice even though the MIC is lowest of the three
Principles of Antibacterial Therapy:
Synergy and Antagonism of Antibiotics

**Synergy**
Log Number of Bacteria
- No Antibiotic
- A
- A + B

**Indifference**
Log Bacteria
- No Antibiotic
- A
- A + B

**Antagonism**
Log Bacteria
- No Antibiotic
- A
- A + B

Bacteriostatic agents which include most protein synthesis inhibitors (except aminoglycosides), prevent growth but don’t kill the organisms.

Principles of Antibacterial Therapy:
Bacteriostatic or Bactericidal

**Bacteriostatic**
- Control
- Log # bacteria

**Bactericidal**
- Bactericidal agents which include cell wall inhibitors (usually), quinolones, aminoglycosides, and daptomycin

Bactericidal agents required for meningitis, endocarditis and infections in neutropenic hosts.
# DEALING WITH RESISTANT PATHOGENS

## Community
- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated

## Hospital
- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Practice appropriate infection control
- Avoid prophylactic therapy unless supported by scientific evidence
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated
- Practice de-escalation
- Use early IV to PO switch

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