Principles of Antibiotic Use

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Conflicts of Interest

• None
Goals of Lecture

• **Current anti-infectives**
  » Antibiotic development
  » Mechanisms of action

• **Practical classification of microbes for choosing an antibiotic**
  » Diagnosis
  » Choosing an appropriate antibiotic therapy

• **Antimicrobial Resistance**
  » Factors impacting development and spread of resistance
  » Mechanisms of Resistance
  » Methods for Testing Resistance

• **Antibacterial Stewardship**
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 1960–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA’s Center for Drug Evaluation and Research (CDER).
TRENDS IN ANTIMICROBIAL DEVELOPMENT

- Therapy directed at emerging drug resistance
- 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)
CAVEATS IN EVALUATING NEW DRUGS

- Most studies powered to demonstrate equivalence
- Studies rarely (if ever) compare newer agents head to head (e.g., daptomycin versus linezolid, voriconazole versus caspofungin)
- Phase III study sizes preclude demonstrating rare side effects
- Phase III studies conducted in highly selected populations
  - May not uncover drug interactions
  - Will not demonstrate safety in all patient populations
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
Antibiotics Approved Since 2010

2010

Ceftaroline

2011

Telavancin*

2012

Tedizolid

2013

Dalbavancin

2014

Oritavancin

2015

Ceftazidime

Avibactam

Ceftolozane Tazobactam
Mechanisms of Action of Antibiotics

TMP-SMX = trimethoprim-sulfamethoxazole.

ANTIBACTERIALS: MECHANISMS

• Interference with cell wall synthesis (bactericidal)
  » **Penicillins:**
    • Oxacillin, ampicillin, piperacillin
  » **Cephalosporins:**
    • 1°, 2°, 3°, 4°, 5° cephalosporins
  » **Carbapenems:**
    • Imipenem, meropenem, ertapenem, doripenem
  » **Monobactams:**
    • Aztreonam
  » **Glycopeptides:**
    • Vancomycin, Dalbavancin, Oritavancin, Telavancin
ANTIBACTERIALS: MECHANISMS

- Inhibition of DNA gyrase (bactericidal)
  - **Quinolones:**
    - Ciprofloxacin, levofloxacin, moxifloxacin
ANTIBACTERIALS: MECHANISMS

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

- Antimetabolites
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole

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

- Degradation of DNA
  - Metronidazole

- Cyclic lipopeptide (effects calcium transport)
  - Daptomycin
Practical Classification of Microbes for Choosing an Antibiotic
DIAGNOSIS

Direct Visualization

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

Ziehl-Neelsen Stain of TB
DIAGNOSIS

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

• Antigen tests
  » Very useful for following (and sometimes diagnosing) viral infections: HIV, HBV, HCV, EBV, CMV
  » Occasionally useful for other pathogens (e.g., cryptococcus)
DIAGNOSIS

• Serology
  » For bacterial infections, generally not useful in early diagnosis (usually requires acute and convalescent tests)
  » For viral infections, IgM may allow early diagnosis (e.g., HepA)
DIAGNOSIS

• PCR and other “molecular” tests
  » Increasingly used (e.g., pertussis); allows diagnosis of nonculturable pathogens (e.g., norovirus) and faster identification
  » Subject to false positives
Ten Factors to Consider When Selecting an Antibiotic

1. Appropriate diagnostic evaluation
2. Appropriate spectrum of coverage
3. Evidence of efficacy
4. Local, national and international patterns of resistance
5. Evidence or track record for the specified infection
6. Achievable serum, tissue, or body fluid concentration (e.g. cerebrospinal fluid, urine)
7. Patient safety
   » Allergy
   » Toxicity of antibiotic
8. Formulation (IV vs. PO) and bioavailability
9. Adherence/compliance
10. Cost
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
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

Kollef Chest 115:462, 1999
# Antibiotics with Gram (+) Activity

<table>
<thead>
<tr>
<th><strong>S. aureus</strong></th>
<th><strong>MRSA</strong></th>
<th><strong>VRE</strong></th>
<th><strong>E. faecalis</strong></th>
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</thead>
<tbody>
<tr>
<td>Nafcillin/Oxacacillin</td>
<td></td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Amp/Sulb, Pip/Tazo</td>
<td></td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Ceftaroline (only)</td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Vancomycin</td>
<td></td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Clindamycin +/-</td>
<td></td>
<td>Vancomycin</td>
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<tr>
<td>Quin/Dalf</td>
<td>Quin/Dalf</td>
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<td>Linezolid</td>
<td>Vancomycin</td>
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<td>Daptomycin</td>
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<td>Daptomycin</td>
<td>Vancomycin</td>
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<td>Telavancin</td>
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<tr>
<td>TMP-SMX</td>
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<td>Daptomycin</td>
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# Antibiotics with Gram (-) Activity

<table>
<thead>
<tr>
<th></th>
<th><em>E. coli</em></th>
<th><em>K. pneumoniae</em></th>
<th><em>Enterobacter</em></th>
<th><em>P. aeruginosa</em></th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td></td>
<td></td>
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<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>Piperacillin</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>Pip/Tazo</td>
<td>Pip/Tazo</td>
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<td>Pip/Tazo</td>
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<tr>
<td>Cephalosporins</td>
<td>Cephalosporins</td>
<td>3rd, 4th, 5th gen.</td>
<td>Ceftaz/Cefepime</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Carbapenems</td>
<td>Carbapenems</td>
<td>Carbapenems</td>
<td>Imip, Mero, Dori</td>
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<tr>
<td>Aztreonam</td>
<td>Aztreonam</td>
<td>Aztreonam</td>
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<tr>
<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

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

- Chloramphenicol
- Metronidazole*
- Clindamycin* Highly active
Principles of Antibacterial Therapy: Synergy and Antagonism of Antibiotics

Synergy

Indifference

Antagonism

Hours

Log Number of Bacteria

Log Bacteria

No Antibiotic

A

B

A + B

A + B

A
Principles of Antibacterial Therapy: Bacteriostatic or Bactericidal

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

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

Bactericidal agents required for meningitis, endocarditis and infections in neutropenic hosts.
Antibacterial Resistance
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).

Livestock-Associated Methicillin and Multidrug Resistant Staphylococcus aureus Is Present among Industrial, Not Antibiotic-Free Livestock Operation Workers in North Carolina

Jessica L. Rinsky, Maya Nadimpalli, Steve Wing, Devon Hall, Dothula Baron, Lance B. Price, Jesper Larsen, Marc Stieger, Jill Stewart, Christopher D. Heaney

Published: July 2, 2013

Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters

Anne F.C. Leonard, Lihong Zhang, Andrew J. Balfour, Ruth Garside, William H. Gaze

Prevalence of Veterinary Antibiotics and Antibiotic-Resistant Escherichia coli in the Surface Water of a Livestock Production Region in Northern China

Xuelian Zhang, Yanxiao Li, Bei Liu, Jing Wang, Chenghong Feng, Min Gao, Lina Wang

Published: November 5, 2014 • DOI: 10.1371/journal.pone.0111026
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.
Developing Resistance
Timeline of Key Antibiotic Resistance Events

**ANTIBIOTIC RESISTANCE IDENTIFIED**
- penicillin R Staphylococcus 1940
- tetracycline R Shigella 1959
- methicillin R Staphylococcus 1962
- penicillin R pneumococcus 1965
- erythromycin R Streptococcus 1968
- gentamicin R Enterococcus 1979
- ceftazidime R Enterobacteriaceae 1987
- vancomycin R Enterococcus 1988
- levofloxacin R pneumococcus 1996
- imipenem R Enterobacteriaceae 1996
- KDR tuberculosis 1998
- linezolid R Staphylococcus 2000
- vancomycin R Staphylococcus 2001
- PDR Acinetobacter and Pseudomonas 2004/5
- ceftaroline R Neisseria gonorrhoeae 2009

**ANTIBIOTIC INTRODUCED**
- 1943 penicillin
- 1950 tetracycline
- 1953 erythromycin
- 1960 methicillin
- 1967 gentamicin
- 1972 vancomycin
- 1985 imipenem and ceftazidime
- 1996 levofloxacin
- 2000 linezolid
- 2003 daptomycin
- 2009 ceftaroline
- 2010 ceftaroline

Dates are based upon early reports of resistance in the literature. In the case of pan drug-resistant (PDR)-Acinetobacter and Pseudomonas, the date is based upon reports of healthcare transmission or outbreaks. Note: penicillin was in limited use prior to widespread population usage in 1943.
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
ESKAPE Pathogens

**E**nterococcus faecium (VRE)

**S**taphylococcus aureus (MRSA)

**K**lebsiella and *Escherichia coli* producing ESBL

**A**cinetobacter baumannii

**P**seudomonas aeruginosa

**E**nterobacteriaceae
MICROORGANISMS WITH A THREAT LEVEL OF URGENT

*Clostridium difficile*
Carbapenem-resistant *Enterobacteriaceae*
Drug-resistant *Neisseria gonorrhoeae*
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 Antibiotic Resistance

- Bacteria are capable of becoming resistant through several mechanisms
- One or many mechanisms may exist in an organism
- Multidrug-resistant bacteria often have multiple mechanisms
- Genes encoding resistance may exist on plasmid or chromosome
Mechanisms of Resistance

Antibiotic Degrading Enzymes

• Sulfonation, phosphorylation, or esterification
  » Especially a problem for aminoglycosides

• $\beta$-lactamases
  » Simple, extended spectrum $\beta$-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
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
Methods for Testing Resistance and Efficacy
Methods for Testing Resistance: Minimal Inhibitory Concentration

Known quantity of bacteria placed into each tube

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

Increasing antibiotic concentration

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

Methods for Testing Resistance: Automated Minimal Inhibitory Concentration

Well Plate for MIC Testing

Many Labs Use Automated Testing
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.

Susceptible
Methods for Testing Resistance: E-test Strip
### Concept of Breakpoint to Determine Susceptibility

**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

<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>
Ten Factors to Consider When Selecting an Antibiotic

1. Appropriate diagnostic evaluation
2. Appropriate spectrum of coverage
   » Know your resistance patterns
3. Evidence of efficacy
4. Local, national and international patterns of resistance
5. Evidence or track record for the specified infection
6. Achievable serum, tissue, or body fluid concentration (e.g. cerebrospinal fluid, urine)
7. Patient safety
   » Allergy
   » Toxicity of antibiotic
8. Formulation (IV vs. PO) and bioavailability
9. Adherence/compliance
10. Cost
Additional Slides
Antibacterial Stewardship
Why So Much Empiric Therapy?

- Need for prompt therapy with certain infections
  - Life or limb threatening infection
  - Mortality increases with delay in these cases
- Cultures difficult to do to provide microbiologic definition (i.e. pneumonia, sinusitis, cellulitis)
- Negative cultures
- Provider Beliefs
  - Fear of error or missing something
  - Not believing culture data available
  - “Patient is really sick, they should have ‘more’ antibiotics”
  - Myth of “double coverage” for gram-negatives e.g. pseudomonas
  - “They got better on drug X, Y, and Z so I will just continue those”
Antibiotic Stewardship

• Definition: A system of informatics, data collection, personnel, and policy/procedures which promotes the optimal selection, dosing, and duration of therapy for antimicrobial agents throughout the course of their use

• Purpose:
  1. Reduce antibiotic consumption and inappropriate use
  2. Improve patient outcomes
  3. Increase adherence/utilization of treatment guidelines
  4. Reduce adverse drug events
  5. Decrease or limit antibiotic resistance

• Is pertinent to inpatient, outpatient, and long-term care settings

• Is practiced at the
  » Level of the patient
  » Level of a health-care facility or system, or network

Ohl CA, Luther VP. *J. Hosp. Med.* 2011;6:S4
Dellit TH, et. al. *Clin Infect Dis.* 2007;44:159-177
Ohl CA, Luther VP. *J. Hosp. Med.* 2011;6:S4
Antibiotic Stewardship Improves Clinical Outcomes

AMP = Antibiotic Management Program
UP = Usual Practice

To Increase Directed Therapy for Inpatients:

- Define the infection 3 ways
  - Anatomically, microbiologically, pathophysiologically

- Obtain cultures before starting antibiotics

- Use imaging, rapid diagnostics and special procedures early in the course of infection

- Have the courage to make a diagnosis

- Do not rely solely on “response to therapy” to guide therapeutic decisions; follow recommended guidelines

- If empiric therapy is started, reassess at 48-72 hours
Rapid Diagnostic Tests

Rapid MRSA screening

PNA FISH
To Increase use of Directed Therapy for Outpatients:

- **Define the infection 3 ways**
  - Anatomically, microbiologically, pathophysiologically

- **Obtain cultures before starting antibiotics**
  - Often difficult in outpatients

- **Narrow therapy often with good supporting evidence**
  - Amoxicillin or amoxicillin/clavulinate for AOM, sinusitis and CAP
  - Penicillin for Group A Streptococcal pharyngitis
  - 1st generation cephalosporin or clindamycin for simple cellulitis
  - Trimethoprim/sulfamethoxazole or cipro/levofloxacin for cystitis
Principles of Antibiotic Stewardship

• **Principle 1**
  » Treat Infection, not colonization

• **Principle 2**
  » Do not treat sterile inflammation or abnormal imaging without evidence of infection

• **Principle 3**
  » Do not treat viral infections with antibiotics

• **Principle 4**
  » Limit duration of therapy to an appropriate time
Other Principles of Antibiotic Stewardship

- Re-evaluate, de-escalate or stop therapy at 48-72 hours based on diagnosis and microbiologic results
- Re-evaluate, de-escalate or stop therapy with transitions of care (e.g. ICU to step-down or ward)
- Do not give antibiotic with overlapping activity
- Do not “double-cover” gram-negative rods with 2 drugs with overlapping activity
Other Principles of Antibiotic Stewardship

- Limit duration of surgical prophylaxis to <24 hours perioperatively
- Use rapid diagnostics if available (e.g. respiratory viral PCR)
- Prevent infection
  - Use good hand hygiene and infection control practices
  - Remove catheters
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