Hot Topics in Pediatrics

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Objectives

- Describe empiric treatments for HAP/CAP/VAP
- Recall how to interpret sensitivity reports
- Recognize new microorganisms
- Identify the effects of drug shortages on the healthcare system
Choosing an Anti-infective

Empiric Therapy

- Most common organisms
- Local resistance patterns
- Drug shortages

Definitive Therapy

Susceptibilities

Choosing an Anti-infective

Empiric Therapy

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Definitive Therapy

Susceptibilities
Diagnosis

- Community-Acquired Pneumonia (CAP)
- Hospital-Acquired Pneumonia (HAP)
- Ventilator-Associated Pneumonia (VAP)

CAP

Definition:

- Development of a pneumonia that was acquired in the community

CAP Organisms

Gram-positive
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Staphylococcus aureus*

Gram-negative
- *Haemophilus influenzae*
- *Moraxella catarrhalis*

Atypical
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*

Viruses
- Influenza
- Parainfluenza
- RSV

CAP Empiric Treatment

<table>
<thead>
<tr>
<th></th>
<th>Presumed bacterial pneumonia</th>
<th>Presumed atypical pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully immunized</td>
<td>Ampicillin or penicillin G</td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td>+/- Clindamycin or vancomycin</td>
<td></td>
</tr>
<tr>
<td>Not fully immunized</td>
<td>Ceftriaxone or cefotaxime</td>
<td>Azithromycin</td>
</tr>
<tr>
<td></td>
<td>+/- Clindamycin or vancomycin</td>
<td></td>
</tr>
</tbody>
</table>

Ampicillin

- **Dose**
  - 50 mg/kg IV every 6 hours (max 2000 mg)
- **Class**
  - Penicillin
- **MOA**
  - Inhibits bacterial cell wall synthesis by binding to PBPs, resulting in cell lysis
- **Adverse reactions**
  - Diarrhea, anemia, thrombocytopenia, skin rash, sore mouth

Azithromycin

- **Dose**
  - 10 mg/kg on day 1, followed by 5 mg/kg on days 2-5
- **Administration**
  - IV or PO
- **Class**
  - Macrolide
- **MOA**
  - Inhibits RNA protein synthesis
- **Adverse reactions**
  - Diarrhea, nausea, vomiting, pain at injection site
HAP

Definition:

- Development of a pneumonia ≥ 48 hours after hospital admission, which was not incubating prior to admission

VAP

Definition:

- Patient must be mechanically ventilated for >2 calendar days prior to development of pneumonia
- The ventilator was in place on the date of development, or the day before
HAP/VAP Organisms

Gram-positives
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Gram-negatives
- *Pseudomonas aeruginosa*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Acinetobacter* species
- *Haemophilus influenzae*

HAP/VAP Empiric Therapy

- Early onset
- Low risk for multidrug resistant organisms

- Antibiotic choices
  - Ampicillin/Sulbactam
  - Ceftriaxone

References:
Ampicillin/Sulbactam

- **Dose**
  - 50 mg/kg (AMP) IV every 6 hours (max 2,000 mg)
- **Class**
  - Penicillin
- **Adverse reactions**
  - Diarrhea, skin rash, thrombophlebitis

Ceftriaxone

- **Dose**
  - 50-100 mg/kg IV divided every 12-24 hours (max 2000 mg)
- **Class**
  - Cephalosporin (3rd generation)
- **Contraindications**
  - Hyperbilirubinemic neonates
  - Concomitant use with IV calcium products in neonates
- **Adverse reactions**
  - Diarrhea, skin rash
HAP/VAP Empiric Treatment

- Late-onset disease
- Risk for MDROs

**Antibiotic choices**
- Antipseudomonal β-lactam/carbapenem
  - Plus
- MRSA agent
  +/−
- 2nd antipseudomonal agent


Antipseudomonal Agents

- Piperacillin/tazobactam
- Cefepime
- Ceftazidime
- Meropenem
**Piperacillin/Tazobactam**

- **Dose**
  - 100 mg/kg (PIP) IV every 6-8 hours (max 3000 mg)
- **Class**
  - Penicillin (antipseudomonal)
- **Administration**
  - Y-site compatible with vancomycin at specific concentrations
- **Adverse reactions**
  - Diarrhea, skin rash, pruritis, agitation, headache, increased AST

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**Cefepime**

- **Dose**
  - 50 mg/kg IV every 12 hours (max 2000 mg)
- **Class**
  - Cephalosporin (4th generation)
- **Adverse reactions**
  - Headache, skin rash, hypophosphatemia, increased transaminases
Meropenem

- **Dose**
  - 20 mg/kg IV every 8 hours (max 2000 mg)

- **Class**
  - Carbapenem

- **Administration**
  - Y-site compatible with vancomycin

- **Adverse reactions**
  - Hypoglycemia, headache, glossitis, anemia

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MRSA Agents

- Vancomycin
- Daptomycin
- Linezolid
- Ceftaroline

Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2015; September 27, 2015.
Vancomycin

- **Dose**
  - 15 mg/kg IV every 6-8 hours (max 2000 mg)
- **Goal trough**
  - 15-20 mCg/mL
- **MOA**
  - Inhibits cell wall synthesis
- **Monitoring**
  - sCr, BUN, urine output
- **Adverse reactions**
  - Erythematous rash, chills, neutropenia

Linezolid

- **Dose**
  - 10 mg/kg every 8-12 hours (max 600 mg)
- **Administration**
  - IV or PO
- **MOA**
  - Inhibits bacterial protein synthesis
- **Adverse reactions**
  - Serotonin syndrome, vertigo, pruritus, tongue discoloration
Patient is diagnosed with late-onset VAP. What empiric antibiotic therapy should be initiated?

a) Ampicillin/Sulbactam  
b) Ceftriaxone  
c) Piperacillin/Tazobactam + Meropenem  
d) Cefepime + Vancomycin

Empiric Antibiotic Choice

- Most common organisms
- Local resistance patterns
  - Antibiograms
- Drug shortages
  - Ampicillin/Sulbactam
  - Piperacillin/Tazobactam
  - Meropenem

There's a drug shortage. I'm thinking of replacing your meds with eight hugs a day before & after meals!
Choosing an Anti-infective

Empiric Therapy

Local resistance patterns

Drug shortages

Most common organisms

Susceptibilities

Definitive Therapy

Utilizing Microbiological Data

GRAM STAINS
&
CULTURES/SUSCEPTIBILITIES
Gram Stain Descriptions

Gram Stain
- Gram-positive (purple)
- Gram-negative (pink)

Morphology
- Coccus
- Bacillus
- Spiral

Aggregation
- Pairs
- Chains
- Clusters

Gram Stain Description

"Bacterial morphology diagram" by Mariana Ruiz
Presumptive Identification

<table>
<thead>
<tr>
<th>Gram Stain Findings</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci in clusters</td>
<td>Staphylococci</td>
</tr>
<tr>
<td>Gram-positive cocci in chains</td>
<td>Streptococci and enterococci</td>
</tr>
<tr>
<td>Gram-positive diplococci</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram Stain Findings</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative coccobacilli</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Gram-negative diplococci</td>
<td><em>Neisseria species, Moraxella species</em></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><em>Pseudomonas aeruginosa, E. coli, K. pneumoniae</em></td>
</tr>
</tbody>
</table>


Culture & Susceptibilities

Microorganism Identified

Minimum Inhibitory Concentrations (MICs) Determined

MICs Compared to Reference MICs
Interpretation Susceptibilities

- **Susceptible**
  - Microorganism’s MIC to a specific antibiotic is ≤ MIC needed to inhibit growth at normal recommend dose

- **Resistant**
  - Microorganism’s MIC to a specific antibiotic is ≥ MIC needed to inhibit growth at normal recommend dose

- **Intermediate**
  - Microorganism’s MIC to a specific antibiotic approaches or exceeds the concentrations that can be obtained with normal recommended doses and clinical response is likely to be less than susceptible strain


What to do with this Info?

- Broaden therapy
- Change antibiotics to appropriate therapy
- De-escalate therapy
- Discontinue antibiotics

Other Uses for MICs

Pharmacokinetic Monitoring

- **Vancomycin**
  - AUC:MIC > 400

- **Aminoglycosides**
  - Peak:MIC 10-12


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Example: *E. Coli*

<table>
<thead>
<tr>
<th>ORGANE</th>
<th>Final Colony Count</th>
<th>ESCHERICHIA COLI</th>
<th>10/28/14-0724</th>
<th>CML</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCHERICHIA COLI</td>
<td>&gt;100,000 Colonies/ml</td>
<td>10/28/14-0724</td>
<td>CML</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Interp</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPICILLIN</td>
<td>&lt;4</td>
<td></td>
</tr>
<tr>
<td>CEFPIROXON</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>&lt;0.25</td>
<td></td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>MEROFENEM</td>
<td>&lt;0.25</td>
<td></td>
</tr>
<tr>
<td>NITROFRANCOXIN</td>
<td>&lt;16</td>
<td></td>
</tr>
<tr>
<td>TROFACIN</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>TRIMET/SULFA</td>
<td>&lt;20</td>
<td></td>
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<tr>
<td>LEVOFLOXACIN</td>
<td>&lt;0.12</td>
<td></td>
</tr>
<tr>
<td>PENICILLIN/TAZOBACTAM</td>
<td>&lt;4</td>
<td></td>
</tr>
<tr>
<td>EXT SPECTRUM BETA LAUTARINGE</td>
<td>NEO</td>
<td></td>
</tr>
</tbody>
</table>

*Interpretations are based on CLSI 2010-11 revised breakpoints.*
Example: *E. Coli*

**BLOOD CULTURE ORGANISM REPORT**

**Organism:** *Escherichia coli*

**Interpretation of MICs:**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>$R \geq 32$</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>$S \leq 1$</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>$R \geq 4$</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>$S \leq 1$</td>
</tr>
<tr>
<td>Meropenem</td>
<td>$S \leq 0.25$</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>$S \leq 1$</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>$R \geq 8$</td>
</tr>
<tr>
<td>ERT Spectrom Beta Lactamase</td>
<td>- NEO</td>
</tr>
</tbody>
</table>

*MIC interpretations are based on CLSI 2010-11 revised breakpoints.*

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**New Bugs**

**Old Bugs Can Learn New Tricks**
Mechanisms of Resistance

- **Antimicrobial penetration**
  - Permeability changes
  - Active efflux pumps

- **Changing the target**
  - Modification of antibiotic target
  - Overproduction of the target

- **Altering the antibiotic**
  - Enzymatic modification of the antibiotic
  - Degradation of the antimicrobial agent


Multidrug-Resistant Organism

- **Multidrug-resistant (MDR)**
  - Non-susceptible to $\geq 1$ agent in $\geq 3$ antimicrobial categories

- **Extensively drug-resistant (XDR)**
  - Non-susceptible to $\geq 1$ agent in all but $\leq 2$ antimicrobial categories

- **Pandrug-resistant (PDR)**
  - Non-susceptible to all antimicrobial agents listed

ESKAPE Pathogens

- E: *Enterococcus faecium*
  - Vancomycin-resistant *E. faecium* (VRE)
- S: *Staphylococcus aureus*
  - Methicillin-resistant *S. aureus* (MRSA)
- K: *Klebsiella pneumoniae*
  - *K. pneumoniae* carbapenemase-hydrolyzing β-lactamase (KPC)
- A: Acinetobacter baumannii
- P: *Pseudomonas aeruginosa*
- E: *Enterobacter* species


Is this an MDRO?

BLOOD CULTURE ORGANISM REPORT Final 11/03/14-0726 CHE
Organism: 1

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>M.I.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPICILLIN</td>
<td>2</td>
<td>&gt;32</td>
</tr>
<tr>
<td>CEFTAXIME</td>
<td>3</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>3</td>
<td>&gt;1</td>
</tr>
<tr>
<td>OXACILLIN</td>
<td>3</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>MEROXIN</td>
<td>4</td>
<td>&lt;=0.02</td>
</tr>
<tr>
<td>TIPRAMICIN</td>
<td>3</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>TETRAMICIN/CHLALFA</td>
<td>8</td>
<td>&lt;=32</td>
</tr>
<tr>
<td>PIPERACILLIN/TAZOBACTAM</td>
<td>3</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>EXT SPECTRUM BETA LACTAMASE</td>
<td>-</td>
<td>NEG</td>
</tr>
</tbody>
</table>

5-1-8 Interpretations are based on CLSI 2010-11 revised breakpoints.

a) Yes, it is a MDR
b) Yes, it is a XDR
c) Yes, it is a PDR
d) No it is not
Choosing an Anti-infective

Empiric Therapy

Definitive Therapy

Most common organisms

Local resistance patterns

Drug shortages

Susceptibilities

Drug Shortages
Reported Drug Shortages

Figure 1: National drug shortages from January 2001 to September 15, 2011. Each column represents the number of new shortages identified during that year. (From Fox ER, University of Utah Drug Information Service.)

Reasons for Drug Shortages

Impact of Drug Shortages

- Increased hospital costs
  - Gray-market
- Safety risks
  - Compromised clinical outcomes
  - Medication errors
- Affect availability of alternative medications
- Strained professional relationships


Antibiotics

<table>
<thead>
<tr>
<th>Shortage Reason</th>
<th>No. of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>General manufacturing/manufacturing delays or problems</td>
<td>35</td>
</tr>
<tr>
<td>Supply and demand</td>
<td>19</td>
</tr>
<tr>
<td>Raw material shortage</td>
<td>13</td>
</tr>
<tr>
<td>Discontinued</td>
<td>10</td>
</tr>
<tr>
<td>Regulatory issues/regulatory problems</td>
<td>5</td>
</tr>
<tr>
<td>Regulatory import bar</td>
<td>3</td>
</tr>
<tr>
<td>Natural disaster</td>
<td>1</td>
</tr>
<tr>
<td>Business decision</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>61</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
</tr>
</tbody>
</table>

Preparing for Drug Shortages

1. Validate drug shortage
2. Assess current inventory
3. Identify alternative drug, or therapeutic equivalents
4. Prioritize patients to receive short supply drug

Identifying Antibiotic Alternatives

- Similar spectrum of activity
- Comparable or lower adverse effect profile
  - Pharmacokinetic monitoring
- Administration
- Acquisition cost
### Example: Piperacillin/Tazobactam

<table>
<thead>
<tr>
<th>Indication: Suspected pseudomonal infection</th>
<th>Indication: Post-operative perforated appendicitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefepime</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### What is the known cause of most drug shortages?

a) Pharmacy wants to restrict use of high cost drugs  
b) FDA regulations  
c) Manufacturing  
d) Raw materials
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