Antimicrobial Prescribing

John C. Rotschafer, Pharm.D., FCCP
Professor
Department of Experimental and Clinical Pharmacology
College of Pharmacy
University of Minnesota
Office: 612-624-2183
e-mail: rotsc001@umn.edu
Course web page: http://www.courses.ahr.umn.edu/pharmacy/6124/index.htm

Overview

• Organization for tonight
  – Microbiology Review
  – Antibiotic Susceptibility Testing & Bacterial Resistance
  – Antibiotic Pharmacology/Pharmacodynamics & Treatment

Acknowledgement

• Many thanks to Thomas Feldstein, Pharm. D. for sharing course content & slides
Antibiotic Prescribing

• Most situations will involve:
  – S/SST, UTI, URTI, & LRTI
  – You will not have nor will you obtain a culture
  – Often treat empirically
  – Variety of guidelines to identify appropriate diagnostic work and empiric antibiotic selection
  – Need empiric antibiotic selection & possible alternative agent if toxicity or treatment failure
  – Will likely work with a limited number of antibiotics that you know well

Overview to Antibiotic Prescribing

• Questions to be addressed:
  – Bacterial infection
  – Involved site/s
  – Likely pathogens
  – Resistance issues
  – Allergies
  – Pregnant or breast feeding
  – Normal hepatic &/or renal function
  – Efficacy
  – Safety
  – Cost
  – Compliance issues
    – Route, #cap/tabs/day, frequency, duration, and cost
    – Possible antibiotic selections
    – Formulary considerations

Prescribing Resources

• Epocrates or equivalent hand held technology
• Stanford pocket guide or equivalent
  – www.sanfordguide.com
• CDC guidelines
• ICSI guidelines
  – http://www.icsi.org/knowledge/browse_category.asp
• IDSA Guideline
  – http://www.IDSA.org
• Hospital antibiogram or pocket guide
• World Wide Web
  – PubMed
  – Google
• “Safer in America” - No trailing zeros & intervals written out
• Host of other resources
Plan of Attack!

• Simplify Microbiology…
  – ~ 100 pathogens will be isolated in an institution
  – But only 20 species are common
  – Put them in 5 groups, and…
  – Know just 13 pathogen types
• Simplify Antimicrobial agents…
  – Organize into classes, throw out a lot, concentrate on most useful ones
• Simplify Diseases and ABX Therapy
  – Most common diseases, Most common pathogens, Most common antibiotics (drugs of choice)

A somewhat abbreviated list (TOP 50)

<table>
<thead>
<tr>
<th>Gram-positive cocci</th>
<th>Gram-negative cocci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Hemophilus influenzae (occas-bacilli)</td>
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<td>Staphylococcus epidermidis</td>
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<td>Salmonella typhi</td>
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Common Bacterial Isolates (TOP 20)
### 13 Pathogen (types) in 5 Classes

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<td><em>Salmonella typhimurium</em></td>
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<tr>
<td><em>Streptococcus sanguis</em></td>
<td><em>Shigella flexneri</em></td>
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<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Streptococcus milleri</em></td>
<td><em>Citrobacter freundii</em></td>
</tr>
</tbody>
</table>

### Gram-negative bacilli

| *Haemophilus influenzae* (cocco-bacilli) | *Neisseria meningitidis* |
| *Neisseria gonorrhoeae* | *Moraxella catarrhalis* |

### Enterobacteriacea

| *Escherichia coli* (E.K.P. | *Providencia stuartii* |
| *Klebsiella pneumoniae* | *Serratia marcescens* |
| *Proteus vulgaris* | *Providencia stuartii* |
| *Enterobacter sp* | *Providencia stuartii* |
| *Serratia marcescens* | *Pseudomonas aeruginosa* |
| *Salmonella typhi* | *Pseudomonas cepacia* |
| *Salmonella enteritidis* | *Bacteroides fragilis* |
| *Shigella sp* | *Bacteroides* |

### Simplified Microbiology: “5 classes”

- **Gram (+) cocci**
  - *Staph*
  - *Strep*
  - *Enterococcus*

- **Gram (-) cocci & coco-bacilli**
  - *Neisseria*
  - *H. flu*
  - *Morasella catarrhalis*

- **Enterobacteriacea**
  - EKP: *E. coli, Klebsiella, Proteus*
  - ESP: *Enterobacter, Serratia, Providencia*

- **Pseudomonas aeruginosa**

- **Anaerobes: Bacteroides fragilis**
Example 1:

“Describe the spectrum of activity of Cephalosporins:”

1st Generation Cephalosporins:
(IV cefazolin, PO cephalexin)
“Gram-positive and some gram negative”
• Staph, Strep, and EKP

2nd Generation Cephalosporins:
(IV & PO cefuroxime, PO Cefprozil)
“1st Gen. Activity + mixed gram negatives”
• Staph, Strep, and EKP
• H. flu, Neisseria, M. cat

3rd Generation Cephalosporins:
Broad spectrum (IV ceftriaxone or PO cepodoxime)
“2nd Gen. Activity + good gram negative”
• Staph, Strep, EKP
• ESP
• EKP antipseudomonal (IV Cefepime)
“mainly gram-negative”
• All gm (-), including Pseudomas
• OK Staph coverage, no anaerobes

Example 2:

“Which antibiotics have activity against Staph?”:

Penicillins?
• Antistaph pens
• Oxacillin
• B-l inhibitor Combos

Cephalosporins?
• all but Cefazidine and Cefixime

Macrolides?
• Not very good

Quinolones?
• Fair, some better

Clindamycin?
• Yes!

Vancomycin?
• Yes, but reserve for MRSA

MRSA Alternatives:
• Synercid
• Linezolid
• Daptomycin

Confirming the presence of infection

• Non-Specific Signs and Symptoms
  – Fever
    • Normal temp 98.6°F 37°C
    • Fever 100.4°F 38°C
    • 102°F 39°C
    • 104°F 40°C
  – WBC count with differential
    • ↑WBC with left shift (↑ immature neutrophils - bands)
  – Pain and Inflammation (swelling, erythema, etc)
    • Monitoring extent of inflammation:
    • CRP (c-reactive protein), ESR (erythrocyte sedimentation rate)

• Disease-specific signs and symptoms
  – e.g. pneumoniae, otitis media, sinusitis, osteoarthritis,
    UTI/STD, CNS infection, abdominal infection, etc
**WBC Differential**

<table>
<thead>
<tr>
<th>WBCs (5000-10,000 cells/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
</tr>
<tr>
<td>Neutrophils (PMNS) 55-75%</td>
</tr>
<tr>
<td>Bands 3-5% <em>Segs</em></td>
</tr>
<tr>
<td>Eosinophils 0-5%</td>
</tr>
<tr>
<td><em>shift to the left</em></td>
</tr>
<tr>
<td>Agranulocytes</td>
</tr>
<tr>
<td>Lymphocytes 20-40%</td>
</tr>
<tr>
<td>Monocytes 6-7%</td>
</tr>
<tr>
<td>T-cells</td>
</tr>
<tr>
<td>B-cells</td>
</tr>
</tbody>
</table>

**Other Tests**

*Non-specific signs of inflammation*

- **ESR (erythrocyte sedimentation rate)**
  - “how far RBCs fall in 1 hour”
  - RBCs are neg.-charged & repel each other.
  - Acute phase reactants bind (-) charge, RBC attract each other, clump, and fall.
- **CRP (C-reactive protein)**
  - 0.5-1.0 Normal
  - 1.0-1.5 Moderate inflammation
  - > 10 Suggestive of infection

**Identification and Classification of the Pathogen**

- Staining characteristics
- Morphology
- Spatial arrangements
- Antibody/antigen tests
- Biochemical tests
- Gene markers
Microscopic Examination

• Staining Characteristics (gram+, gram -, cocci, bacilli)
  – The Gram Stain
    • Crystal violet primary stain, Iodine added to enhance stain. Alcohol decolorization, safranin counterstain (pink).

Microscopic Examination

• Morphology
  Cocci (spheres)
    “Clusters” (eg. Staph)  “Chains” (eg. Strep)
  Bacilli (rods)
    • Enterocacteriaceae (eg., e.coli, kleb, proteus, entb)
    • Pseudomonas
    • Treponema (spiral-shaped)
    • Lactobacillus (filamentous)

Bacteria

<table>
<thead>
<tr>
<th>Gram (+)</th>
<th>Gram (-)</th>
</tr>
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<tbody>
<tr>
<td>Cocci</td>
<td>Bacilli</td>
</tr>
<tr>
<td></td>
<td>Cocci</td>
</tr>
<tr>
<td>Staphylococcus sp.</td>
<td>C. aliphilus</td>
</tr>
<tr>
<td>Streptococcus sp.</td>
<td>L. monocytogenes</td>
</tr>
<tr>
<td>Enterococcus sp.</td>
<td>Nocardia sp.</td>
</tr>
<tr>
<td>Anaerobes:</td>
<td>Moraxella catharhals</td>
</tr>
<tr>
<td>Peptococcus</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td></td>
</tr>
<tr>
<td>Anaerobes:</td>
<td>Clostridium sp.</td>
</tr>
<tr>
<td>Anaerobes:</td>
<td>梭状芽胞杆菌</td>
</tr>
<tr>
<td>Anaerobes:</td>
<td>Bacteroides</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Cocci</th>
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<tr>
<td>Cocci</td>
<td>Bacilli</td>
</tr>
<tr>
<td>Haemophilus sp</td>
<td>Bordetella pertussis</td>
</tr>
</tbody>
</table>

Anaerobes:
Entrobacteriaceae
Lulo, Bifidobacter, Proteo,
Enterobacter, Serratia
Salmonella, Shigella
Pseudomonas
Anaerobes:
Bacteroides
Microscopic Examination

• Staining Characteristics (cont.)
  – Other Stains
    • Acid-fast stain (mycobacteria, nocardia)
    • India Ink (cryptococcus)

Classification of Bacteria

Gram-positive Cocci: Staph and Strep

<table>
<thead>
<tr>
<th>Clusters</th>
<th>Chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>Staph. aureus (+) Coagulase+</td>
<td>S. pneumoniae (pneumococcus, diplococcus)</td>
</tr>
<tr>
<td>Staph. epidermidis (-) Coagulase-</td>
<td>S. pyogenes</td>
</tr>
</tbody>
</table>

Anaerobes:
P. aerogenes
Peptostreptococcus

Enterococci:
E. faecalis, E. faecium, E. durans

Microscopic Examination

• Morphology (cont)
  Cocco-bacilli
  – Haemophilus influenzae
  – Bordetella pertussis
Cultures

• Most definitive method for the diagnosis and eventual treatment of infection
• Most outpatient infections treated empirically
• Requires appropriate collection and transportation to the laboratory
  – There is a time window that comes into play
• Avoid contamination with normal flora
• Rapid detection methods
  – (e.g., Bactec)

Antibody and Antigen Detection

• Detection & quantification of antibodies directed against a specific pathogen or its components
• Techniques
  – Immunofluorescence: CMV, RSV, Varicella, Treponema pallidum (syphilis), Borrelia burgdorferi (lymes disease)
  – Latex agglutination: Meningococcal antigens in CSF, Legionella pneumophilia
  – Enzyme-linked Immunoassay (Ella): HIV, Herpes, RSV, Pneumococcus, N. gonorrhea, Helicobacter pylori
  – PCR: DNA amplification looking for genetic “fingerprint”
  – Gene Probes:
  – Nanotechnology:

Classification of Bacteria

<table>
<thead>
<tr>
<th>Gram (+) Coccii</th>
<th>Gram (-) Bacilli</th>
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<tbody>
<tr>
<td>Clusters: Staph</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Conglomerate: S. aureus</td>
<td>E.coli</td>
</tr>
<tr>
<td>Coagulase (+)</td>
<td>Klebsiella (K pneumoniae, K oxytoca)</td>
</tr>
<tr>
<td>Chains: Strep</td>
<td>Proteus (P. mirabilis, P. vulgaris)</td>
</tr>
<tr>
<td>Diplococcus: S. pneumoniae</td>
<td>Enterobacter sp.</td>
</tr>
<tr>
<td>Gp A: hemolytic: S. pyogenes</td>
<td>Seratia sp.</td>
</tr>
<tr>
<td>Gp A: nonhemolytic: Viridans group</td>
<td>Pseudomonas sp.</td>
</tr>
<tr>
<td>Gp B: agrupicola</td>
<td>Staphylococci sp.</td>
</tr>
<tr>
<td>Gp D: Streptococcus</td>
<td>Staphylococci sp.</td>
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<tr>
<td>Enterococcus sp.</td>
<td>Chlorobacter sp.</td>
</tr>
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<td>Anaerobes: Peptococcus, Peptostreptococcus</td>
<td>Metagenella sp.</td>
</tr>
<tr>
<td>Gram (+) Bacilli</td>
<td>Pseudomonas aerugiens</td>
</tr>
<tr>
<td>Bacillus (B. anthracis, B. cereus)</td>
<td>Bacillus fragilis, Bacillus sp.</td>
</tr>
<tr>
<td>Clostridium sp.</td>
<td>Fusobacterium</td>
</tr>
<tr>
<td>C. difficile, C. perfringens, C. tetani, C. sordellum</td>
<td>Gram (-) Coccii</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>Meningococcus ornithini</td>
</tr>
<tr>
<td>Corynebacterium diphteriae</td>
<td>Neisseria sp. (N. meningitidis, N. gonorrhoeae)</td>
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<tr>
<td>JK group Corynebacterium</td>
<td></td>
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Hemolytic Patterns

- **Example**
  - Group A beta hemolytic streptococci
    - *S. pyogenes*
  - **Hemolytic patterns on sheep blood agar**
    - Alpha- greenish-brown zone surround colonies
    - Incomplete hemolysis
    - Beta- Clear zone surround colonies
    - Complete hemolysis
    - Gamma- No evidence of hemolysis
    - No hemolysis

**Gram Positive**

**Catalase Test**

Enzyme reaction with hydrogen peroxide
**Gram positive Coagulase Test**

Enzyme that binds fibrinogen. Causes clumps.

**Classification of Bacteria**

*Gram-positive Bacilli*

- **Clostridium**
  - C. difficile: *pseudomembranous colitis*
  - C. perfringens: *gas gangrene*
  - C. tetani: *tetanus*
  - C. botulinum: *botulism*

- **Diphtheroids**
  - Corynebacterium diphtheriae, JK group
  - Listeria monocytogenes

*Other Gram (-) Bacilli (special growth requirements)*

- Haemophilus species
- Campylobacter species
- Legionella pneumophilia
- Bordetella pertussis
- Brucella species
- Francisella species
- Helicobacter pylori

*Gram Negative COCCI*

- Neisseria meningitidis
- Neisseria gonorrhoeae
- Moraxella catarrhalis

*Gram Negative BACILLI*

- Enterobacteriaceae (FAMILY)
  - Escherichia coli
  - Salmonella species
  - Shigella species
  - Yersinis species
  - Proteus species
  - Providencia species
  - Enterobacter species
  - Serratia species
  - Citrobacter species
  - Morganella species
  - Pasturella species
  - Vibrio species
  - Aeromonas
  - Plesiomonas

*Other Gram (-) Bacilli (special growth requirements)*

- Haemophilus species
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- Bordetella pertussis
- Brucella species
- Francisella species
- Helicobacter pylori
Classification of Bacteria

**Gram-Negative Bacilli**

- **Enterobacteriaceae** “gut and GU”
  - *E. coli*, *Klebsiella* sp., *Proteus* (mirabilis, vulgaris),
  - *Enterobacter* sp., *Serratia* sp., *Providencia* sp.,
  - *Salmonella*, *Shigella* sp., *Citrobacter* sp
- **Pseudomonas** “Waterbug!”
  - *P. aeruginosa*
  - *P. cepacia* (Burkholderia)
  - *Stenotrophomonas maltophilia*
- **Anaerobic** “Gut, aspiration, chronic RTIs”
  - *Bacteroides*, *Bacteroides* sp.
  - *Fusobacterium* sp

Risk Factors for *P. aeruginosa*

- Neutropenia
- Malignancy
- Immunosuppression
- Burns
- Cystic Fibrosis
- HAP/VAP

Classification of Bacteria

**Gram-Negative Cocci**

- *Moraxella catarrhalis*
- *Neisseria* sp
  - *Neisseria gonorrhoeae* (gonococcus)
  - *Neisseria meningitidis* (meningococcus)
Classification of Bacteria
*Gram-Negative Cocco-bacilli*

- *Haemophilus influenzae*  “kids, smoke”
- *Bordetella pertussis*  “Whooping cough”

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Classification of Bacteria
*Miscellaneous bacteria*

- *Mycobacterium* (acid-fast bacilli)
  - *M. avium-intracellulare* complex:
    - *M. bovis, M. fortuitum, M. tuberculosis*
- *Ureaplasma urealyticum*
- *Chlamydiae sp.*
- *Mycoplasma pneumoniae*
- *Nocardia*
- *Rickettsia* (Rocky mountain spotted fever)
- *Borrelia burgdorferi* (Lyme Disease)
- *Treponema pallidum* (syphilis)

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Anaerobic Bacteria

- *Gram (+)*
  - Peptococcus
  - Peptostreptococcus
  - Clostridium sp
- *Gram (-)*
  - Bacteroides fragilis
  - Bacteroides sp.
  - Fusobacterium sp
  - Prevotella sp
  - Polyphyromonas
Is there a doctor in the house?

• Lab identifies a nonfermenting gram negative rod that is oxidase positive.

Is there a doctor in the house?

• Lab identifies gram positive cocci in clusters. The organism is catalase positive, coagulase positive, & mecA positive

Is there a doctor in the house?

• Lab identifies tiny gram negative coccobacilli.
Colonization vs. Infection

Normal Colonizing Flora

• Skin
  – Staph, Strep, diptheroids (Corynebacterium), Propionibacteriaceae
• GI tract
  – Bacteroides, Clostridium, Diptheroids, Enterobacteriaceae (E.coli, Kleb), Enterococcus
• Upper Respiratory Tract
  – Bacteroides, Haemophilus, Neisseria, Strep
• Genital tract
  – Coryne, Enth, Lacto, Mycop, Staph, Strep

Most Common Community-acquired Pathogens

• Skin & Soft Tissue Infection
  (Excludes pressure sores or diabetic foot ulcers)
  – S. pyogenes
  – S. aureus
• Urinary Tract Infections
  (1st time)
  – E.coli
  – S. saprophyticus

Potential CAP Pathogens

• Typical
  – S. pneumoniae
  – H. influenzae
  – M. catarrhalis
• Atypical
  – C. pneumoniae
  – L. pneumophila
  – Mycoplasma
• Viruses
• Fungi
• Less Common pathogens
  – N. meningitidis
  – S. pyogenes
  – B. pertussis
  – CA MRSA
  – M. tuberculosis
  – Chlamydia psittaci
  – Coxiella burnetii
  – B. anthracis
  – Y. pestis
  – F. tularensis
CAP Risk Groups

- No Comorbidity
  - *Mycoplasma, Chlamydia, S. pneumoniae*
- Smoker
  - *S. pneumoniae, H. influenzae, & M. catarrhalis*
- Alcoholic
  - *S. pneumoniae, anaerobes, gram negatives*
- Epidemic
  - *Legionella*
- Animal/Bird Reservoir
  - *Q-fever, psittacosis, tularemia*
- Airway Obstruction
  - *Anaerobes*


Susceptibility Testing

- MIC: Minimum Inhibitory Concentration
- MBC: Minimum Bactericidal Concentration
- Serum Inhibitory Titer (SIT)
- Serum Bactericidal Titer (SBT)
Susceptibility Testing
Minimum Inhibitory Concentration (MIC)

• Definition:
  – MIC is the lowest antimicrobial concentration that prevented visible growth of an organism after 24 hours of incubation
  – MBC is not a routinely available test, primarily research tool

Bactericidal vs Bacteriostatic

• Definition
  – Bactericidal – Actual bacterial killing
    • MBC / MIC ≤ 4
  – Bacteriostatic – Inhibition of bacterial growth
    • MBC / MIC > 4
  – Tolerance
    • MBC / MIC ≥ 32
    - Optimal therapy for a particular pathogen does not equate to optimal therapy for all
    • Collateral damage resistance scenario
    • Resistance transfer from another vector (vanA to S. aureus)
  – Presumption cidal is better

Susceptibility Testing

• Macrodilution method
• Microdilution method
• Kirby-Bauer disk diffusion method
• E-test
• Automated methods
Susceptibility Testing
The Macrodiution Method

Broth: 10^4-10^6 CFU/ml (pathogen)
- Mix pathogen with serial dilutions of antibiotic
- Incubate overnight
- 1st clear tube = MIC

Control 0.5 1 2 4 8 ug/ml 16 ug/ml

Antibiotic conc. MIC = 2 ug/ml

Susceptibility Testing
The Microdiution Method

• Automated: serial dilutions of several antibiotics are incubated in a 96-well microtiter plate.

12 Different Antibiotics

MIC/MBC dilution testing
Susceptibility Testing
The Disk-diffusion method (Kirby Bauer Method)

- Paper discs impregnated with various abxs are placed on agar plates, seeded with a lawn of bacteria (pts. pathogen). Zone of inhibition is related to MIC.

1 = Resistant
2 = Sensitive
3 = Intermediate
4 = Resistant
5 = Sensitive
6 = Resistant
7 = Resistant

Disk diffusion Sensitivity Testing (Kirby-Bauer)

Susceptibility Testing
The E-test (epsilometer test)
**Etest diffusion sensitivity testing**

**ESBLs Detection Methods: Inhibition by Clavulanic Acid**

© Ronald J. Jones (Reprinted with Permission of Author). ESBL Etest Prescribing Information – AB BIODISK

---

**Susceptibility Testing**

*Automated Methods*

- **The Vitek system**
  - Growth measured by photometric assessment of turbidity every hour for up to 15 hours.
  - Uses linear-regression to produce an algorithm-derived MIC

- **The Microscan system**
  - Uses fluorogenic substrate hydrolysis as an indicator of bacterial growth
  - Uses linear-regression to produce an algorithm-derived MIC -
The Bacterial Advantage

• The modern antibiotic era is ~ 65 years old while bacteria have been here for millennia
• Bacteria have the ability to adapt to the environment, bacteria are natural survivors
• Bacteria spontaneously mutate continuously looking for a selective advantage
• Bacteria have rapid growth rates & can rapidly replace the former generation.
Antimicrobial % Susceptibility:
P. aeruginosa, USA, 2002-2004

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>TRUST 6 2002</th>
<th>TRUST 7 2003</th>
<th>TRUST 8 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>79.7</td>
<td>80.6</td>
<td>78.1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>NT</td>
<td>79.5</td>
<td>79.9</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>76.7</td>
<td>72.3</td>
<td>72.4</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>85.8</td>
<td>87.0</td>
<td>81.8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>81.9</td>
<td>78.8</td>
<td>81.3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>67.4</td>
<td>68.8</td>
<td>63.5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>67.7</td>
<td>65.3</td>
<td>60.4</td>
</tr>
</tbody>
</table>

Isolates (labs): 998 (36) 882 (36) 888 (36)

No antimicrobials were above 82% S for 2004
% Suscep is similar for ciprofloxacin and levofloxacin

Thornsberry et al, IDSA 2003, abstr/poster 222.

12 Steps to Prevent Antimicrobial Resistance in Hospitalized Adults
1. Vaccinate
2. Get the catheters out
3. Target the pathogen
4. Access the experts
5. Use antimicrobials wisely
6. Practice antimicrobial control
7. Treat infection, not contamination
8. Treat infections, not colonization
9. Know when to say “no” to vanco
10. Stop treatment when infection is cured or unlikely
11. Isolate the pathogen
12. Break the chain of contagion

Mechanisms of Antibiotic Resistance
- Influx-Block Porin Channel
- Efflux-Pump
- Enzyme Inactivation
- Target Alteration
- Metabolic Bypass
- Environment Factors

A ~ Antibiotic
**Gram Positive Resistance**

Primary mechanism of beta-lactam resistance in G+’s is an alteration of penicillin binding protein affinity (PBP)

- MRSA (mecA positive) PBP alteration & beta-lactamase producer
- MRSE PBP alteration & beta-lactamase producer
- PRSP

Enterococci 98% PBP alteration
- 2 % beta-lactamase producer
- Have enzymes that inactivate aminoglycosides
- Bypass the effect of vancomycin

ISA/GISA
Over production PBP-2 & thickened cell wall

---

**Influences that Increase Antibiotic Prescribing**

July 1998 Survey of all primary care MD’s in Massachusetts

APUA Newsletter Vol 19 2001

- 499 usable responses out of ~6,000 questionnaires (8%)
  - 93% agreed that physicians over prescribe antibiotics

<table>
<thead>
<tr>
<th>Factor</th>
<th>% MD’s Factor influenced Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purulent Discharge</td>
<td>64%</td>
</tr>
<tr>
<td>Dx Uncertainty</td>
<td>62%</td>
</tr>
<tr>
<td>Patient request</td>
<td>59%</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>48%</td>
</tr>
<tr>
<td>Fever</td>
<td>47%</td>
</tr>
<tr>
<td>Tx Uncertainty</td>
<td>36%</td>
</tr>
<tr>
<td>Payer Policy-therapeutic</td>
<td>26%</td>
</tr>
<tr>
<td>Time Pressure</td>
<td>26%</td>
</tr>
<tr>
<td>Return visit cost</td>
<td>20%</td>
</tr>
<tr>
<td>Litigation concern</td>
<td>19%</td>
</tr>
<tr>
<td>Payer policy-QA</td>
<td>13%</td>
</tr>
<tr>
<td>Drug promotion</td>
<td>7%</td>
</tr>
<tr>
<td>Resistance concern</td>
<td>5%</td>
</tr>
<tr>
<td>Cost</td>
<td>2%</td>
</tr>
</tbody>
</table>

---

**Cost of Nosocomial Infections**

Roberts, R SHEA 2001

- Retrospective cohort study of patients at Cook County with hospital acquired infections (HAI-CDC criteria)
  - Randomly selected patients from 1998 discharge database with ≥5 ICD-9 diagnoses
  - Severity of illness measured using Apache III scores
  - Costs calculated from hospital perspective

- 193 (164 medical & 29 surgical) patients (41/193 with HAI)
  - Medicine average cost of hospitalization with HAI $24,762 vs. $6,202 without
  - Surgical average cost of hospitalization with HAI $52,422 vs. $20,823 without

Confounding variable analysis showed suspected HAI added $13,236 (SE $1,146) & documented HAI added $18,223 (SE $2,225)
**P. aeruginosa Resistance**

**ICU patients with nosocomial infections**

<table>
<thead>
<tr>
<th>% resistance 2002</th>
<th>% increase in resistance (2002 vs. 1997-2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem&lt;sup&gt;R&lt;/sup&gt; <em>P. aeruginosa</em></td>
<td>22.3%</td>
</tr>
<tr>
<td>Quinolone&lt;sup&gt;R&lt;/sup&gt; <em>P. aeruginosa</em></td>
<td>32.8%</td>
</tr>
<tr>
<td>3rd Ceph&lt;sup&gt;R&lt;/sup&gt; <em>P. aeruginosa</em></td>
<td>30.2%</td>
</tr>
</tbody>
</table>

R = resistant


---

**Collateral Damage of Normal Flora**

**Antibiotic Fragging**

Hospital/NH Flora

*Antibiotic Delivery*  

*Soup Flora*  

*GI Flora*  

*Infected Site*  

*GI Flora*  

*Skin Flora*

---

**Relationship between fluoroquinolone use & changes in susceptibility to fluoroquinolones**


- Observed changes in 11 pathogens at 10 U.S. teaching hospitals 1991-2000
- Data demonstrated significant decreases in fluoroquinolone susceptibility for *P. aeruginosa* (25.1%), *P. mirabilis* (11.9%), *E. coli* (6.8%), & *S. aureus* (26.8%)
- Change in fluoroquinolone susceptibility linked to increase in fluoroquinolone use
Antimicrobial Agents

The Penicillins

- Natural Penicillins
  - Penicillin G (Benzyl Pen G, Procaine Pen G, Benzathine Pen G)
  - Penicillin V (Pen VK- Penoxymethyl)
- Penicillinase-resistant Penicillins (anti-staph pens)
  - Nafcillin, Methicillin, Oxacillin, Cloxacillin, Dicloxacillin
- Extended-spectrum Penicillins
  - Ampicillin, Amoxicillin
- Antipseudomonal Penicillins
  - Carbenicillin, Ticarcillin, Piperacillin
- β-Lactamase Inhibitor Combinations
  - Augmentin (Amox + clavulanate), Timentin (Ticar + clavulanate), Unasyn (Ampicillin + sulbactam), Zosyn (Piperacillin+tazobactam)
The Penicillins

- Natural Penicillins (Pen G)
  - In past, main use: penicillin susceptible strep. Limited use now
  - Still used for Strep throat (S. pyogenes)
- Penicillinase-resistant Penicillins (anti-staph pens)
  - Main use: Staph
- Extended-spectrum Penicillins (Ampicillin, Amoxicillin)
  - Amox main use: Strep, some H. flu (60%), some E.coli (70%)
  - Amp IV/main use: in combo with AG, less activity vs. S. pneum
- Antipseudomonal Penicillins (Ticar, Pip)
  - Used for gm (-) pathogens and in combo with AG for Pseudomonas
- β-Lactamase Inhibitor Combinations
  - Stable against BL (+) orgs: Staph, H. flu, M. cat, E.coli, Kleb.
  - Timentin, Zosyn: above, plus Pseudomonas (with AG)

The Cephalosporins

- First Generation Cephalosporins
  - IV (Cefazolin), PO (Cephalexin)
    - Staph, Strep
    - EKP (E.coli, Klebsiella, Proteus)
- Second Generation Cephalosporins
  - Cefuroxime (IV/PO), Cefpodoxil (PO), Cefdinil (PO)
    - Staph, Strep, E.coli, plus H. influenzae and M.catarrhalis
    - Antianaerobic 2nds (cefoxitin, cefotetan): OK B. fragilis,
    - moderate Staph, Strep, EKP, H. flu, M. cat
- Third Generation Cephalosporins
  - IV: Broad spectrum: Ceftriaxone, Ceftazidime
    - PO: Cefibuten
      - Staph, Strep, H. flu, M. cat, Enterobacteriacea
  - Antipseudomonal: Ceftazidime (Fortaz), Cefepime (Maxipime)

Miscellaneous β-Lactams

- Imipenem-cilastatin (Primaxin)
- Meropenem (Merrem)
  - Broad spectrum
    - Gm (+)s, except MRSA and Corynebacterium JK
    - Gm (-)s, including pseudomonas
- Aztreonam (Azactam)
  - Gram-negatives, including Pseudomonas
Macrolides, Azalides, & Ketolides

- Erythromycin
- Azithromycin (Zithromax)
- Clarithromycin (Biaxin)
- Telithromycin (Ketek)

  - Traditionally have had broad-spectrum activity, now have limited activity against S. pneumoniae and H. influenzae (except telithromycin)
  - Main use: typical & intracellular RTI pathogens
    - Mycoplasma, Chlamydia, Legionella

Fluoroquinolones

- Ciprofloxacin (Cipro)
- Levofloxacin (Levaquin)
- Gatifloxacin (Tequin)
- Moxifloxacin (Avelox)
- Gemifloxacin (Factive)

Aminoglycosides

Gram-negatives, including Pseudomonas, often used in combination with B-lactams:

- Gentamicin (Garamycin)
- Tobramycin (Nebcin, Tobrex)
- Amikacin (Amikin)

Miscellaneous Aminoglycosides
- Neomycin (main use topical)
- Streptomycin (syphilis, TB, enterococcal endocarditis)
- Netilmicin (not used)
### Tetracyclines & Glycycline

- Tetracycline (Achromycin, Sumycin)
- Demeclocycline (Declomycin)
- Doxycycline (Vibramycin)
- Minocycline (Minocin)
- Tigecycline (Tygacil)
  - Broad-spectrum. Limited use:
    - Tetracycline: acne
    - Doxy: PID, CAP

### Miscellaneous Antibiotics

- Chloramphenicol (Chloromycetin)
- Clindamycin (Cleocin)
  - Staph, Strep, Anaerobes
- Metronidazole (Flagyl)
  - Parasites, anaerobes
- Polymyxin B (Aerosporin)
- Polymyxin E (Colistin)
- Trimethoprim- Sulfamethoxazole (Bactrim, Septra)
  - Broad-spectrum: traditionally has been used for resp. tract infections, but is limited by S. pneumonia resistance.

### Retail Charge for 10 day Supply

January 2004

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor</td>
<td>500mg TID</td>
<td>$101.39</td>
</tr>
<tr>
<td>Loracarbef</td>
<td>400mg BID</td>
<td>$124.39</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>200mg BID</td>
<td>$105.69</td>
</tr>
<tr>
<td>Cefixime</td>
<td>400mg QD</td>
<td>$87.99</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>500mg BID</td>
<td>$167.99</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>500mg BID</td>
<td>$175.69</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>300mg BID</td>
<td>$98.99</td>
</tr>
<tr>
<td>Amox/Clav</td>
<td>875/125mg BID</td>
<td>$122.99</td>
</tr>
<tr>
<td>Amox/Clav</td>
<td>2000/125 BID</td>
<td>$67.39</td>
</tr>
</tbody>
</table>

$ Augmentin®

$ AugmentinXR®
Retail Charge for 10 day Supply
January 2004

- Ciprofloxacin 750mg Q12H $125.39
  - Cipro®
- Levofoxacin 500mg/ Q24H $106.99
- Levofoxacin 750mg Q24H (5 day) $107.69
  - Levaquin ®
- Moxifloxacin 400mg QD $100.69
  - Avelox ®
- Gatifloxacin 400mg QD $96.99
  - Tequin ®

Retail Charge for 10 day Supply
Twin Cities January 2004

- Clarithromycin 500mg BID $93.69
  - Biaxin ®
- Clarithromycin XL $41.39
  - Biaxin ®
- Zithromycin Z-Pack $49.69
  - Zithromax ®
- Telithromycin 800mg (2-400mg) QD $86.68-92.69/$126.89-127.95
  - Ketek®
- Telithromycin KETEK Pak® $66.39 - $63.78

Antitubercular Agents

- Isoniazid
- Ethionamide
- Thiacetazone
- Rifampin
- Rifabutin
- Pyrazinamide
### Antiviral Agents

- Acyclovir
- Valacyclovir
- Famciclovir
- Ganciclovir
- Ribavirin
- Amantidine

### Antiretroviral Agents (HIV)

- **Nucleoside reverse transcriptase inhibitors**
  - Didanosine
  - Lamivudine
  - Stavudine
  - Zalcitabine
  - Zidovudine
- **Non nucleoside reverse transcriptase inhibitors**
  - Delavirdine, Nevirapine
- **Protease inhibitors**
  - Indinavir
  - Nelfinavir
  - Ritonavir
  - Saquinavir

### Antifungal Agents

- Amphotericin B
- Lipid based Amphotericin B products
- Fluconosine
- Caspofungin
- **Azole Antifungals**
  - Ketoconazol
  - Fluconazol
  - Itraconazol
  - Voriconazol
Drugs of Choice

• Staph
  – Not MRS: PRP, βLIC, Clinda, Vanco, TMP/SMX
  – MRS: Vancomycin + Rifampin or Gentamicin
• Strep
  – Not DRSP: PenG/V, Amox, Amp, 1st Ceph, Macrolide
  – DRSP: Amox, Amox-clav, Quinolone, Ceftriaxone IM/IV, Vancomycin IV
• Enterococcus
  – Serious infect: (IV) Ampicillin + Gentamicin
  – UTI: Amp, Amox, Doxycl, Nitrofurantoin

PRP (penicillinase-resistant pen), βLIC (β-lactamase inhibitor combination), DRSP (drug-resistant S. pneumoniae)

Drugs of Choice

• Neisseria
  – N. gonorrhoeae: Ceftriaxone, Cefixime, Cefpodoxime
  – N. meningitidis (meningitis): 3rd Ceph, CAP
• Haemophilus influenzae
  – βL(-): Amoxicillin, ampicillin, azithromycin
  – βL(+): Amoxicillin-clav, 2nd/3rd Ceph,
• Moraxella catarrhalis
  – Amoxicillin-clavulanate, TMP/SMX, Macrolide

Drugs of Choice

• E.coli, Klebsiella
  – 1st Ceph, Aminoglycoside, βLIC, 2nd-3rd Ceph, Quinolone
• Proteus
  – Ampicillin, TMP/SMX, most antibiotics
• Enterobacter
  – Imipenem, meropenem, cefepime + aminoglycoside,
  – Anti Ps Pen, TMP/SMX, 3rd + aminoglycoside
• Serratia
  – 3rd Ceph + aminoglycoside, βLIC, TMP/SMX, ESP, imipenem, meropenem
Drugs of Choice

- **Pseudomonas aeruginosa**
  - Piperacillin+tazobactam or Cefepime
  - Tobramycin (High dose)
  - Ciprofloxacin (400mgQ8H) or levofloxacin (750mg Q24H)
  - Imipenem or meropenem
  - Therapy should be a combination of beta-lactam and fluoroquinolone or aminoglycoside
  - May not need to be as aggressive with UTI

- **Bacteroides fragilis**
  - PO: Amoxicillin-clavulanate, metronidazole, clindamycin
  - IV: Metronidazole, βLIC, clindamycin, Zoyn, Unasyn, or imipenem

---

Pharmacokinetics vs Pharmacodynamics

Pharmacokinetics - mathematically describes the relationship of antibiotic concentration vs time (half-life, distribution volume, AUC, etc.)

Pharmacodynamics - describes the relationship of antibiotic concentration vs pharmacologic effect or bacterial death (PD Outcome Parameters)

Pre-clinical & through Phase I - Phase IV

In-vitro ↔ Animal ↔ Human

---

Pharmacodynamic Outcome Parameters

- **AUC / MIC = 100 / 0.5 = 200**
- **Cmax / MIC = 8 / 0.5 = 16**
- **T > MIC ~ 24hrs**
- **AUC = 100 mg h / L**
- **Cp-max Free Drug**
- **mg/L**
- **MIC=0.5**
- **Time (hrs)**
Proposed Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&gt;MIC</td>
<td>β-lactams, macrolides, aztreonam, carbapenems &amp; clindamycin</td>
</tr>
<tr>
<td>AUC/MIC</td>
<td>Aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin &amp; telithromycin quinupristin/dalfopristin</td>
</tr>
<tr>
<td>Cp-max/MIC</td>
<td>Aminoglycosides &amp; fluoroquinolones</td>
</tr>
</tbody>
</table>

*Covariance of parameters with antibiotic dose

2003 IDSA CAP Guidelines

- Healthy & no previous antibiotic therapy (3 months)
  - Macrolide or Doxycycline
- Healthy but has had previous antibiotic therapy
  - Respiratory fluoroquinolone
  - Advanced macrolide plus high dose amoxicillin
  - Advanced macrolide plus high dose amoxicillin/clavulanate
- Comorbidities present (COPD, CHF, diabetes…)
  - No previous antibiotics
    - Advanced macrolide or Respiratory fluoroquinolone
  - Previous antibiotics within past 3 months
    - Respiratory fluoroquinolone or Advanced macrolide and beta-lactam

*Clin Infect Dis 37:1405-1433, 2003

Colds and Antibiotics

MN Pharmacist 58:39-40, 2004

- Telephone survey
  - 27% patients believe taking antibiotics make them feel better more quickly
  - 32% patients believe taking antibiotics during a cold prevent more serious illness
  - 48% expect antibiotic Rx when visiting MD
Antibiotic Overview

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>BL</th>
<th>MAC</th>
<th>FQ</th>
<th>DOX</th>
<th>Ket</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCN-R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macro-R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

• Antibiotic choice highly dependent on specific agent selected
• For S. pneumoniae with PCN MIC > 2 mg/L, vancomycin, FQ, or ketolide probably best choice depending on circumstances

Summary: Guidelines for Treatment of Community-Acquired Infections

• Sinusitis (Oto & Allergy)
  Health Partnership
  – Amoxicillin-clavulanate
  – Amoxicillin
  – Cefuroxime
  – Ceftazidime
  – Enhanced-affinity quinolones

• AECB (ATS/SCAI)
  – Simple (<3/yr): Doxycycline, macrolides
  – Complicated: Amoxicillin, quinolones
  – Complicated w/pseudomonal: Ciprofloxacin

• CAP (IDSA/ATS/CDC)
  – See IDSA 2003 Guidelines
  – New joint IDSA/ATS guideline due Spring 2005
Treatment of Acute Otitis Media: 
Consensus Recommendations 2002

- Based on DRSP Therapeutic Working Group (CDC) recommendations 1999
  - Most active agents: Amoxicillin-clavulanate and Ceftriaxone IM

- Modifications
  - Removal of cefuroxime (Ceftin)
  - Does not decrease NP carriage of PRSP
  - True Allergy: recommendations (azithromycin, clindamycin, EES/sulfasoxazole)
  - Dose of amoxicillin: high vs. traditional


Summary of Consensus Recommendations
Antibiotics

<table>
<thead>
<tr>
<th>Low Risk: No PRSP</th>
<th>Risk Factor: Age, Day care, Previous Abs</th>
<th>Amoxicillin 80-90 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Abs</td>
<td></td>
<td>Amoxicillin 80-90 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Consider tympanocentesis for failures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftriaxone 50mg/kg IM</td>
</tr>
</tbody>
</table>

Penicillin Allergy:
- Azithromycin
- Clindamycin
- (if Staph aureus, H. flue and M. cat can be ruled out)
- EES/SMX


Summary

- Use “simplified list” of pathogens
- Know “most common” pathogens for “most common” diseases
- Pharmacokinetic/pharmacodynamic (PK/PD) profiles can be used to predict efficacy and determine “therapeutic” doses
- “Real Science”: PK/PD parameters, bacterial eradication studies, and clinical outcome studies are now used to develop treatment guidelines
Stuart Smalley Closing Thoughts

• Remember:
  – Every time you use an antibiotic, you are conducting your own experiment in Darwinian theory!
  – Wash your hands, there are some bad bugs out there!