Bacterial Resistance of Respiratory Pathogens

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Antibiotic Misuse

- ~150 million courses of antibiotic prescribed by office based prescribers
  - Estimated 50-66% of prescriptions unnecessary
- Represents 25% increase over 1980
- Use in children < 15 years 3X greater than other age groups
- Most common Dx
  - Common respiratory
  - URTI
  - Bronchitis
  - Sinusitis
  - Pharyngitis
Antibiotic Misuse

- Enormous problem
  - Problem spans the farmers feedlot to children’s day care center to the physician’s office to the acute care hospital
  - Problem for 3rd world countries & western civilization
  - Pressure on clinician to prescribe
  - Issue that involves patient compliance

- Solutions to this problem will require a multidisciplinary approach
Introduction

- Antibiotic resistance to standard therapy with common bacteria is an ever increasing problem
- Bacteria have strategic advantages
  - Naturally mutate
  - Extraordinary rates of growth
  - Produce a “new generation” of bacteria with genetic advantage
Resistant Bacteria

- AMP-R *H. influenzae*
- PCN- R *S. pneumoniae*
- Multiple antibiotic resistant *Enterococci*
- Methicillin resistant staphylococci
- Vancomycin resistant staphylococci
- *M. tuberculosis*
- *N. gonorrhoeae*
- *S. pyogenes*
- Gram negative bacteria
Antibiotic Therapeutic Approach

- Objective decision making
  - Use antibiotics only when needed
  - Be selective and use minimum number
  - Optimize pharmacodynamic outcome parameters
    - Peak / MIC ratio
    - AUC / MIC ratio
    - Time > MIC
  - Optimize antibiotic dose & interval
Therapeutic Approach

- URTI & LRTI Dilemma
  - Bacterial pathogen & antibiotic susceptibility often unknown
    - Gram stain often not done
    - Sputum or sinus often not cultured
  - + Chest X-ray
- Treatment guidelines may not be current with level of bacterial resistance or incorporate new agents
Antibiotics

- **Antibiotics kill bacteria:**
  - Transport to the site of infection
  - Transport into the bacteria (Influx)
  - Binding to a strategic site
    - PBP
    - Ribosome
    - DNA Gyrase
  - Metabolically poisoning the bacteria
    - Time dependent
    - Concentration dependent
Common Mechanisms of Bacterial Resistance

  - Enzyme is made up of amino acids
  - Altering amino acids sequence changes potency (ESBL)
  - Result of beta-lactamase
    - Open antibiotic beta-lactam ring
    - Regenerate enzyme
  - Over 50 different plasmid enzymes
  - Several chromosomally enzymes
    - Richmond Sykes or Bush Type I enzymes
Antibiotic Destruction

- **Macrolides**
  - Enzyme alters the 50S ribosome
  - Resistance to erythromycin means resistance to all current macrolides
- **Efflux**
  - Newer macrolides still likely effective
Antibiotic Destruction

- Target alteration
  - Beta-lactams
    - Alteration of penicillin binding proteins (PBP’s)
      - Methicillin resistant S. aureus (MRSA) or S. epidermidis (MRSE)
      - alteration of PBP-2
    - Penicillin Resistant S. pneumoniae
    - Enterococcus
S. pneumoniae

- Pneumococcal Sentinel Surveillance System, November 1996)
  - Sensitive (PCN MIC $\leq 0.06$ mg/L)
  - Nonsusceptible (PCN MIC 0.12 - 1.0 mg/L)
  - Resistant (PCN MIC $\geq 2.0$ mg/L)
**S. pneumoniae**

- Mechanism of resistance
  - Modification of penicillin binding proteins (PBP’s)
  - Resistance is not the result of beta-lactamase production
    - Magnitude of resistance correlates with extent of PBP alteration
    - Common in serotypes 6B, 9V, 14, 19A, 19F, and 23F
S. pneumoniae Vaccination

- Pneumovax
  - Adult
- Prevnar
  - Pediatric
- Reported shortages with both vaccines
Haemophilus influenzae

Ampicillin Resistant

AMP-R
H. influenzae

- Mechanism of ampicillin resistance
  - Resistance is the result of beta-lactamase
    - Most common form of resistance
  - Beta-lactamase negative ampicillin resistant strains have been reported
    - Probably the result of alteration of PBP
    - Presently a rare occurrence
**H. influenzae type B (Hib)**

- Vaccine is directed at type B *H. influenzae*
  - Unknown whether vaccination with Hib vaccine will protect against other typeable or nontypeable strains of *H. influenzae*
- Vaccine has virtually wiped out cases of Hib meningitis
**Moraxella catarrhalis**
Beta-lactamase Positive
**M. catarrhalis**

- Mechanism of resistance
  - Resistance is the result of beta-lactamase production
  - Resistance is not the result of alteration of PBP’s
  - Nationally and locally virtually 100% of *M. catarrhalis* produce beta-lactamase
Atypical Respiratory Pathogens
Atypical Pathogens
(M. pneumoniae, L. pneumophila, C. pneumoniae)

- Bacterial pathogens without a cell wall
  - Cannot use beta-lactam antibiotics
- Obligate intracellular pathogen
  - Antibiotic must penetrate into the cell
    - Can use macrolides, tetracyclines, or quinolones
    - Cannot use beta-lactam antibiotic
Therapeutic Options

- **Amoxicillin or 1st Generation Cephalosporin**
  - Will not cover atypical pathogens
  - Will not cover PCN-R *S. pneumoniae*
  - + *H. influenzae* coverage
  - Requires multiple doses per day for 10-14 days
  - High dose amoxicillin therapy associated with significant diarrhea
  - Expensive
Therapeutic Options

- **TMP/SMX**
  - Will not cover atypical pathogens
  - Will not cover PCN-R *S. pneumoniae*
  - Resistance to other pathogens has grown over the years
  - BID schedule
  - Relatively inexpensive
Therapeutic Options

- Beta-lactamase inhibitors or Advanced Generation Cephalosporin
  - Will not cover atypical pathogens
  - Will not cover PCN-R *S. pneumoniae*
  - *H. influenzae* coverage
  - Convenience factor variable
  - Expensive
Therapeutic Options

- Clarithromycin/Azithromycin
  - Will cover atypical pathogens
  - Probably will not cover PCN-R
    - *S. pneumoniae* due to cross resistance
  - + *H. influenzae* coverage (Biaxin)
  - Convenience factor variable
  - Expensive (Biaxin > Zithromax)
Therapeutic Options

- Ciprofloxacin
  - Poor Streptococcal coverage
  - Generally not considered CAP agent
  - + Atypical pathogens
  - ? PCN-R *S. pneumoniae*
  - Not recommended for pediatrics
  - BID schedule
  - Expensive
Patient Compliance

- The right diagnosis, antibiotic, dose, and interval meaningless if the patient does not take the drug
- PO better than IV/IM
- QD or BID better than TID or QID
- Short course better than 10 to 14 days
Conclusions

- Patterns of resistance are evolving
- Practitioners must remain current on changing trends
- Need to maintain contemporary treatment guidelines
- Avoid antibiotic misuse
- Must strictly enforce infection control
- Need new antibiotics
- Each prescription for an antibiotic is an experiment in Darwinian theory