Antimicrobial Resistance
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Disclosures
- I have nothing to disclose.

Objectives
- Discuss antimicrobial resistance
- Discuss Antimicrobial Stewardship Programs (ASP)
The History of Medicine

- 2000 B.C. – Here, eat this root
- 1000 A.D. – That root is heathen. Here, say this prayer.
- 1850 A.D. – That prayer is superstition. Here, drink this potion.
- 1920 A.D. – That potion is snake oil. Here, swallow this pill.
- 1945 A.D. – That pill is ineffective. Here, take this penicillin.
- 1955 A.D. – Oops...bugs mutated. Here, take this tetracycline.
- 1960-1999 – 39 more “oops”...Here, take this more powerful antibiotic.
- 2000 A.D. – The bugs have won! Here, eat this root.

— Anonymous

Antimicrobial History (1)

- Ancient Egyptians used honey as a wound dressing
- Contains small amounts of hydrogen peroxide and the stickiness of honey provided a wound dressing
- In ancient Serbia, old bread was pressed on wounds to help prevent infection
- Many of the molds that grew on the bread contained early, raw forms of penicillin
- 1640
- John Parkinson wrote about mold’s effectiveness as an antibiotic in his book on pharmacology
- 1870
- Sir John Scott Burdon-Sanderson observed and recorded his observation that a culture fluid that had been manually placed with mold would not produce bacteria
- 1877
- Louis Pasteur determined that cultures of bacillus anthracis specked with the penicillium notatum could not easily sustain growth

Antimicrobial History (2)

- 1927
  - German Gerhard Domagk found that an industrial dye, prontosil rubrum, had antibacterial action against staphylococci and hemolytic streptococci
  - Sulfonamide was the first antimicrobial
  - Received Nobel Prize
- 1928
  - British Alexander Fleming observed the antibiotic effects of penicillium
  - Pencillinum notatum had destroyed staphylococcus
  - Scientists dubbed it a “miracle drug”
  - Penicillin was finally isolated in 1939
  - Early 1940s large-scale fermentation processes were developed for the production of penicillin
- 1940
  - Russian Selman Waksman isolated a fungus that eventually led to the development of the anti-tuberculosis drug streptomycin
What is Antimicrobial Resistance?

- Ability of organisms to resist the effects of an antimicrobial
  - Organisms change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to cure or prevent infections
  - The microbes have a better survival rate
    - continue to multiply causing more harm

Antimicrobial Resistance (2)

- Selected Pressure
  - Susceptible microbes are killed easily with antimicrobials leaving organisms that are resistant
  - They can then pass on their resistance genes
    - Replication
    - Conjugation
      - Plasmids carrying the genes jump from one organism to another
  - “This process is a natural, unstoppable phenomenon exacerbated by the abuse, overuse and misuse of antimicrobials in the treatment of human illness and in animal husbandry, aquaculture and agriculture.”

Antimicrobial Resistance (3)

- Abuse, Overuse and Misuse of Antimicrobials
  - Increase in drug-resistant organisms
    - Primary cause is repeated and improper uses of antimicrobials
  - Increased pressure on physicians inevitably leads to “defensive” and unnecessary prescribing as a means of forestalling potential complications
  - In North America it is estimated that physicians in both Canada and the United States over-prescribe antibiotics by 50%
Antimicrobial Resistance (4)

- Causal associations between antimicrobial use and the emergence of antimicrobial resistance
  - Changes in antimicrobial use are paralleled by changes in prevalence of resistance

**Fluoroquinolone Use and Resistance Rates in PSA and Gram-Negative Bacilli**


Antimicrobial Resistance (5)

- Causal associations between antimicrobial use and the emergence of antimicrobial resistance (cont)
  - Antimicrobial resistance is more prevalent in health care-associated bacterial infections, compared with those from community-acquired infections
  - Patients with health care-associated infections caused by resistant strains are more likely than control patients to have prior antibiotic exposure
  - Areas within hospitals with the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use
  - Increased length of exposure to antimicrobials increases the likelihood of colonization with resistant organisms

Antimicrobial Resistance (6)

- There is an association between development of antimicrobial resistance and mortality
  - Meta-analysis
    - Patients with MRSA bacteremia had an increased risk of mortality compared to patients with MSSA bacteremia

Cosgrove et al CID 2003
Fewer Drugs Created to Combat Antibiotic Resistance

- Fewer antimicrobials are being developed to combat antibiotic resistance.

Antimicrobial Development vs. Resistance

- Graph showing the development of antimicrobials and the increase in resistance.

Ampicillin

- Is a member of the Semi-synthetic penicillin class.
- Works on the cell wall and is a beta-lactam antibiotic.
- Has activity against gram positive and gram negative organisms.
  - *Streptococcus*
  - *Enterococcus*
  - *Listeria*
  - Gram negative coverage is very limited since there is increased resistance.
- Does not cover for *Staphylococcus* organisms.
- Crosses over to the CNS.
- Is a bacteriocidal drug.
Nafcillin
- Interferes with the cell wall and is a member of the penicillinase-resistant penicillin class
- Has activity against gram-positive organisms
  - MSSA
  - *Streptococcus*
- Does not work against MRSA
- This is the BEST antibiotic to use against MSSA
- Is a bactericidal drug
- Crosses over to the CNS

Vancomycin
- Is a member of the glycopeptide class
- Interferes with cell wall formation
- Covers for gram positive organisms
  - *Staphylococcus* (MSSA/MRSA/CaNS)
  - *Streptococcus*
  - *Enterococcus*
- Little to no activity against gram negative organisms
- There is some resistance brewing
  - VRE, VRSA, and VISA
- Crosses over to the CNS
- Side Effects
  - Red Man’s Syndrome
  - Flushing and sometimes hypotension
  - Histamine mediated
  - Need to slow down the infusion rate and pretreat with benadryl

Linezolid
- Oxazolidinone
- Active against gram-positive organisms
  - *Streptococcus*
  - *Staphylococcus* (MRSA, MSSA and CaNS)
  - *Enterococcus*
- Resistant organisms like VRE, VRSA and VISA
- Mechanism of actions is on the ribosome
- See both bactericidal (S. pneumoniae) and bacteriostatic (S. aureus) activity
- Gets great penetration in the lung
  - Much better than vancomycin
- Crosses over to the CNS
- Side effects
  - Neutropenia
  - Thrombocytopenia
Clindamycin
- Is a member of the lincosamide class
- Is active against gram-positive and anaerobe organisms
  - Streptococcus
  - Staphylococcus (MSSA, MRSA)
  - Anaerobes ABOVE the GI tract
- DOES NOT cross over CNS
- Mechanism of action is against ribosomes
  - Is a bacteriostatic drug

Aminoglycosides
- This is a class of antibiotics that include gentamicin, tobramycin and amikacin
- Mechanism of action is binding to the ribosome so they are bacteriostatic
- Is active against gram-positive and gram-negative organisms
  - S. aureus – DO NOT use alone
  - E.coli
  - Klebsiella
- Side Effects
  - Renal insufficiency
  - Aminoglycosides DO NOT cross over into the CNS

Cefotaxime/Ceftriaxone
- Are a member of the cephalosporin class
  - These are third generation cephalosporins
- Works against the cell wall so it is a beta-lactam antibiotic
- Is active against gram-positive, gram-negative and anaerobic organisms
  - Streptococcus
  - Some staphylococcus (MSSA only)—so not a primary drug against MSSA
  - Citrobacter
  - Enterobacter
  - E.coli
  - Klebsiella
- NO PTA coverage
- Has good CSF penetration
- NICU babies are usually put on Cefotaxime (Claforan) vs. Ceftriaxone because of the interaction with HAL and the bilirubin displacement
Ceftazidime

- Is a member of the cephalosporin class
- It is a third generation cephalosporin
- Works against the cell wall so it is a beta-lactam antibiotic
- Crosses over to the CNS
- Is active against gram-positive, gram-negative and anaerobic organisms
  - Same coverage as Cefotaxime and Ceftriaxone but also covers PSA

Cefepime

- Is a member of the cephalosporin class
  - It is a fourth generation cephalosporin
- Works against the cell wall so it is a beta-lactam antibiotic
- Crosses over to the CNS
- Is active against gram-positive, gram-negative and anaerobic organisms
  - Same coverage as third generation cephalosporins but also covers PSA
  - Also covers Enterobacter, Serratia and Citrobacter better due to its stability against ampC chromosomal beta-lactamases

Piperacillin/Tazobactam

- Is a member of the extended-spectrum penicillin class
- Tazobactam is added to combat pathogens who become immune to the beta-lactams by producing beta-lactamases
  - It is a second beta-lactam
- Is active against gram-positive, gram-negative and anaerobe organisms
  - Enterococcus
  - Enteric gram negatives
  - PSA
  - Gut anaerobes
- This is an awesome abdominal infection drug
- Crosses over to the CNS
Meropenem

- This is a member of the carbopenem class
- Is active against the cell wall so it is bactericidal
- Is active against gram-positive, gram-negative and anaerobe organisms
  - Enteric gram negatives
  - PSA
  - Gld anaerobes
- The ultimate antibiotic against resistant GNR that have both ampC beta-lactamases and ESBLs
- Meropenem is used in pediatrics (vs. imipenem) because of the decreased risk of seizures
- Great CNS penetration

Beta Lactams

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
  - aztreonam
- Beta-lactamase inhibitor
  - Pip/tazo

Beta Lactams

- Mechanism of Action:
  - Inhibit the growth of sensitive bacteria
  - Inactivates a family of enzymes on the cell membrane inhibiting cell wall synthesis
    - Penicillin-binding proteins (PBPs)
  - Process is bactericidal
Beta Lactam Resistance (1)
- Three general mechanisms
  - Decreased penetration to the target site
  - Alteration of the target site
  - Inactivation of the antibiotic by bacterial enzyme

Beta Lactam Resistance (2)
- Decreased Penetration:
  - Outer membrane of GNR
    - Barrier
    - Ex: PSA with some cephalosporins

Beta Lactam Resistance (3)
- Alteration of Target Site:
  - Target sites = PBPs in the cytoplasmic membrane
  - Alterations of PBPs can influence their binding affinity for beta lactams
    - PCN resistance in pneumococci
    - MRSA
    - H. Influenza
Beta Lactam Resistance (4)
- Inactivation of Bacterial Enzyme:
  - Production of beta-lactamase
    - the major mechanism of resistance to the beta-lactam antibiotics
    - Penicillinase
    - Cephalosporinases
    - Beta-lactamases (cleaves both PCNs and cephalosporins)
    - Carbopenemase

Beta Lactam Resistance (5)
- Transmitted via chromosome or plasmid
  - Chromosome
    - Affects the whole species
    - Inducible resistance
  - Plasmid
    - Affects only an individual strain
    - Mostly produces beta-lactamase constitutively
      - ESBL

Staph aureus resistance (1)
- MRSA
  - Alterations of PBPs make resistance to methicillin
    - Requires mec gene
    - mecA encodes PBP2A that establishes resistance to methicillin
    - Occurs when oxacillin MIC \( \geq 4 \) mcg/mL
**Staph aureus resistance (2)**
- Macrolide/Lincosamide Resistance
  - Plasmid Mediated (ermA and ermC genes)
    - Can exhibit inducible clindamycin resistance when erythromycin is R and clindamycin is S
      - D-test
    - Also can exhibit constitutive resistance
      - Erythromycin R and Clindamycin R

**Staph aureus resistance (3)**

**Staph aureus resistance (4)**
- VISA
  - First reported case of diminished vanc susceptibility in a clinical isolate was 1997
  - S. aureus had a unusually thickened cell wall
    - Contained peptides capable of binding vanc
Staph aureus resistance (5)
- VRSA
  - First reported in 2002
  - S. aureus received a vanA gene plasmid from VRE
  - Due to the synthesis of an alternative cell wall terminal peptide which Vanc cannot bind to
  - At least 7 reported cases of infection in US

Staph aureus resistance (6)
- Vancomycin Susceptibilities
  - Vanc susceptible: \( \leq 2 \) mcg/mL
  - Vanc intermediate (VISA): 4 – 8 mcg/mL
  - Vanc resistant (VRSA): \( \geq 16 \) mcg/mL

Staph aureus resistance (7)
- Heteroresistant strains of S. aureus
  - Contain subpopulations of bacteria with VISA and VSSA
  - The MIC for the entire population of the strain is within the susceptible range
  - Can see vanc failures, prolonged bacteremia, etc
  - There is no test yet to determine hVISA
    - May try to grow the culture longer
What is ASP?

- “The optimal selection, dose and duration of an antimicrobial that results in the best clinical outcome for the treatment of infection, with minimal toxicity to the patient and minimal impact on subsequent development of resistance”

ASP (2)

- IDSA and SHEA published guidelines to help institutions develop ASP
  - Endorsed by multiple organizations
    - AAP
    - PIDS
  - Majority of the evidence supporting the guidelines come from adult studies

ASP (3)

- Primary goal
  - Optimize clinical outcomes while minimizing unintended consequences of antibiotic use
    - Toxicity
    - Selection of resistant organisms
- Secondary goal
  - Reduce health care cost without compromising quality of care
ASP (4)
- Core ASP strategies
  - Prospective audit with intervention and feedback to a prescriber
  - Formulary restriction and preauthorization of antimicrobial use

Dellit TH et al. CID 2007

ASP (5)
- Prospective audit with intervention and feedback
  - ASP reviews patients on antimicrobials
    - ID physician or clinical pharmacist with ID training
  - Inappropriate orders will start interactions between ASP and the prescribing physician
    - Advisement is given on appropriate antimicrobial selection, dosing and duration of therapy
  - Can result in reduced inappropriate use of antimicrobials


ASP (6)
- Prospective audit with intervention and feedback
  - Medium sized hospital
  - Prospective audit with intervention and feedback resulted in a 22% reduction in the use of IV broad spectrum antimicrobial over a 7 year period
ASP (7)

- Formulary restriction and preauthorization requirements for specific agents
  - Can lead to immediate and significant reductions in antimicrobial use and cost
  - May be beneficial as part of a multifaceted response to a nosocomial outbreak of infection

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ASP (8)

- Additional ASP strategies
  - Education
    - Grand rounds
    - In service programs
  - Antimicrobial order forms
  - De-escalation of therapy
  - Conversion from IV to PO therapy

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