Bugs 'N Drugs
General Principles of Antimicrobial Therapy
Hina N. Patel, Pharm.D., BCPS

I. Basic Considerations
   a. Empiric treatment
      i. Site of infection
      ii. Likely pathogens
      iii. Hospital specific antibiogram
   b. Antibiotic spectrum of activity
   c. Penetration of antibiotic into body tissues
   d. Toxicity
   e. Allergies
   f. Cost

II. Susceptibilities (MIC and MBC)
   a. MIC – minimum inhibitory concentration (reported with culture)
   b. MBC – minimum bactericidal concentration
   c. Relationship between drug concentration and MIC
      i. Must have concentrations at least 5-10 times the MIC to be susceptible
      ii. Susceptible, intermediate and resistant are based on peak concentration:MIC ratios
      iii. Inhibitory index = peak concentration/MIC (should be 5-10)

III. Resistance
   a. Mechanisms of resistance
      i. Antibiotic inactivation (beta lactamases)
      ii. Target site alteration by the bacteria (changes in PBPs and DNA gyrases)
      iii. Changes in the ability of the antibiotic to penetrate the cell wall of the bacteria
   b. Significant problems with Enterobacter, Klebsiella, Pseudomonas, Acineterbacter, Serratia, VRE, MRSA, TB

IV. Combination Therapy
   a. Rationale for combination therapy
      i. Prevention of resistance to a single agent
      ii. Treatment of polymicrobial infection
      iii. Empiric therapy in immunocompromised patient
      iv. Synergism with certain combinations
   b. Beta-lactam + aminoglycoside **or** quinolone combinations are effective
   c. No good rationale to use double beta lactam therapy in most situations
   d. Benefit to combination therapy (synergy, decreased resistance, broader spectrum)
   e. Disadvantages include increased cost, superinfection, possible drug antagonism
   f. Pathogens usually requiring combination therapy
      i. Pseudomonas – anti-pseudomonal beta lactam + aminoglycoside
      ii. Enterobacter
      iii. Serratia
      iv. Enterococcus (except for UTI) ampicillin or vancomycin + gentamicin

PENICILLINS

- bactericidal
- interferes with peptide cross-linking required to produce stable cell walls
- development of resistance due to beta lactamase production and changes in PBPs
- may accumulate in renal failure and cause seizures
- good tissue penetration (except prostate and uninflammed meninges)

Natural

Penicillin G (IV)
Penicillin V (po)
Non-penicillinase producing GPC and gram positive anaerobes
S. pyogenes, S. pneumoniae, S. agalactiae, N. meningitides, Clostridium spp, corynebacterium

Benzathine Penicillin (IM)
Rheumatic fever, prophylaxis, syphilis
Procaine Penicillin (IM)
Pharyngitis

Antistaphylococcal (Penicillinase resistant penicillins)
Nafcillin (IV, po - Unipen)
Dicloxacillin (po – Dynapen; only useful oral agent)
NOT FOR *MRSA, MRSE OR ENTEROCOCCI*

Extended Spectrum
Ampicillin (IV, po)
Amoxicillin (po)
Gram positive and gram negative coverage
Streptococcus species (incl some *Enterococci*), *Listeria, H. flu, E. coli Proteus mirabilis, Salmonella, Shigella*
DO NOT USE IF PENICILLINASE PRODUCING

Combinations with beta-lactamase inhibitors:
Non anti-pseudomonal
Amoxicillin plus clavulanate (po - Augmentin)
Extends *H. flu* and *Staph* coverage
Ampicillin plus sulbactam (IV - Unasyn)
Extends spectrum of ampicillin including *B. fragilis* and *H. flu*

Anti-pseudomonal
Ticarcillin plus clavulanate (IV – Timentin)
Pipercillin plus tazobactam (IV – Zosyn)
Pseudomonas spp; extends *Enterobacteriaceae, Enterococci* and *B. fragilis*

CEPHALOSPORINS

- **DO NOT USE IN: *MRSA, ENTEROCOCCI, LISTERIA MONOCYTOGENES***
- beta lactam antibiotics
- act on cell wall similar to penicillins
- divided into 4 "generations" based on antimicrobial spectrum
- resistance via production of beta lactamases
- 1st generation has good activity versus gram positive except *MRSA and MRSE,* and moderate activity versus community acquired gram negative such a *E. coli* and *klebsiella*
- 2nd generation has intermediate activity versus gram positive and gram negative
- 3rd generation has expanded activity versus the *Enterobacteriaceae* including those that produce beta lactamase
- 4th generation (cefepime) has expanded gram negative coverage including *pseudomonas* spp.; no anaerobic coverage

First Generation

Cephalexin (po – Keflex)

Useful in cellulitis, osteomyelitis; alternative for UTI

Cefazolin (IV – Ancef, Kefzol)

Useful in surgical prophylaxis

Gram positive and some gram negative activity

MSSA, S. pneumoniae, P. mirabilis, E. coli, K. pneumoniae

Second Generation

Cefuroxime (po, IV – Ceftin, Zinacef)

Community acquired infections

Gram positive (*pneumococci* and *S. aureus*); increased activity against *H. flu, E. coli, Klebsiella* and *Proteus*

Cefoxitin (IV – Mefoxin)

Increased anaerobic activity, including excellent *B fragilis* coverage

Cefotetan (IV – Cefotan)

Anaerobes, including *B fragilis*

Third Generation

Cefotaxime (IV – Claforan)

Ceftriaxone (IV – Rocephin)

Meningitis and gram negative sepsis

Excellent gram negative activity including all *Enterobacteriaceae* species, though most *Enterobacter cloacae* are now resistant

DO NOT USE IN PSEUDOMONAS INFECTIONS

Ceftazidime (IV – Fortaz, Tazidime)

Reserve for *Pseudomonas spp.*

Fourth Generation

Cefepime (IV – Maxipime)

Pneumonia, gram negative sepsis and serious infections in immunocompromised

Activity against most staph, strep, and most gram negative organisms including *serratia, pseudomonas* and *enterobacter*; NO ANAEROBES

*****Hematological effects secondary to N-methylthiotetrazole (NMTT) side chain:**

Causes hypoprothrombinemia by inhibiting Vit K dependent clotting factors

Cefamandole, Cefoperazone, Cefotetan

Causes disulfiram-like reaction to alcohol

CARBAPENEMS

- beta lactam antibiotic active against cell wall
- broad spectrum active against gram positive (including ampicillin sensitive e*nterococci*), gram negative (including *pseudomonas spp*.) and anaerobes
- no activity against *MRSE, Stenotrophomonas maltophilia, Pseudomonas cepacia* and *MRSA*
- concentration dependent killing
- for serious polymicrobial infections such as sepsis, infectious pancreatitis, pneumonia, soft tissue infections and peritonitis

Imipenem (IV – Primaxin)

Slightly more activity versus gram positive and a little less activity with gram negative compared to meropenem

Risk of seizures more common in renal failure

Meropenem (IV – Merrem)

Similar spectrum of activity as imipenem

Little or no risk of seizures

MONOBACTAMS

- beta lactam antibiotic active against cell wall
- ONLY gram negative organisms including *pseudomonas*
- no anaerobe or gram positive activity

Aztreonam (IV- Azactam)

AMINOGLYCOSIDES

- interferes with bacterial protein synthesis
- bactericidal with concentration dependent killing
- active against most gram negative organisms including *pseudomonas, serratia*
    - Pseudomonas aeruginosa (combine with anti-pseudomonal penicillin)
        - amikacin > tobramycin > gentamicin
    - Serratia (combine with third generation cephalosporin)
        - gentamicin ≤ amikacin > tobramycin
- for pneumonia, febrile neutropenia, UTI and pyelonephritis
- used for synergy in combination with other antibiotics
- main toxicities are nephrotoxicity and ototoxicity

Gentamicin (IV – Garamycin)
Tobramycin (IV – Nebcin)
Amikacin (IV- Amikin)

MACROLIDES

- bacteriostatic
- act on bacterial 50s ribosomal subunit affecting protein synthesis
- very lipophilic and concentrate in macrophages (*legionella, mycoplasma, bordotella* and *chlamydia*
- for community acquired pneumonia, atypical pneumonia, *Chlamydia* infections, strep infections, bacterial conjunctivitis, skin and soft tissue infections, HIV related infections and campylobacter enteritis

Erythromycin (po, IV)
Broad spectrum including gram positive organisms such as *group A strep, S. pneumoniae, S. aureus*, as well atypical pneumonia organisms (*legionella* and *mycoplasma*); most aerobic gram negatives resistant

Azithromycin (po, IV - Zithromax)
Active against *staph, strep, N. gonorrhea, mycoplasma, H. influenzae, M. catarrhalis, chlyamydia* and *salmonella*

Clarithromycin (po - Biaxin)
Active against *staph, strep* (including pneumococcus*), C. trachomatis, M. catarrhalis, mycoplasma, M. avium intracellulare, B. burgdorferi, B. pertussis, legionella, H. pylori* and *H. influenzae*

QUINOLONES

- bind to bacterial DNA-gyrase and interfere with DNA replication
- active against broad range of bacteria including *Enterobacteriaceae, N. gonorrhea, H. flu, M. catarrhalis, pseudomonas, C. trachomatis, mycoplasma* and variable activity against *staph* and *strep*
- some synergy with beta-lactams

Ciprofloxacin (po, IV – Cipro)
Osteomyelitis, peritonitis, pneumonia, sepsis, UTI, infectious diarrhea, gonorrhea, otitis, soft tissue infections (good penetration into lungs, tissue, bone, and peritoneum)
Active against gram negative organisms, no anaerobe coverage, little to no strep coverage

Levofloxacin (po, IV – Levaquin)

Bronchitis, community acquired pneumonia, UTI and sinusitis

Better gram positive activity including *staph, strep* and *Enterococcus faecalis*

TETRACYCLINES

- inhibit the 30s ribosomal subunit affecting protein synthesis
- bacteriostatic
- active against wide variety of organisms including *chlamydia, mycoplasma, spirochetes, rickettsiae* and some protozoans; not very effective against *staph, group A strep*, and *S. pneumoniae*

Doxycycline (po, IV- Vibramycin)

Activity against chlamydial infections, Rocky Mountain spotted fever, Lyme disease

SULFONAMIDES

- inhibit the biosynthesis of folic acid in bacterial cells
- bacteriostatic
- wide spectrum including *S. pyogenes, S. pneumoniae, H. influenzae*

Trimethoprim-sulfamethoxazole (TMP-SMZ) (po, IV – Bactrim)

UTI, pyelonephritis, respiratory tract infections, sinusitis, PCP

Broad gram negative, gram positive and facultative intracellular bacterial coverage

VANCOMYCIN

- active against bacterial cell wall
- primary activity against gram positive organisms (including MRSA, Enterococci, MRSE)
- no gram negative coverage and little anaerobe coverage
- over use can lead to an increase in VRE
- use higher doses for meningitis

ANAEROBIC ANTIBIOTICS

Metronidazole (po, IV – Flagyl)

Intraabdominal infections, brain abcesses, PID, *Trichomonas, C. difficile*

Active against anaerobic gram negative organism, anaerobic protozoa: *B. fragilis, T. vaginalis, Entamoeba histolytica, Giardia lamblia*

Clindamycin (po, IV – Cleocin)

- binds to 50s ribosomal subunit affecting protein synthesis
- bacteriostatic

Intraabdominal sepsis, aspiration pneumonia, empyema, AIDS associated *Toxoplasma*, some gram positive organisms

OXAZOLIDINONES

- acts on 50s subunit of bacteria affecting protein synthesis
- bacteriostatic against enterococci and staphylococci
- bactericidal against most strains of streptococci

Linezolid (po, IV – Zyvox)

Primarily reserved for VRE infection and MRSA (if vancomycin allergy)