Antimicrobials Agents Review

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Disclosure

I, Spencer Durham, have no actual or potential conflict of interest in relation to this program.
Objectives

• At the end of the presentation, the audience will be able to:
  – Identify the different classes of antimicrobial agents and review the individual agents within each class
  – Describe the spectrum of activity of the antimicrobial drug classes
  – Review major adverse effects associated with the antimicrobial drug classes
Introduction

• Antimicrobial therapy crosses into most, if not all, areas of pharmacy practice
• Antimicrobial agents are widely prescribed in the acute care, long-term care, and outpatient settings
  – Frequently prescribed inappropriately (50%)
    • Wrong drug for disease
    • No antibiotic indication
• Limited development of new antibiotics, particularly novel antibiotics
• Antimicrobial resistance is rapidly increasing
Antimicrobial Considerations

• Consider:
  – Local susceptibility patterns
  – Overuse of specific antimicrobials in the local institution or area
    • Example: Fluoroquinolone overuse
  – Institutional formulary restrictions
  – Overall cost effectiveness
    • IV to PO conversions
    • Use of new, expensive antibiotics v. cheaper antibiotics with potential equal efficacy
Antimicrobial Considerations

- **Empiric therapy**
  - Broad-spectrum agent(s) with reliable coverage against the most likely causative pathogens

- **Definitive therapy**
  - Can generally only be done after obtaining culture and sensitivity results
  - May use other tests to guide therapy, such as PCRs

- **Duration of treatment**
  - Not well-defined, usually based on experience rather than evidence
  - Generally, 7-14 days for most infections
• Bacterial Pathogens
  – Normal commensal flora
    • Bacteria normally present in humans
    • Not pathogenic under usual circumstances
      – Can be if given appropriate opportunity
  – Sterile site growth
    • Blood stream
    • CSF
  – Nonsterile sites
    • Sputum
    • Wound
### Gram-positive Bacteria

<table>
<thead>
<tr>
<th>Cocci in Clusters</th>
<th>Cocci in Pairs/Chains</th>
<th>Other</th>
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<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Clostridium species</em></td>
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<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td><em>Streptococcus pyogenes</em> (group A)</td>
<td><em>Listeria monocytogenes</em></td>
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<td>• Other coagulase-negative staphylococci</td>
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<td><em>Staphylococcus saprophyticus</em></td>
<td><em>Streptococcus agalactiae</em> (group B)</td>
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<td><em>Viridans group streptococci</em></td>
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<td><em>Enterococcus faecalis</em></td>
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<td><em>Enterococcus faecium</em></td>
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Gram-Negative Bacteria

• Bacilli (rods)
  – Anaerobic
    • Bacteriodes
  – Facultative
    • Escherichia coli
    • Klebsiella
    • Proteus
    • Pseudomonas aeruginosa
    • Enterobacter
    • Serratia
Pharmacodynamics

• Minimum inhibitory concentration (MIC)
  – Bacteria are mixed with increasing concentrations of an antibiotic on microdilution plates
  – MIC = Mixture with the lowest concentration of antibiotic where there is no visible growth
  – ***Remember, just because an antibiotic has the lowest MIC for a pathogen, does not mean it is the best choice
• The number associated with the MIC is variable by drug, so the lower the number does not necessarily mean a bacteria is more sensitive to the drug
• **Bactericidal**
  • Actually destroys the organism
    • No help from immune system is required
    • Cell wall synthesis inhibitors (beta-lactams, vancomycin)
    • Aminoglycosides
    • Fluoroquinolones
  • Preferred for certain disease states
    • Endocarditis
    • Meningitis
    • Infections in neutropenic patients
    • Osteomyelitis
    • Sepsis
Pharmacodynamics

• Bacteriostatic
  • Inhibit growth of organism without killing it
  • Once antibiotics are removed, the organism can begin growing again
  • Works in conjunction with the patient’s immune system to clear the infection
  • Protein synthesis inhibitors (exception: aminoglycosides)
    • Tetracyclines
    • Clindamycin
    • Linezolid
    • Macrolides
Pharmacodynamics

• **Time dependent killing**
  – Duration of time drug remains above the MIC reflects bacterial inhibition
    • Beta-lactams
    • Vancomycin

• **Concentration dependent killing**
  – Ratio of peak concentration of the drug to the MIC
    • The higher the concentration, the greater degree of bacterial inhibition
      – Aminoglycosides
      – Fluoroquinolones
      – Daptomycin
Antibiotic MOAs

DNA replication
Nucleotide biosynthesis
Protein synthesis
Topo-isomerase
RNA transcription
mRNA
Protein
Cell wall synthesis
Cytoplasmic membrane integrity
Rifampin
Tigecycline
Aminoglycosides
Macrolides
Linezolid
Clindamycin
Tetracyclines

TMP-SMX = trimethoprim-sulfamethoxazole
Beta-Lactams

- Penicillins
- Cephalosporins
- Carbapenems
- MOA: inhibition of cell wall synthesis
- Bactericidal
- Time-dependent
• **Adverse Effects**
  – Hypersensitivity reactions
    • Mild rash
    • Acute interstitial nephritis
    • Anaphylaxis
  – Some cross-sensitivity between agents
    • Difficult to predict; closer structural relationships are more likely to cross-react
  – Seizures
    • High doses of beta-lactams
    • Particularly associated with the carbapenems (imipenem and ertapenem)
Beta-Lactams

• Generally, well-tolerated and safe antimicrobials
• ALL beta-lactams lack activity against atypical organisms
  – *Mycoplasma pneumoniae*
  – *Chlamydophila pneumoniae*
• Lack MRSA activity
  – Exception: Ceftaroline
Natural Penicillins

- **Penicillin G, Penicillin V**
  - Good activity: *Treponema pallidum* and most streptococci
  - Moderate activity: *Streptococcus pneumoniae*, enterococci
  - Poor activity: almost everything else
- **IM (long acting depot formulation)**
  - Procaine, benzathine
    - **FATAL IF GIVEN IV**
- **Treatment**
  - Syphilis (neurosyphilis)
  - Susceptible streptococcal infections such as pharyngitis or endocarditis
Aminopenicillins

• Amoxicillin, ampicillin
  – Good activity: streptococci, enterococci, *N. meningitidis*
  – Moderate activity: enteric gram-negatives, *Haemophilus*
    • Would NOT generally use for empiric therapy, but could consider for targeted therapy
  – Poor activity: staphylococci, anaerobes

• Treatment:
  – Upper respiratory infections
  – Infections due to *Enterococcus*
  – Select gram-negative infections
Penicillinase-Resistant Penicillins

• Nafcillin, dicloxacillin
  – Good activity: MSSA, streptococci
  – Poor activity: Gram (-), enterococci, anaerobes, MRSA
• Sometimes called the “anti-staphylococcal penicillins”
  – Used for MSSA, but NOT MRSA
• Eliminated by liver
  – No renal adjustment
• Used for MSSA infections, endocarditis, and SSTI’s
• Limited utility for empiric treatment now due to increasing MRSA
• **Amoxicillin/clavulanate**
  – MSSA, streptococci
  – Respiratory pathogens, some enteric gram-negative pathogens (*E.coli, Klebsiella, etc.*)
  – Some anaerobic coverage

• **Ampicillin/sulbactam**
  – Same as amoxicillin/clavulanate
  – *Acinetobacter*

• **Piperacillin/tazobactam**
  – MSSA, streptococci
  – Excellent gram-negative coverage
  – *Pseudomonas*
  – Anaerobic pathogens
Cephalosporins

• Grouped into generations
  – 1st generation
    • Cefazolin, cephalaxin, cefadroxil, cephalothin
  – 2nd generation
    • Cefuroxime, cefoxitin, cefotetan, cefprozil
  – 3rd generation
    • Ceftriaxone, cefotaxime, ceftazidime, cefdinir, cefpodoxime, cefixime, ceftibuten
  – 4th generation
    • Cefepime
  – “5th” generation
    • Ceftaroline
  – Other: Ceftolazone/tazobactam; ceftazidime/avibactam
Cephalosporins

• As a general rule, when moving from the 1\textsuperscript{st} to the 4\textsuperscript{th} generation, gram-positive activity stays the same and gram-negative activity increases
  – However, NUMEROUS important exceptions to this rule exist
• NO cephalosporins cover enterococci
• Most have little or no activity against anaerobes
  – Exception: some 2\textsuperscript{nd} generation agents
• Ceftazidime and cefepime cover \textit{Pseudomonas}
• Ceftaroline is the \textbf{ONLY} beta-lactam that covers MRSA
• Potential cross-reactivity with the penicillins
  – Lower generations more likely to cross-react
1st Generation

- **Good activity:** MSSA, streptococci
- **Moderate activity:** some enteric GNRs
  - *E.coli*
- **Poor activity:** enterococci, anaerobes, MRSA, *Pseudomonas*
- **Good alternative to anti-staphylococcal penicillins**
  - Less phlebitis
  - Infused less frequently
- **Do NOT cross blood-brain barrier**
  - Do NOT use for CNS infections
• Similar spectrum of activity to first generation agents, but better gram-negative activity

• Cefotetan
  – Disulfuram-like reaction with ethanol
  – Inhibit vitamin K production and prolong bleeding

• Anaerobic coverage
  – Cefotetan, cefoxitin
  – These are the ONLY cephalosporins that have adequate activity against anaerobes

• Do NOT cross blood-brain barrier
• Greater gram-negative activity compared to first and second generation agents
  – Several important exceptions
• Ceftazidime
  – NOT active against gram-positives
  – ONLY third generation agent with activity against *Pseudomonas*
• Ceftriaxone, cefotaxime, ceftazidime
  – Cross blood-brain barrier
  – CNS infections
• **Cefepime**
  – “Cefazolin + Ceftazidime”
  – Active against many gram-positive and gram-negative organisms, including *Pseudomonas*

• **Good empiric choice for many nosocomial infections**

• **Use associated with increased incidence of *Clostridium difficile* infections and extended-spectrum beta-lactamase (ESBL) production**
  – Also true for third generation agents
• Ceftaroline
  – Does not really fit well into the “generation” scheme usually associated with the cephalosporins
  – **ONLY** beta-lactam antibiotic with activity against MRSA
  – Less gram-negative activity when compared to cefepime
    • Does NOT reliably cover *Pseudomonas*
Other Cephalosporins

• Ceftolazone/tazobactam
  – New cephalosporin combined with an existing beta-lactamase inhibitor

• Ceftazidime/avibactam
  – Existing cephalosporin combined with a new beta-lactamase inhibitor

• Active against ESBL organisms and some carbapenemase-producing organisms

• Place in therapy still to be determined
Carbapenems

- Imipenem/cilastatin, meropenem, doripenem
- Ertapenem
- Extremely broad-spectrum antimicrobials
  - Probably the most broad-spectrum of any class of agents currently available on the market
  - Active against many gram-positive and gram-negative organisms
  - Often used for multi-drug resistant infections
Carbapenems

- **Spectrum of activity:**
  - **Imipenem/cilastatin, meropenem, doripenem:**
    - MSSA, streptococci, *Enterococcus, Listeria*
    - *Pseudomonas* and other gram-negatives, including ESBL-producing organisms, anaerobes
  - **Ertapenem:**
    - Similar to other carbapenems, but NO *Pseudomonas* or *Enterococcus* activity
    - Once daily dosing

- ADRs: Seizures
Monobactam

- **Aztreonam**
  - Safe to give in patients with allergies to other beta-lactams
    - Contains only the four-membered ring of the basic beta-lactam structure
  - Cross-reactivity with ceftazidime
    - Share an identical side chain
  - Only covers gram-negative organisms, including *Pseudomonas*
Glycopeptide

- Vancomycin
- MOA: inhibition of cell wall synthesis
  - Different binding site than beta-lactams
- Bactericidal, time-dependent
- Spectrum of activity: ONLY gram-positives
  - MSSA, MRSA, streptococci, *Clostridium difficile*, enterococci
  - Used for resistant gram-positive infections
  - Vancomycin is increasing
Glycopeptide

• **Adverse Effects (vancomycin)**
  – Ototoxicity
  – Nephrotoxicity
    • Associated with the original formulation ("Mississippi Mud")
  – Red man syndrome
    • Histamine-mediated reaction
    • Slow infusion

• **Dosing**
  – Pharmacokinetically monitored
    • Troughs

• **Oral vancomycin**
  – Poor absorption across intestinal mucosa
  – Only used for *Clostridium difficile* infections
    • IV vancomycin does not reach high enough concentrations to eliminate
• Monitoring:
  – In general, peaks are no longer recommended to be monitored
    • No good correlation with efficacy nor toxicity
  – Best predictor of efficacy is AUC/MIC ratio
    • Difficult to measure clinically, so trough is used as a surrogate marker
  – Trough goal:
    • 10-15 mg/L
    • 15-20 mg/L for pneumonia, osteomyelitis, endocarditis, meningitis, sepsis/bacteremia (POEMS)
Cyclic Lipopeptides

- Daptomycin
- MOA: depolarizes cell membrane, leading to potassium leakage from cell
- Bactericidal, concentration-dependent
- Renal elimination and dose adjustment
- Spectrum of activity
  - Only active against gram-positive organisms, but useful for resistant infections
Cyclic Lipopeptides

• Adverse effects:
  – Muscle pain, myopathy
    • Monitor CPK level at baseline and then periodically
    • Use caution in patients on statins
  – Drug fever

• Inactivated by pulmonary surfactant
  – Cannot be used for treatment of pneumonia or any other pulmonary infections

• Used most commonly in skin/soft tissue infections and bacteremia/sepsis
Streptogramins

• Quinupristin/dalfopristin
• MOA: protein synthesis inhibitor
• Individual agents are bacteriostatic, but combination is bactericidal (synergistic effect)
• Post-antibiotic effect, time-dependent
• Spectrum of activity:
  – Gram-positives ONLY
  – Active against *E. faecium*, NOT *E. faecalis*
Fluoroquinolones

• Ciprofloxacin, levofloxacin, moxifloxacin, delafloxacin

• MOA: inhibit DNA replication and repair through inhibition of topoisomerase II and IV
  – Unique mechanism compared to other classes
  – Active against replicating and non‐replicating bacteria

• Bactericidal, concentration‐dependent

• Renal dose adjustment for all but moxifloxacin

• 80‐100% oral bioavailability
Fluoroquinolones

• Spectrum of activity:
  – Ciprofloxacin: gram-negatives, including *Pseudomonas*, atypicals
  – Levofloxacin: gram-positives (streptococci and MSSA) and gram-negatives, including *Pseudomonas*, and atypicals
  – Moxifloxacin: same as levo, but **WITHOUT** the *Pseudomonas* coverage
  – Delafloxacin: has additional MRSA coverage

• Widespread overuse has caused highly variable resistance patterns, so must know local susceptibilities
Fluoroquinolones

• Adverse Effects – well tolerated overall
  – GI effects
  – Headache
  – Photosensitivity
  – Hypoglycemia
  – Seizures
  – Prolongation of QT interval
  – BBW
    • Achilles tendon rupture (uncommon)
Aminoglycosides

- Gentamicin, tobramycin, amikacin
- MOA: inhibition of protein synthesis
- Bactericidal, concentration-dependent
  - Pronounced post-antibiotic effect
- Renal dose adjustments necessary
- Minimal penetrations into fat tissue, CNS
- Very narrow therapeutic index
  - Nephrotoxicity, ototoxicity
Aminoglycosides

• Spectrum of activity:
  – Gram-negatives, including *Pseudomonas*
  – Synergistic effect when used with beta-lactams against gram-positives
    • Example: ampicillin + gentamicin
  – **NO** activity against anaerobes or atypicals

• Amikacin should be reserved for infections caused by organisms resistant to gentamicin/tobramycin
Macrolides

- Clarithromycin, azithromycin, telithromycin (a ketolide)
  - Erythromycin is rarely used for antimicrobial activity anymore due to resistance
- MOA: protein synthesis inhibitor
- In general, bacteriostatic, with exceptions:
  - Azithromycin is bactericidal against *S. pneumoniae*, *group A streptococci*, and *H. influenzae*
- Pharmacodynamics: difficult to classify
  - Some exhibit both time and concentration dependent activity
Macrolides

• Spectrum of activity:
  – Primary use is against respiratory pathogens
  – Atypicals (*Mycoplasma pneumoniae*),
  – *H. influenzae*,
  – *Moraxella catarrhalis*,
  – *Helicobacter pylori*,
  – *Mycobacterium avium*
  – *Streptococcus pneumoniae*
  – Poor activity: Most other pathogens

• Potent inhibitors of CYP450 enzymes
  – Exception ➔ azithromycin

• Monitor QTc prolongation
• Tetracycline, doxycycline, minocycline
• MOA: protein synthesis inhibitor
• Bacteriostatic, time-dependent
• Spectrum of activity:
  – Atypicals
  – Tick-borne infections (*Rickettsia, Borrelia burgdorferi*)
  – *Plasmodium* species (malaria)
  – Staphylococci (including MRSA), *S. pneumoniae*
  – Poor activity against many GNRs, anaerobes, enterococci
Glycylcycline

- Tigecycline
- MOA: protein synthesis inhibitor
- Bacteriostatic, time-dependent, post-antibiotic effect
- Spectrum of activity:
  - Gram-positives (including MRSA and VRE)
  - Many enteric gram-negatives
    - NOT Pseudomonas or Proteus
  - Anaerobes
- Highly distributes to tissues, but does not maintain adequate concentrations in urine or blood
Tetracyclines and Glycylcyclines

• Adverse Effects
  – GI effects
  – Photosensitivity
  – Esophageal irritation
    • Tetracyclines
  – Dizziness/vertigo
    • Minocycline
  – Tooth discoloration
    • Contraindicated in pregnant women and children < 8 years of age

• Tigecycline: BBW for increase in all-cause mortality
Lincosamide

- Clindamycin
- MOA: protein synthesis inhibitor
- Bacteriostatic, time-dependent
- Spectrum of activity:
  - Gram-positives (including MRSA), anaerobes
  - No activity against gram-negatives or *Enterococcus*
- Also inhibits bacterial toxin production
- Prototypical agent for inducing *C. difficile* infections
• Trimethoprim/sulfamethoxazole (TMP/SMX)
• MOA: inhibits the biosynthesis of folate co-factors needed for DNA and RNA synthesis
• Concentration dependent
• Pharmacodynamics: appears to display both bactericidal and bacteriostatic activity
• Elimination/dose adjustment: renal
Folate Antagonists

• Spectrum of activity:
  – *Staphylococcus aureus* (including community-associated MRSA)
  – *Stenotrophomonas maltophilia* and *Burkholderia cepacia*,
  – *Listeria*,
  – *Pneumocystis jirovecii*
  – Variable activity against enteric GNRs
• No useful activity against *Enterococcus*, anaerobes
• Adverse Effects
  – Dermatologic
    • Rash
  – Hematologic
    • Bone marrow suppression
      – More common with prolonged therapy, but can occur at any point in therapy
  – Renal toxicity
  – Hypersensitivity
    • Steven-Johnson Syndrome
Oxazolidinones

- Linezolid, tedizolid
- MOA: protein synthesis inhibitor
- Bacteriostatic, time-dependent
  - Bactericidal against *Streptococcus* species
- Spectrum of activity
  - Only active against gram-positives, but highly useful resistant infections
    - VRE
Oxazolidinones

• 100% oral bioavailability

• Adverse Effects:
  – Bone marrow suppression
    • Usually occurs after prolonged therapy, but can occur at any time
    • Must carefully monitor CBCs
  – Peripheral neuropathy (uncommon)

• Monoamine oxidase inhibitor
  – Must use very carefully (prefer to avoid) in patients taking SSRIs due to risk of serotonin syndrome
• Metronidazole
• MOA: protein synthesis inhibitor
• Bactericidal, concentration-dependent
• Hepatic elimination
• Dose adjust in both severe renal and hepatic impairment
• Spectrum
  – ONLY active against obligate anaerobes, *H. pylori*
Nitroimidazoles

- Adverse effects:
  - Disulfuram-like reaction
    - Patient counseling point: Do not drink alcohol while taking this medication
  - Neurologic
    - Reversible peripheral neuropathy
  - GI intolerances
- Used most commonly for abdominal infections and *Clostridium* infections
Nitrofurans

• Nitrofurantoin
• MOA: multifactorial, including protein synthesis inhibition and cell wall synthesis inhibition
• Bactericidal in urine, mixed concentration and time‐dependent effects
• Spectrum of activity:
  – *E. coli*, *Staphylococcus saprophyticus*, *Citrobacter*, *Klebsiella*, *Enterococcus*
  • NOT *Proteus*
• No tissue penetration outside of urinary tract
• Do not use in CrCL<30 mL/min
  – Updated in Beers Criteria in 2015
Rifamycins

• Rifampin
• MOA: interferes with bacterial RNA synthesis
• Bactericidal and bacteriostatic depending on the concentration
• Both time and concentration-dependent properties
• Elimination and dose adjustment: hepatic
• Patient counseling: will strain bodily secretions red/orange
Rifamycin

• Spectrum of activity:
  – Gram-positives (*Staphylococcus* and *Streptococcus*), *Neisseria*, *Moraxella*, *H. influenzae*, *Brucella*, *Chlamydophilia*

• In general, always use in combination with another agent due to rapid development of resistance

• Strong CYP inducer (lots of drug interactions)

• Excellent tissue/CNS penetration
Polymyxins

- Colistin (colistimethate sodium), polymyxin B
- MOA: cationic detergent that disrupts cell membrane
- Spectrum of activity:
  - Can be used to treat carbapenemase-producing strains of gram-negative species
  - Many GNRs, including multi-drug resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*; *Stenotrophomonas maltophilia*
  - Poor activity: All gram-positive organisms, anaerobes, *Proteus, Providencia, Burkholderia, Serratia*, Gram-negative cocci
• Adverse effects:
  – Nephrotoxicity
    • Must monitor closely
    • Do not use with other nephrotoxic medications
  – Peripheral neuropathy
• In general, reserve for use in highly-resistant organisms when other drugs cannot be used
• The perfect recipe for a bug to develop resistance to an antibiotic is to give a low concentration of the antibiotic over a prolonged period of time
  – In general, use upper end of dosing range
  – Do not prolong therapy longer than needed, but MUST counsel patients to finish their course of antibiotics!
• Try to use the most narrow-spectrum agent possible as quickly as possible
References

QUESTIONS???