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Antimicrobial Therapy

Site of Action

Cell Wall	Cytoplasm	DNA Inhibitor
<u>β-lactams</u> -Penicillins -Cephalosporins -Monobactams -Carbapenems <u>Glycopeptides</u> -Vancomycin <u>Lipopeptide (Cell Membrane)</u> -Daptomycin	<u>Initiation Complex</u> -Linezolid <u>30 S Ribosome</u> -Aminoglycosides -Tetracyclines <u>50 S Ribosome</u> -Macrolides/Ketolides -Chloramphenicol -Clindamycin -Quinupristin-dalfopristin	Metronidazole Fluoroquinolones TMP-SMZ Rifampin

Cell Wall Inhibitors

β -Lactams

- The 4 major categories of β -Lactams consist of: (1) penicillins, (2) cephalosporins, (3) monobactams, and (4) carbapenems

Penicillins

<p>Natural Penicillins</p> <ul style="list-style-type: none"> Penicillin G/benzylpenicillin Penicillin G procaine Penicillin G benzathine Phenoxyethyl penicillin/penicillin V <p>Penicillinase-Resistant Penicillins</p> <ul style="list-style-type: none"> Methicillin (<i>Staphcillin</i>) Oxacillin (<i>Prostaphlin</i>, others) Nafcillin (<i>Nafcil</i>, <i>Nallpen</i>, Unipen) Cloxacillin (<i>Tegopen</i>, others) Dicloxacillin (<i>Dycill</i>, others) <p>Aminopenicillins</p> <ul style="list-style-type: none"> Ampicillin (<i>Polycillin</i>, others) Amoxicillin (<i>Amoxil</i>, others) 	<p>Carboxypenicillins</p> <ul style="list-style-type: none"> Carbenicillin (<i>Geopen</i>, <i>Geocillin</i>) Ticarcillin (<i>Ticar</i>) <p>Ureidopenicillins</p> <ul style="list-style-type: none"> Mezlocillin (<i>Mezlin</i>) Azlocillin (<i>Azlin</i>) Piperacillin (<i>Pipracil</i>) <p>Penicillins plus β-Lactamase Inhibitors</p> <ul style="list-style-type: none"> Amoxicillin-clavulanic acid (<i>Augmentin</i>) Ampicillin-sulbactam (<i>Unasyn</i>) Ticarcillin-clavulanic acid (<i>Timentin</i>) Piperacillin-tazobactam (<i>Zosyn</i>)
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- **Mechanism of Action:** inhibits cell wall synthesis
- **Antimicrobial Activity**
 - Natural Penicillins: streptococci, enterococci, mouth flora, spirochetes, *Clostridium perfringens*
 - Penicillinase-Resistant Penicillins: staphylococci, streptococci, not enterococcus, not MRSA
 - Aminopenicillins: streptococci, *Listeria monocytogenes*, *Eikenella corrodens*
 - Carboxypenicillins: gram-negative aerobes, streptococci, not enterococcus
 - Ureidopenicillins: streptococci, enterococci, gram-negative aerobes
 - Penicillin plus β -Lactamase Inhibitors: β -lactamase inhibitor gives increased staphylococci and increased anaerobe coverage; some increased gram-negative coverage (eg. *H. influenzae*)
- **Pharmacokinetics:** varies from group to group
- **Side Effects:** in general, β -lactam antimicrobials are fairly safe; rash is most common side effect with all groups; anaphylaxis (IgE mediated) is most serious side effect
- **Clinical Applications**
 - Natural Penicillins: pharyngitis, meningitis, pneumonia, Lyme disease, syphilis, dental abscess
 - Penicillinase-Resistant Penicillins: predominantly for staphylococcal infections
 - Aminopenicillins: upper respiratory infections, meningitis, listeriosis
 - Carboxypenicillins: rarely used, unless in combination with β -lactamase inhibitor
 - Ureidopenicillins: nosocomial pneumonia, empiric coverage in febrile neutropenic host
 - Penicillin plus β -Lactamase Inhibitors
 - Amoxicillin clavulanic acid: upper and lower respiratory infections; skin and soft tissue infections; animal and human bites
 - Ampicillin-sulbactam: lower respiratory infections; head and neck infections; intra-abdominal infections; severe skin and soft tissue infections; animal and human bites
 - Ticarcillin-clavulanic acid: nosocomial infections; intra-abdominal infections
 - Piperacillin-tazobactam: intra-abdominal infections; suspected bacteremia in neutropenic patients; for *Pseudomonas* infections, should be combined with aminoglycosides if used at standard dose (3.375 q6h)

Cephalosporins

1st Generation	2nd Generation	3rd Generation	4th Generation
<u>Oral</u> Cephalexin (<i>Keflex</i> , others) Cephadrine (<i>Velosef</i> , Anspor)	<u>Oral</u> Cefuroxime axetil (<i>Ceftin</i>) Cefaclor (<i>Ceclor</i>)	<u>Oral</u> Cefixime (<i>Suprax</i>) Cefdinir (<i>Omnicef</i>)	<u>IV</u> Cefepime (<i>Maxipime</i>)

Cefadroxil (<i>Duricef</i> , Ultracef)	Cefprozil (<i>Cefzil</i>) Ceftibutin (<i>Cedax</i>) Cefpodoxime (<i>Vantin</i>) *Loracarbef (<i>Lorabid</i>)	<u>IV</u> Ceftazidime (<i>Fortaz</i> , others) Cefoperazone (<i>Cefobid</i>) Ceftriaxone (<i>Rocephin</i>) Cefotaxime (<i>Claforan</i>) Ceftizoxime (<i>Cefizox</i>)	
<u>IV</u> Cefazolin (<i>Ancef</i> , others) Cephalothin (<i>Keflin</i> , others) Cephapirin (<i>Cefadyl</i>) Cephradine (<i>Velosef</i>)	<u>IV</u> Cefamandole (<i>Mandol</i>) Cefonocid (<i>Monocid</i>) Cefuroxime (<i>Zinacef</i>) Cefoxitin (<i>Mefoxin</i>) Cefotetan (<i>Cefotan</i>) Cefmetazole (<i>Zefazone</i>)		

*Loracarbef is not a true cephalosporin (classified as a carbacephem—a modified cephalosporin)

- **Mechanism of Action:** inhibits cell wall synthesis
- **Antimicrobial Activity**
 - First Generation: predominantly gram-positive aerobes; limited gram-negative aerobes
 - Second Generation
 - Group A: Cefuroxime, Cefaclor, Cefprozil, Ceftibutin, Cefpodoxime, Cefamandol, and Loracarbef: good gram-negative aerobes, (especially *Hemophilus influenzae*), good gram-positive aerobes (eg. *Streptococcus pneumoniae*), fair anaerobes; cefuroxime is the only second generation cephalosporin to have good CNS penetration; cefamandole used less often than cefuroxime because of less favorable pharmacokinetics, inferior activity against *H. influenzae*, and toxicity from MTT side chain (increased bleeding); typically used for infections above the diaphragm
 - Group B: Cefotetan, Cefoxitin, Cefmetazole: moderate gram-negative aerobes and excellent anaerobes (note that some species in the *Bacteroides fragilis* group, namely the “DOT” organisms are not covered by cefotetan); typically used for infections below the diaphragm
 - Third Generation
 - Ceftazidime and Cefoperazone: excellent gram-negative aerobes, including *Pseudomonas* species
 - Ceftriaxone, Ceftizoxime, and Cefotaxime: very good gram-negative aerobes (not including *Pseudomonas* species), moderate gram-positive aerobes
 - Cefixime: good gram-negative aerobes (not including pseudomonas), does not cover staphylococci; very active against *Neisseria gonorrhoeae*
 - Cefdinir: similar to cefpodoxime; good coverage for *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Moraxella catarrhalis*, *Staphylococcus aureus* (not MRSA)
 - Fourth Generation: very broad spectrum; covers *Staphylococcus aureus* (not MRSA), streptococcus, and gram-negative aerobes (including pseudomonas); not a strong anaerobe drug
 - *Note: none of the cephalosporins cover enterococcus, listeria, or MRSA
- **Pharmacokinetics:** varies dependent on drug
- **Side Effects:** in general, cephalosporins have low toxicity; most common side effect is rash; for hives and anaphylaxis, cross-reactivity with penicillins estimated at 3-7%; methylthiotetrazole side chain can cause bleeding as well as an antabuse reaction (cefamandole, cefotetan, and cefoperazone)
- **Clinical Applications**
 - First Generation: commonly used for skin and soft tissue infections; prophylaxis for orthopaedic and cardiovascular procedures
 - Second Generation: Group A—above the diaphragm (upper and lower respiratory tract infections); Group B—below the diaphragm (anaerobic infections and intra-abdominal infections)
 - Third Generation: meningitis (except cefoperazone which does not cross CSF); nosocomial infections, especially pneumonias; empiric coverage in neutropenic hosts (ceftazidime); gonorrhea (ceftriaxone and cefixime)
 - Fourth Generation: nosocomial infections, neutropenic hosts

Monobactams

- **Classification of Monobactams:** Aztreonam (*Azactam*) only monobactam currently in use
- **Mechanism of Action:** inhibits cell wall synthesis; bactericidal
- **Antimicrobial Activity:** strictly gram-negative aerobes, especially *Enterobacteriaceae*
- **Pharmacokinetics:** excreted in urinary tract; must adjust doses for renal impairment; approximately 1/3 of drug cleared during hemodialysis
- **Side Effects:** side effects uncommon; minimal cross-reactivity (for hives/anaphylaxis) with other β -Lactams
- **Clinical Applications:** urinary tract infections; nosocomial pneumonia; gram-negative bacteremia; pelvic infections (in combination with other agents); use in penicillin-allergic patient

Carbapenems

- **Classification:** three available: Imipenem plus cilastatin (*Primaxin*), Meropenem (*Merrem*), and Ertapenem (*Invanz*)
- **Mechanism of Action:** inhibits cell wall synthesis
- **Antimicrobial Activity:** Imipenem has extremely broad activity; covers most bacteria except MRSA, coagulase-negative staphylococci, *Enterococcus faecium*, *Clostridium difficile*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*; *Burkholderia cenocepacia* (formerly *Pseudomonas cepacia*); meropenem also has broad spectrum of coverage and similar to imipenem, but doesn't cover *Staphylococcus aureus* as well as imipenem; ertapenem is not as broad-spectrum as imipenem or meropenem (covers gram-positive and anaerobes similar to imipenem, but does not cover *Pseudomonas* or other more extended gram-negative organisms)
- **Pharmacokinetics:** excreted in kidneys
- **Side Effects:** Imipenem can cause nausea and vomiting during infusion; seizures can occur with inappropriately high doses (4 grams/day) or with normal doses in a patient with renal insufficiency; seizures have not been a problem with meropenem or ertapenem; high degree of cross-reactivity for hives/anaphylaxis with penicillins and carbapenems
- **Clinical Applications:** imipenem typically used in critically ill patients with multiple potential infectious sites and to treat multi-resistant gram-negative aerobes; meropenem currently being recommended for intra-abdominal infections in children and adults, as well as for treatment of meningitis in children (recommendations for children are for those at least 3 months of age; ertapenem is approved for complicated skin and soft tissue infection, community-acquired pneumonia, complicated UTI, complicated intra-abdominal infections, acute pelvic infections)

Vancomycin

- **Mechanism of Action:** Vancomycin (*Vancocin*, others) inhibits cell wall synthesis by interfering with second stage of synthesis of peptidoglycan (earlier site than site of penicillin); no cross resistance with penicillin; may also have effect of inhibiting synthesis of RNA
- **Antimicrobial Activity:** excellent activity against gram-positive aerobes (especially staphylococci, streptococci, and enterococci)
- **Pharmacokinetics:** poorly absorbed from GI tract; penetrates well into most areas in body except CNS; not removed by hemodialysis
- **Side Effects:** toxicity more of a problem in earlier preparations; these preparations were known as "Mississippi mud"; ototoxicity is most common serious side effect; rarely develops if serum levels kept below 30 µg/ml; hearing loss is usually permanent; nephrotoxicity rarely seen, higher incidence with concomitant use of aminoglycosides; "red man syndrome" is an infusion associated reaction that results from histamine release and typically consists of itching and rash on the face, neck, and trunk; patients occasionally develop hypotension; can be decreased by slowing infusion or premedicating with an antihistamine; recommended to give intravenous vancomycin over 1 hour
- **Monitoring for Toxicity:** levels usually not needed; if obtained, recommended to draw peak level 1 hour after infusion completed; obtain trough just before administering dose; desired serum levels: peak 20-40 µg/ml and trough 5-10 µg/ml
- **Clinical Applications:** drug of choice for MRSA, coagulase-negative staphylococci, and *Corynebacterium jeikeium*; alternate drug in staphylococcal, streptococcal, and enterococcal infections; commonly used in this setting with penicillin allergic patients; very cost-effective drug to use in hemodialysis patients since typically given once weekly; *Clostridium difficile* colitis, but must be given orally and this regimen is much more expensive than metronidazole

Fosfomycin

- **Mechanism of Action:** Fosfomycin (*Monurol*) does not belong to known antibiotic class; blocks very early step in bacterial cell wall synthesis; specifically, it inactivates enzyme enolpyruvyl transferase (irreversibly blocks condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate); also reduces bacterial adherence to epithelial cells
- **Antimicrobial Activity:** *E. coli* (less effective than TMP-SMX and fluoroquinolones) and *Enterococcus faecalis*; activity against other aerobic gram-negative rods not clearly known
- **Pharmacokinetic:** long half life
- **Side Effects:** diarrhea (10%), headache (10%), and vaginitis (8%)
- **Clinical Applications:** acute uncomplicated urinary tract infection in adults caused by either *E. coli* or *Enterococcus faecalis*; approximately equal in efficacy with nitrofurantoin, but inferior to quinolones or trimethoprim-sulfamethoxazole

Daptomycin

- **Mechanism of Action:** Daptomycin (*Cubicin*) is in a novel antibiotic class known as a cyclic lipopeptides; binds to bacterial membrane and causes rapid membrane depolarization
- **Antimicrobial Activity:** extremely good activity against gram-positive pathogens, including MRSA
- **Pharmacokinetic:** long half life allows for once daily dosing; available in IV form only
- **Side Effects:** few adverse effects; elevation in CPK in about 3%
- **Clinical Applications:** complicated skin and soft tissue infections; under investigation for endocarditis; not indicated for pneumonia (did not perform well in pneumonia trials)

Protein Synthesis Inhibitors

Macrolides/Ketolides

Generic Name	Trade Name
Erythromycin	<i>Eryc</i> , others
Azithromycin	<i>Zithromax</i>
Clarithromycin	<i>Biaxin</i>
Dirithromycin	<i>Dynabac</i>
Telithromycin	<i>Ketek</i>

- **Mechanism of Action:** the macrolides reversibly bind to the domain V of the 50S ribosomal subunit and inhibit protein synthesis; may interfere with binding of chloramphenicol; the ketolides bind to domain V and domain II
- **Antimicrobial Activity**
 - Erythromycin: most gram-positive aerobes (*Streptococcus* species, *Staphylococcus* species), *Mycoplasma pneumoniae*, *Legionella* species, *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Campylobacter jejuni*

- Azithromycin: most gram-positive aerobes (*Streptococcus* species, *Staphylococcus* species); *Hemophilus influenzae*; *Chlamydia trachomatis*; *Legionella* species, *Chlamydia pneumoniae*, *Mycobacterium avium* complex
- Clarithromycin: most gram-positive aerobes (*Streptococcus* species, *Staphylococcus* species), *Hemophilus influenzae*; *Legionella* species, *Mycobacteria*; *Helicobacter pylori*
- Dirithromycin: same spectrum as erythromycin
- Telithromycin: similar as azithromycin but also has good-activity against macrolide-resistant *Streptococcus pneumoniae*

- **Pharmacokinetics**

- Erythromycin: food reduces absorption (except estolate form); excreted primarily in bile; 2-5% excreted in urine
- Azithromycin: penetrates very well into tissues; concentrated in macrophages and polymorphonuclear leukocytes; long half life allows for once daily dosing; drug stays in tissues for 4-5 days after last dose
- Clarithromycin: distributed widely throughout body; long half-life
- Dirithromycin: long half life allows for once daily dosing
- Telithromycin: long-half life allows for once daily dosing

- **Side Effects**

- Erythromycin: GI irritation is most common side effect; cholestatic hepatitis can occur, especially with estolate form; increased theophylline levels; increased anticoagulant effect of coumadin; increased cyclosporin levels
- Azithromycin: GI (less than erythromycin); less drug interactions than erythromycin
- Clarithromycin: GI (less than erythromycin)
- Dirithromycin: GI (less than erythromycin)
- Telithromycin: GI (less than erythromycin)

- **Clinical Applications**

- Erythromycin: community acquired pneumonia, especially in young adults; mycoplasma or legionella infections; soft tissue infections; *Campylobacter jejuni* gastroenteritis
- Azithromycin: upper and lower respiratory tract infections; skin-soft tissue; chlamydia; Lyme disease; *Mycobacterium avium* complex
- Clarithromycin: upper and lower respiratory tract infections, *Mycobacterium avium* complex, other atypical mycobacterium, *Helicobacter pylori*
- Dirithromycin: same as erythromycin
- Telithromycin: community-acquired pneumonia (including multidrug-resistant *Streptococcus pneumoniae*, sinusitis, acute exacerbation of chronic obstructive lung disease)

Aminoglycosides

Generic Name	Trade Name
Amikacin	<i>Amikin</i>
Gentamicin	<i>Garamycin</i> , others
Tobramycin	<i>Nebcin</i>

- **Mechanism of Action:** inhibits protein synthesis by irreversibly binding to 30S bacterial ribosome; uptake across cells is important and is inhibited by anaerobic environment and low pH; considered bactericidal drug
- **Antimicrobial Activity:** most gram-negative bacilli, but typically not *Burkholderia cenocepacia* (formerly *Pseudomonas cepacia*) or *Stenotrophomonas (Xanthomonas) maltophilia*; has good activity against enterococcus and staphylococcus, but generally used in combination to treat these organisms; some aminoglycosides have activity against mycobacteria

- **Pharmacokinetics:** poor oral absorption; must be given IV in order to achieve adequate serum levels; poor penetration across blood-brain barrier; very high urinary concentrations; excreted in kidneys; removed by hemodialysis
- **Side Effects:** 1) nephrotoxicity (increased likelihood with hypotension, increased duration of therapy, concomitant liver disease, and administration of other nephrotoxic drugs); 2) ototoxicity (irreversible); 3) neuromuscular blockade (enhanced by underlying conditions or drugs that affect the neuromuscular junction); 4) shock-like syndrome has been described with once daily aminoglycoside administration
- **Monitoring for Toxicity:** toxicity can be minimized by estimating dose using creatinine clearance and by adjusting dose based on peak and trough levels; creatinine clearance (ml/min)=[(140-age) X wt in kg] ÷ [serum creatinine x 72]; for females multiply results by 0.85; as a rough guideline one can use 100 ml/min as a normal creatinine clearance; for example if patient's creatinine clearance is 50 ml/min then the patient has ~50% of normal renal function; therefore reduce the total daily dose by 50% (do not adjust loading dose); one can decrease the total daily dose by reducing each dose or by increasing the dosing interval (most recommend decreasing dosing interval); more accurate estimates can be made using appropriate tables; peak levels should be drawn 1 hour after start of infusion (for example:30 minutes after completing a 30-minute intravenous infusion or 40 minutes after completing a 20-minute intravenous infusion); normal peak levels (µg/ml): gentamicin 4-6; tobramycin 4-6; amikacin 20-30; troughs should be drawn immediately before the next dose is administered; normal levels (µg/ml): gentamicin 1-2; tobramycin 1-2; amikacin 5-10
- **Once Daily Dosing:** in recent years, once daily aminoglycoside dosing (approximately 5 mg/kg) has become preferable by many, mainly because of less nephrotoxicity; monitoring of levels is not the same as with conventional three times a day aminoglycoside dosing and monitoring of levels should be done in conjunction with someone who has expertise in this matter; in general, once daily aminoglycoside dosing should not be used in patients with endocarditis
- **Clinical Applications:** gram-negative infections; endocarditis caused by enterococci or viridans streptococci (in combination with ampicillin, penicillin, or vancomycin); tularemia and plague (streptomycin)

Tetracyclines

- **Mechanism of Action:** inhibit protein synthesis by binding to 30S ribosomes
- **Antimicrobial Activity:** rickettsia; some spirochetes; chlamydia; brucella
- **Pharmacokinetics:** absorption decreased by consumption of dairy products, aluminum hydroxide gels, sodium bicarbonate, calcium and magnesium salts, and iron; metabolized by liver and concentrated in bile; excretion primarily in urine; penetrates well into body tissues
- **Side Effects:** GI irritation; acute fatty necrosis of the liver; photosensitive dermatitis; brown discoloration of teeth and retard bone growth in fetuses and children; vulvovaginal candidiasis; vestibular toxicity with minocycline
- **Clinical Applications:** Lyme disease; brucellosis; chlamydia; RMSF; acne; bronchitis and pneumonia; not indicated for empiric therapy of UTI

Chloramphenicol

- **Mechanism of Action:** inhibits protein synthesis by binding to 50 S ribosome
- **Antimicrobial Activity:** *Hemophilus influenzae*; *Neisseria meningitidis*; *Streptococcus pneumoniae*; most gram-positive aerobes; rickettsia
- **Pharmacokinetics:** distributed widely in tissues (including CSF); primarily metabolized by liver and excreted in kidneys
- **Side Effects:** can inhibit hepatic microsomal metabolism of other drugs; aplastic anemia is most serious side effect; idiosyncratic and irreversible (1 in 25,000); typically develops weeks-months after completing therapy; reversible bone marrow depression; dose-related and reversible; far more common than idiosyncratic aplastic

anemia; gray-baby syndrome; results from very high serum levels and manifests as abdominal distention, cyanosis, and vasomotor collapse

- **Clinical Applications:** most commonly used in children to treat meningitis and rickettsia

Clindamycin

- **Mechanism of Action:** inhibits protein synthesis by binding to 50 S ribosome
- **Antimicrobial Activity:** gram-positive cocci (except MRSA and enterococci); most anaerobes; activity against some protozoa (*Toxoplasma gondii* and *Babesia microti*)
- **Pharmacokinetics:** penetrates most body fluids except CSF; metabolized in liver; eliminated in urine and feces
- **Side Effects:** most common side effect is pseudomembranous colitis caused by *Clostridium difficile*
- **Clinical Applications:** intra-abdominal or intrapelvic infections; skin and soft tissue infections; diabetic foot infections; anerobic lung abscess; in combination with quinine for babesiosis; in combination with pyrimethamine for toxoplasmosis (if patient allergic to sulfonamides); topically used for acne

Quinupristin-Dalfopristin

- **Mechanism of Action:** Quinupristin-dalfopristin (*Synercid*) is a streptogramin that has a 30:70 ratio of quinupristin and dalfopristin: both components work by blocking protein synthesis and they have synergistic activity when used together; dalfopristin inhibits early phase of protein synthesis and quinupristin inhibits late phase of protein synthesis
- **Antimicrobial Activity:** *E. faecium* (NOT *E. faecalis*); staphylococcus (MSSA, MRSA, coag-); streptococcus (*S. pyogenes*, *S. pneumoniae*)
- **Side Effects:** infusion site inflammation, arthralgias, myalgias (all dose related)
- **Clinical Applications:** vancomycin-resistant *E. faecium* infections; complicated skin and soft tissue infections

Linezolid

- **Mechanism of Action:** Linezolid (*Zyvox*) is an oxazolidinone that inhibits protein synthesis; specifically it binds to bacterial 23S ribosome of the 50S subunit and prevents the formation of a functional 70S initiation complex; available in both oral and intravenous forms
- **Antimicrobial Activity:** broadest agent against gram-positive organisms. Spectrum of activity includes *E. faecium* and *E. faecalis* (including VRE); staphylococcus (MSSA, MRSA, coag-); streptococcus (*S. pyogenes*, *S. pneumoniae*)
- **Side Effects:** weakly inhibits monoamine oxidase but has not been clinical problem; can decrease platelet count, especially with duration that exceeds 14 days; can cause “serotonin syndrome” in persons on SSRI (manifested as fever, agitation, tremor, and confusion)
- **Clinical Applications:** vancomycin-resistant enterococcal infections; complicated skin and soft tissue infections; pneumonias caused by gram-positive organisms

Agents that Block DNA Synthesis

Fluoroquinolones

Generic Name	Trade Name
Ciprofloxacin	<i>Cipro</i>
Gatifloxacin	<i>Tequin</i>
Levofloxacin	<i>Levaquin</i>
Moxifloxacin	<i>Avelox</i>
Norfloxacin	<i>Noroxin</i>
Ofloxacin	<i>Floxin</i>

- **Mechanism of Action:** bactericidal; inhibits DNA topoisomerases II and IV—enzymes involved in DNA supercoiling and chromosome partitioning
- **Antimicrobial Activity:** excellent activity against most *Enterobacteriaceae*, fastidious gram-negative bacilli, and gram-negative cocci (*Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Moraxella catarrhalis*); good activity against *Staphylococcus aureus*; older agents less active against streptococcus; all have only moderate activity against enterococcus; minimal activity against anaerobes; some fluoroquinolones have activity against mycoplasma, legionella, chlamydia, rickettsia, and mycobacteria; Levofloxacin, Gatifloxacin, Moxifloxacin, and Sparfloxacin have improved *Streptococcus pneumoniae* coverage compared with older fluoroquinolones (Ciprofloxacin, Norfloxacin, and Ofloxacin).
- **Pharmacokinetics:** excellent oral absorption; decreased absorption with sucralfate, antacids that contain aluminum or magnesium, and with supplements that contain zinc, iron, or calcium; good penetration into tissues (except for CSF); the fluoroquinolones available IV are Ciprofloxacin, Levofloxacin, Gatifloxacin, and Moxifloxacin.
- **Side Effects:** GI and CNS symptoms are most common side effects; may increase levels of theophylline, especially with Ciprofloxacin; may have affect on cartilage, therefore contraindicated in children, adolescents, pregnant women, and breast feeding women; fluoroquinolones can cause false-positive urine screen for opiates; rare effect of Achilles heel rupture
- **Clinical Applications:** preferred agent in the following circumstances: 1) complicated UTI that involves resistant gram-negative organism; 2) UTI in sulfa allergic patient; 3) chronic bacterial prostatitis; 4) empiric therapy of infectious diarrhea that is associated with fevers and WBC's in stool; 5) invasive external otitis; 6) pneumonia in cystic fibrosis patients; 7) certain cases of chronic osteomyelitis; 8) newer fluoroquinolones (Levofloxacin, Gatifloxacin, and Moxifloxacin) indicated for community-acquired pneumonia; 9) intravenous fluoroquinolones indicated for hospitalized patients with community-acquired pneumonia and nosocomial pneumonia.

Metronidazole

- **Mechanism of Action:** bacteria produce enzyme known as nitroreductase that reduces Metronidazole (*Flagyl*) thus liberating toxic intermediate compounds that disrupts bacterial DNA
- **Antimicrobial Activity:** *Trichomonas vaginalis*; *Entamoeba histolytica*; *Giardia lamblia*; most anaerobic bacteria; clostridia
- **Pharmacokinetics:** absorbed well after oral administration; metabolized in liver; excreted in urine and feces

- **Side Effects:** nausea, metallic taste (oral); antabuse-like reaction; prolongation of prothrombin time; avoid during first trimester of pregnancy and during periods of breast feeding
- **Clinical Applications:** anaerobic infections (not pulmonary); trichomoniasis; bacterial vaginosis; *Clostridium difficile*-associated diarrhea; giardiasis; amebiasis

Trimethoprim-Sulfamethoxazole

- **Mechanism of Action:** Trimethoprim-sulfamethoxazole (*Bactrim/Septtra*) works by sequentially inhibiting the production of folic acid, first by sulfamethoxazole (SMX) then by trimethoprim (TMP); SMX competitively inhibits the bacterial enzyme that converts para-aminobenzoate to folic acid; TMP competitively inhibits the activity of the bacterial enzyme dihydrofolate reductase that converts folic acid to folic acid
- **Antimicrobial Activity:** most *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella* species, *Staphylococcus saprophyticus*; not active against anaerobes, *Pseudomonas aeruginosa*, and some *Staphylococcus aureus*
- **Pharmacokinetics:** TMP and SMX widely distributed in tissues; high concentrations of TMP in prostatic secretions; metabolites of TMP and SMX excreted in urine
- **Side Effects:** skin (erythema, urticaria, pruritis, erythema multiforme); GI (nausea, vomiting, anorexia); bone marrow depression (anemia, thrombocytopenia, leukopenia); avoid use in patients with folate deficiency, G-6-PD deficiency, concomitant administration of methotrexate, and pregnant women
- **Clinical Applications:** UTI; prostatitis; traveler's diarrhea; upper respiratory infections; *Pneumocystis carinii* pneumonia (treatment and prophylaxis); nocardiosis

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