	AMINOGLYCOSIDES	SULFONAMIDES	TRIMETHOPRIM	QUINOLONES
Info/Notes	• Natural & semi-synthetic • Gentamicin, tobramycin, amikacin	Synthetic derivatives of *p*-aminobenzene acids (PABA) sulfonamide = anti-infectives	• Structural analog of the pteridine portion of dihydrofolic acid	
Spectrum of Action	• Mostly gram -ve, some gram +ve • No anaerobes because they lack oxygen needed for energy-dependent diffusion to enter cell ► Gentamycin: AMG of choice ► Tobramycin: AMG for *P. aeuroginosa* ► Amikacin: for organisms resistant to other AMGs; ctive against **Mycobacterium avium-intracellulare (MAI)** in AIDS patients	• Broad spectrum activity against gram-positive and gram-negative bacteria • In general, only bacteriostatic but may also work as bactericidal • Gram-positive except enterococci • Gram-negative except *P. aeruginosa* • NO anaerobes • *Pneumocystis carinii* (AIDS patients)	• Broad spectrum: gram-positive and gram-negative bacteria; little activity against aerobic bacteria • *P. aeruginosa*, enterococci & MRSA are resistant	• 1st gen: moderate gram-negative activity (minimal systemic distribution) • 2nd gen: expanded gram-negative activity & covers atypicals (limited gram-positive) o Ciprofloxacin = most active quinolone against *P. aeruginosa* • 3rd gen: expanded gram-negative and atypical activity; improved gram-positive • 4th gen: improved gram-positive, maintain gram-negative, gain anaerobic coverage
Uses	• Often used in combination with other antibiotics for synergistic effect (β-lactams make bacterial cell wall more porous → enhance AMG transport) • Severe infections of abdomen & UTI • Bacteremia & endocarditis • CNS infections (meningitis, ventriculitis) • Bone & joint infections, SSTIs • Plague, pneumonia, tuberculosis	• UTI • Neocardiosis • Toxoplasmosis (parasitic disease) • Prophylaxis against certain infections • UTI (upper/lower, prostatitis) • Respiratory tract infections (bronchitis, otitis media, pneumonia) • Pulmonary infections secondary to *P. carinii* (treatment & prevention) • GI infections: salmonella, shigella, Traveler's Diarrhea	• As effective as combination therapy for treatment of respiratory or UTI • Useful in patients allergic to sulfonamides • Drug resistance = problem	• Prostatitis • GU infections • Respiratory diseases • Skin and soft tissue infections • Gastroenteritis • Sexually transmitted diseases
Mechanism of Action	• Bactericidal (concentration-dependent) • Inhibitor of protein synthesis 1. Actively transported across bacterial cell membrane (disrupt membrane permeability for entry via Mg/Ca ions) 2. Inhibit bacterial protein synthesis through **irreversible** binding to 30S bacterial ribosomes 3. Binding interferes with an initiation complex between mRNA & 30S subunit 4. Misreading of mRNA → incorporation of incorrect AA into peptide → lethal for cell	• Prevent normal bacterial utilization of PABA (structural analog) for synthesis of folic acid (pteroylglutamic acid) • Trimethoprim exerts synergistic effect when used with a sulfonamide o Plasma ratio 1:20 most effective • Simultaneous administration of sulfonamide + TMP introduces sequential blocks in the pathway by which microorganisms synthesize THF from precursor molecules	• Binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF)	• Bactericidal (concentration-dependent) • Rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in DNA-enzyme complexes of DNA gyrase (gram-negative) & type IV topoisomerase (gram-positive) → rapid bacterial death
Pharmaco-kinetics	A • Poor oral absorption (highly polar cations = poorly absorbed from GIT) o Absorption from GIT potentiated with GI ulcers • Parenteral administration (IV = 10% bound to plasma proteins) • Available as topical preparations	A • Rapidly absorbed from GIT (70-100%) • Can be detected in urine within 30 min • Peak plasma levels in 2-6 h, $t_{1/2}$ = 10 h • Small intestine = major site of absorption, but some drug also absorbed in stomach	A • Well-absorbed in GI • Peak blood levels in 2 hours • $T_{1/2}$ = 11 hour	A • Well-absorbed following oral (moderate-excellent bioavailability) • Oral serum drug levels comparable to IV dosing = early transition from IV to oral therapy = potential reduction of treatment costs • Food doesn't impair absorption
	D • To all tissues (except CNS – although adequate concentration when meninges are inflamed)	D • Readily passes through placenta and reaches fetal circulation (can cause antibacterial & toxic effects)	D • Drug [tissue] > [urine] > [plasma] (100x) • Enters CSF if inflammation is present	D • Widely distributed throughout body • Tissue penetration higher than concentration in plasma, stool, bile, prostatic and lung tissue • Intracellular concentration exceptional in **neutrophils and macrophages** • CSF fluid levels poor = inadequate first line treatment of meningitis
	E • Glomerular filtration • Metabolism doesn't occur in host • Plasma half-life = 2-hour (normal) o 30-60 hrs in anephric patients = increased toxicity & PAE • In renal cortex, half-life = 100 hr (repetitive administration → renal cortical accumulation & toxicity)	E • Eliminated partly as unchanged drug, partly as metabolic products • Some exhibit diurnal variations in excretion (excreted 3x more at night) • Large fraction excreted in urine • Half-life depends on renal function • In acidic urine, older sulfonamides are insoluble and may precipitate → form crystalline deposits → can cause urinary obstruction	E	E • Half-life varies (1.5 – 16 hours) o Administered q12-24h • Eliminated by renal and non-renal routes (dose adjustment in renal or hepatic impairment) o Majority excreted renally o Sparfloxacin, moxifloxcin, trovafloxacin also hepatic

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Mechanism of Resistance	• Drug doesn't reach target (poor penetration)
	• Drug not active (plasmid-mediated bacterial transferase enzymes acetylate, adenylate or phosphorylate AMGs)
	• Target is altered (mutations in proteins of ribosome)
		• Result of mutations that cause:
		  ○ Overproduction of PABA
		  ○ Production of a folic-acid synthesizing enzyme with low affinity for sulfonamides
		  ○ Loss of permeability to sulfonamide
		• Dihydropteroate synthase with low sulfonamide affinity encoded on transmissible plasma (resistant cells emerge under selective pressure)
			• Changes in dihydrofolate
			• Impermeability
			• Overproduction of dihydrofolate reductase
			• Production of plasmid encoded TMP-resistant form of dihydrofolate reductase
				• Enzyme mutation → changes in binding site of drug → less affinity = less effective
				• Mutations in porin proteins in outer membrane → decrease drug permeability
				• Mutation that enhances efflux pumps

Side/ Adverse Effects; Toxicities	• Very potent with serious toxicities (related to dose and duration of therapy)
	• Nephrotoxicity: increases in SCr 4-5 days after therapy
	  ○ Monitor SrCr levels every 3 days
	  ○ Renal dysfunction = reversible
	• Ototoxicity (and vestibular) = irreversible
	  ○ Damage to inner ear (prolonged exposure) → decreased hearing, tinnitus & vertigo
	  ○ Damage to CN-8 (dose-dependent and saturable)
	  ► Decreased risk by limiting therapy to 7-10 days
	  ► If symptoms develop, stop therapy
	• Neuromuscular blockade: after large doses, decrease in both releases of ACh from presynaptic terminal & AChR sensitivity in post-synaptic site
	  ○ Use with caution in Parkinson's and myasthenia gravis
	  ○ Reverse by giving **calcium gluconate** or **neostigmine**
	• Headache, paresthesia (tingling, pricking, numbness of skin), dizziness, vertigo, skin rash, fever, allergic reactions (rare)
		• Fever, skin rashes, NVD
		• Urinary tract problems (following precipitation of drug in urine)
		• Disorders of hematopoietic system
		• Hypersensitivity: rashes, angioedema, **Stevens-Johnson syndrome** (longer-acting agents)
		  ○ If allergic to one, allergic to all
		• Crystulluria hydration → nephrotoxicity
		  ○ Alkalinisation of urine prevents problem
		  ○ Sulfisoxazole & SMX less liable to cause crystulluria
		• **Kernicterus:** in newborns, sulfa drugs displace bilirubin from serum albumin binding sites → bilirubin accumulates in basal ganglia and thalamus (baby's BBB not fully developed)
			• Serious side effects rare (except AIDS pts)
			• Blood dyscariasis
			• Hepatotoxicity
			• Long-term use → borderline folic acid deficiency in alcoholic or malnourished pts (because TMX also inhibits dihydrofolate reductase in these conditions)
			• Megoblastic anemia (low RBC), thrombocytopenia & granylocytopenia
				• GI: NVD, abdominal pain
				• CNS: headache, dizziness, drowsiness, confusion, insomnia, fatigue, depression, somnolence, seizures, vertigo, restlessness, tremor
				• Dermatologic : rash, photosensitivity, pruritis

		• GI: nausea, vomiting • Photosensitivity • In high doses → folic acid deficiency, anemia, leukopenia and thrombocytopenia • In patients with glucose-6-phosphate dehydrogenase deficiency: hemolytic anemia, granulocytopenia and thrombocytopenia can also occur • Allergic reactions: dermatologic reactions occasionally seen		
Drug Interactions	• May increase effects of anticoagulants • Cephalothin may increase renal toxicity • Diuretics may increase renal toxicity and ototoxicity • Any drug producing nephrotoxicity may enhance this effect		• Reduces therapeutic effect of cyclosporine → risk of nephrotoxicity	• Not synergistic in combination with other antibiotics (indifferent or additive) • Cipro + rifampin = antagonistic effects against *S. aureus* • Increase risk of CNS stimulation and convulsions (GABA) if used with NSAIDs • May lead to hypo and/or hyper-glycemia if used with anti-diabetic agents • Probenecid causes quinolones to stay in body longer • H_2 blockers decrease absorption • Chelate with cations (Al^{3+}, Mg^{2+}, Ca^{2+}, Fe^{2+}, Zn^{2+}) = reduce absorption and bioavailability (lower drug concentration)

Warnings & Contra-Indications	• Monitor drug levels to prevent toxicities
	• Neuromuscular blocker effects enhanced (can lead to respiratory depression and paralysis)
		• Avoided in pregnant women, newborns and infants less than 2 months of age
		  ○ Danger of kernicterus
			• Contraindicated in pregnancy
			  ○ Can interfere with development of fetus' neural tube	