
Integrated Activities and Tools for Antimicrobial Stewardship



An Introduction to Key Antibiotic Concepts

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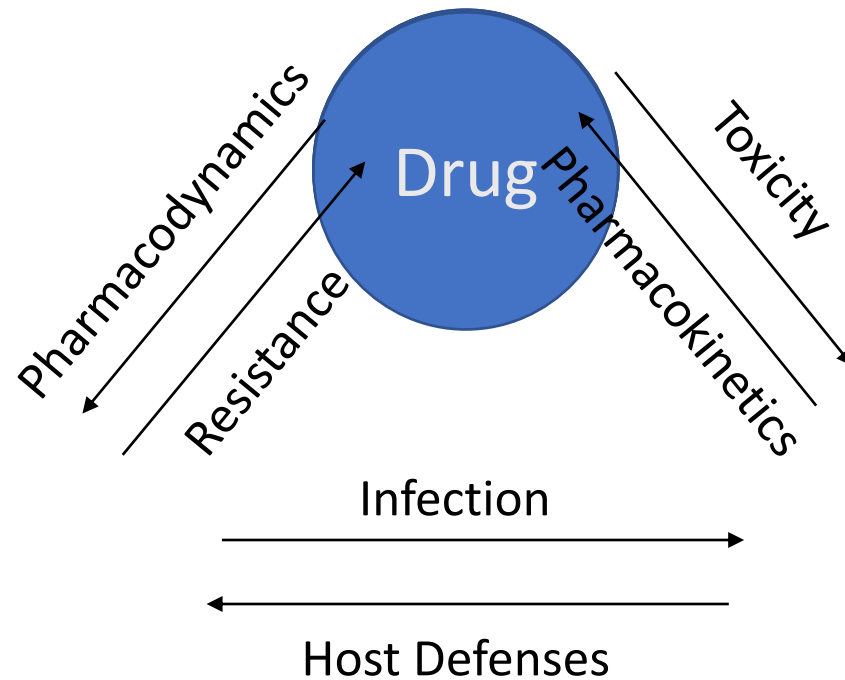
Infectious Diseases

Henry Ford Hospital – Detroit, MI

Learning Objectives

- Understand basic pharmacokinetic and pharmacodynamic concepts
- Review antibiotic class mechanism of action
- Review antibiotic class general spectrum of activity

Antimicrobial Drug Effects



Minimum Inhibitory Concentrations

Limitations?	
<ul style="list-style-type: none">• Time course of therapy?	<ul style="list-style-type: none">• Rate of bacterial kill (log/CFU)?
<ul style="list-style-type: none">• Dose-kill relationship?	<ul style="list-style-type: none">• Post-antibiotic effect?
<ul style="list-style-type: none">• Which testing method is the most accurate?	<ul style="list-style-type: none">• Antimicrobial tolerance?

Pharmacokinetic Concepts

What the body does to the drug

Absorption

- IV administration is rapid and complete
- IV/PO conversion recommended for high bioavailable drugs

Distribution

- Highly dependent on drug class
- Tissue penetration is important for specific infections

Metabolism

- Some antimicrobials are eliminated through hepatic system
- Source of some drug interactions

Excretion

- Most antimicrobials require dose adjustment in renal dysfunction

Pharmacodynamic Concepts

What the drug does to the organism

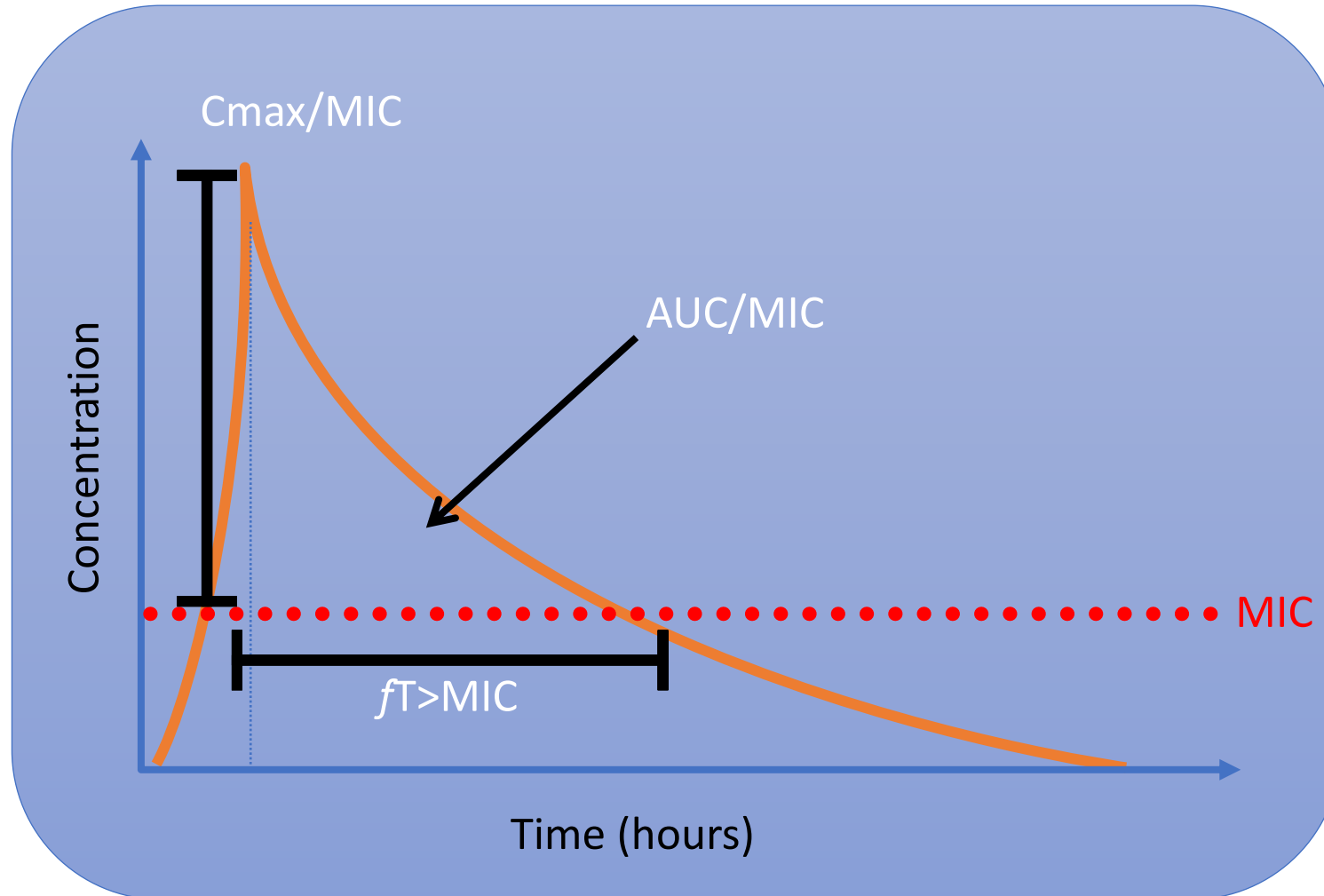
Concentration Dependent Killing

- As concentration increases, extent of bacterial killing increases
- Goal of therapy: maximize concentration of drug exposure

Time Dependent Killing

- The longer the duration of exposure, the greater the antibacterial activity
- Goal of therapy: optimize duration of drug exposure

Pharmacodynamic Parameters



Pharmacodynamic Measures Correlated with Efficacy

Activity Pattern	Agent/Class	PK/PD Measure
Concentration Dependent	Aminoglycosides	C _{max} /MIC
	Daptomycin	C _{max} /MIC; AUC/MIC
	Metronidazole	C _{max} /MIC; AUC/MIC
	Quinolones	C _{max} /MIC; AUC/MIC
Time Dependent	Beta-lactams	<i>f</i> time > MIC
	Clindamycin	AUC/MIC
	Macrolides	AUC/MIC
	Linezolid	AUC/MIC
	Tetracyclines	AUC/MIC
	Vancomycin	AUC/MIC

Which of these antimicrobials have concentration dependent activity?

- Aminoglycosides

- Clindamycin

- Metronidazole

- Macrolides

- Tetracyclines

- Beta-lactams

- Daptomycin

- Vancomycin

- Quinolones

- Linezolid

Antibiotic Mechanism of Action

Why should we care about drug mechanism?

- Optimizing PK/PD → improve efficacy, minimize toxicity
 - Beta-lactams- rash, anaphylaxis, neurotoxicities
 - Macrolides- QT prolongation, diarrhea, hepatotoxicity
 - Quinolones- C. difficile, QT, neurotoxicities, musculoskeletal effects, photosensitivity
 - Tetracyclines- Photosensitivity, GI upset
 - Vancomycin- Nephrotoxicity, rash, thrombocytopenia
 - Daptomycin- Musculoskeletal
 - Aminoglycosides- Nephrotoxicity, ototoxicity, musculoskeletal effects
- Better understand potential mechanisms of resistance
- Identify (eventually) novel bacterial targets

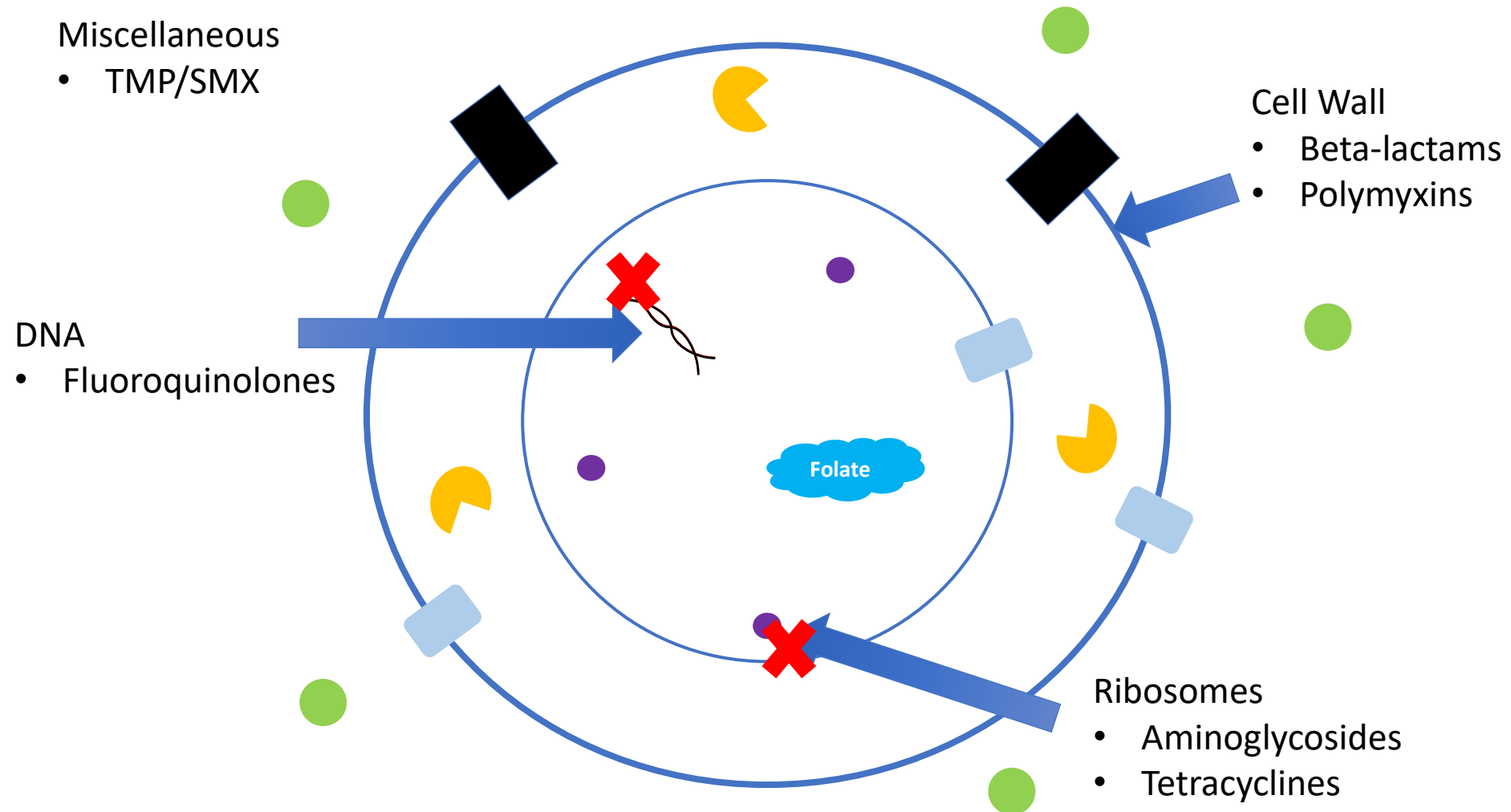
EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines



EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole

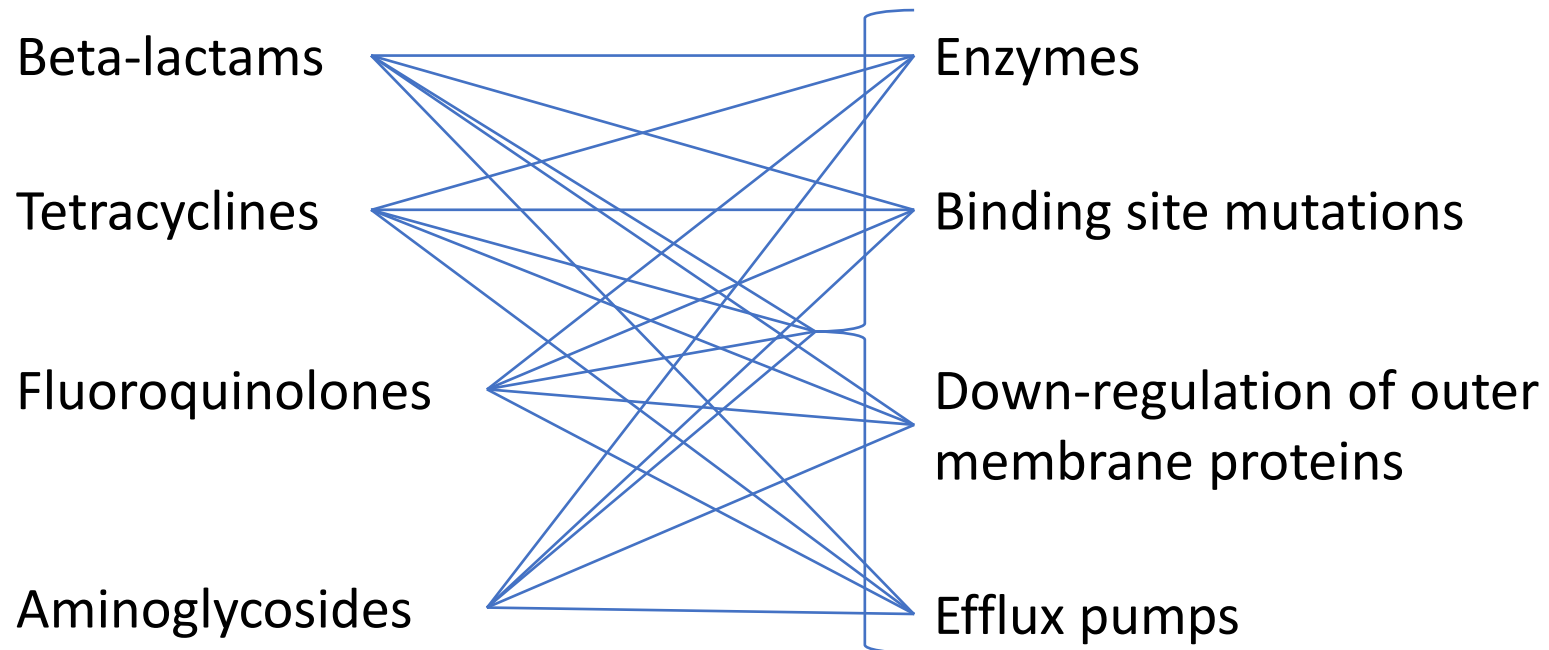


General Mechanisms of Action (& Resistance)



Knowledge Question

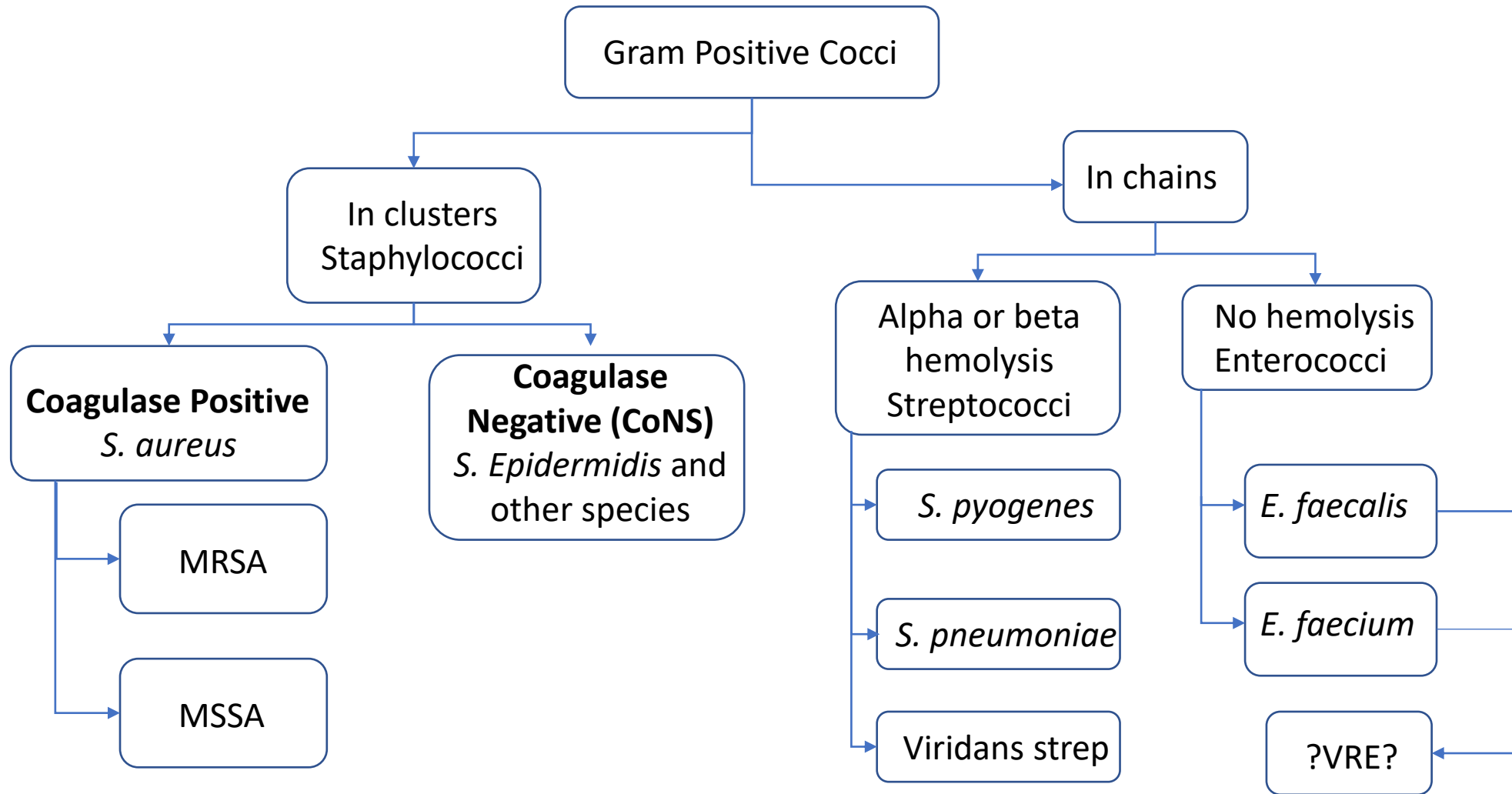
- Which resistance mechanisms are employed against these antibiotics?

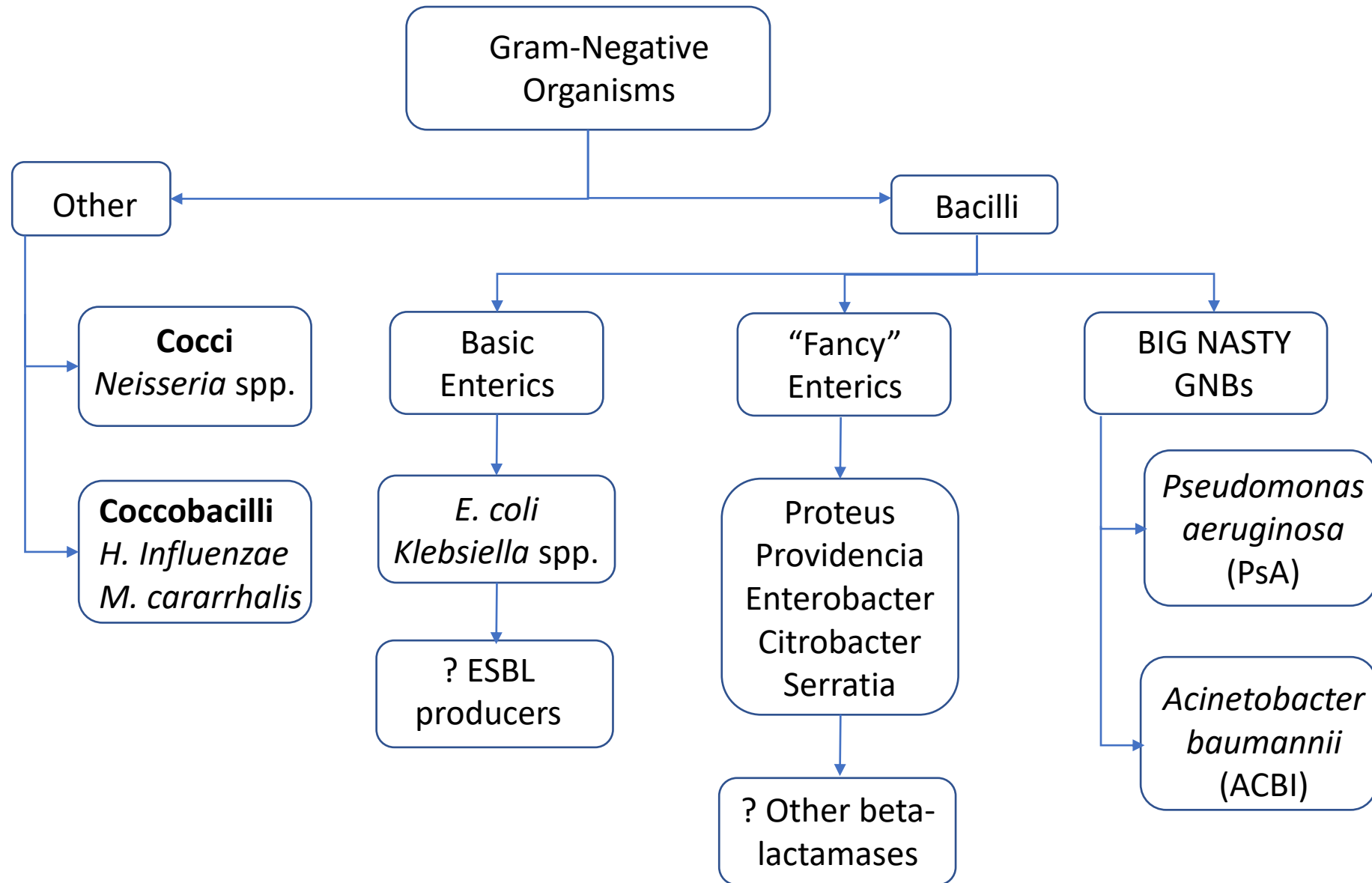


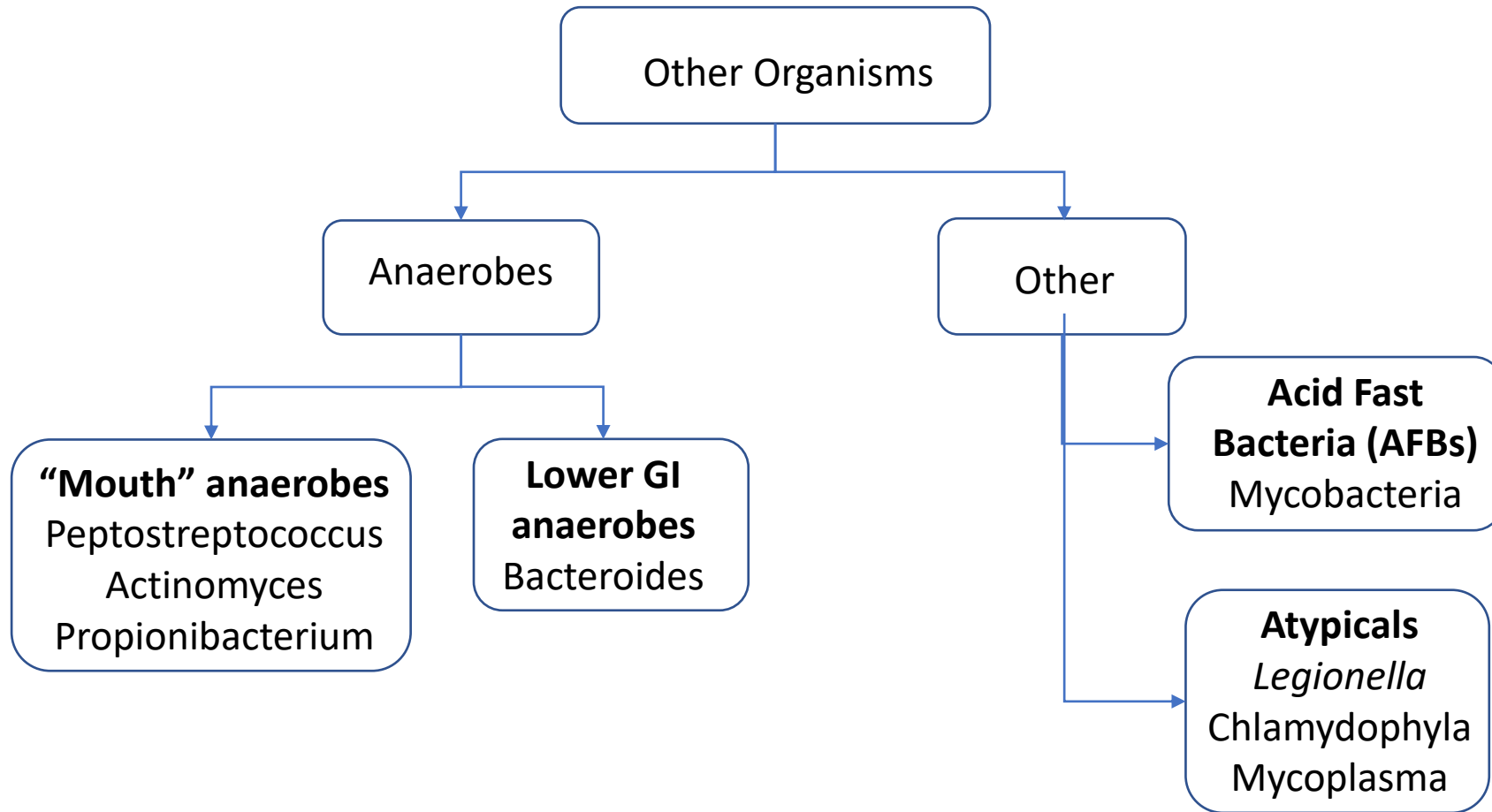
Antibiotic Spectrum of Activity: General Considerations

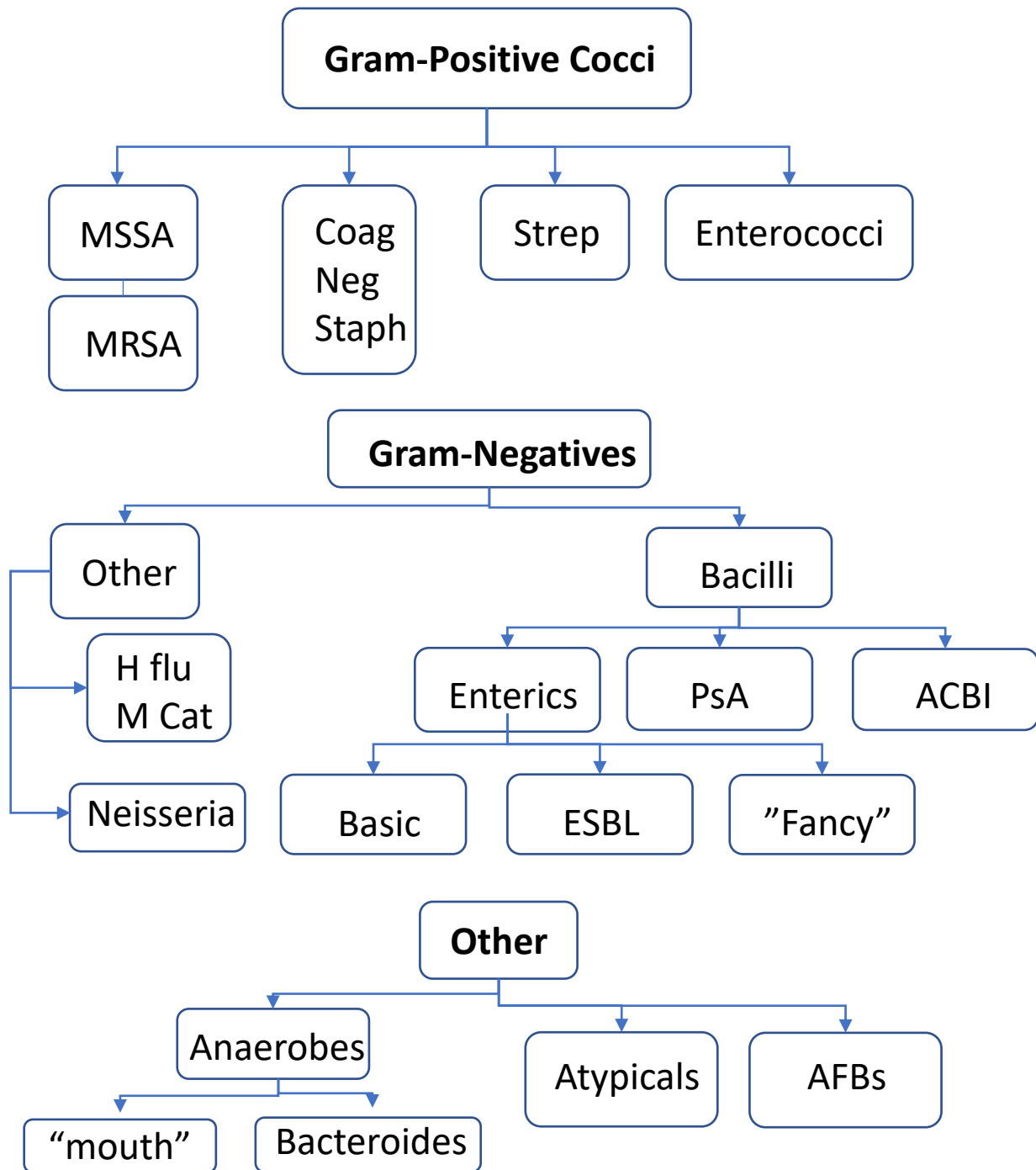
Caveat

- “Coverage” trends here are based on general, empirical data.
 - You should always be aware of local microbiology, patient risk factors, and known culture/susceptibility results when available.
 - *In vitro* activity is NOT the same thing as “it’s ok to use for every infection type and severity”.
- This portion of the presentation is a basic guide and is not intended as a replacement for actual references.







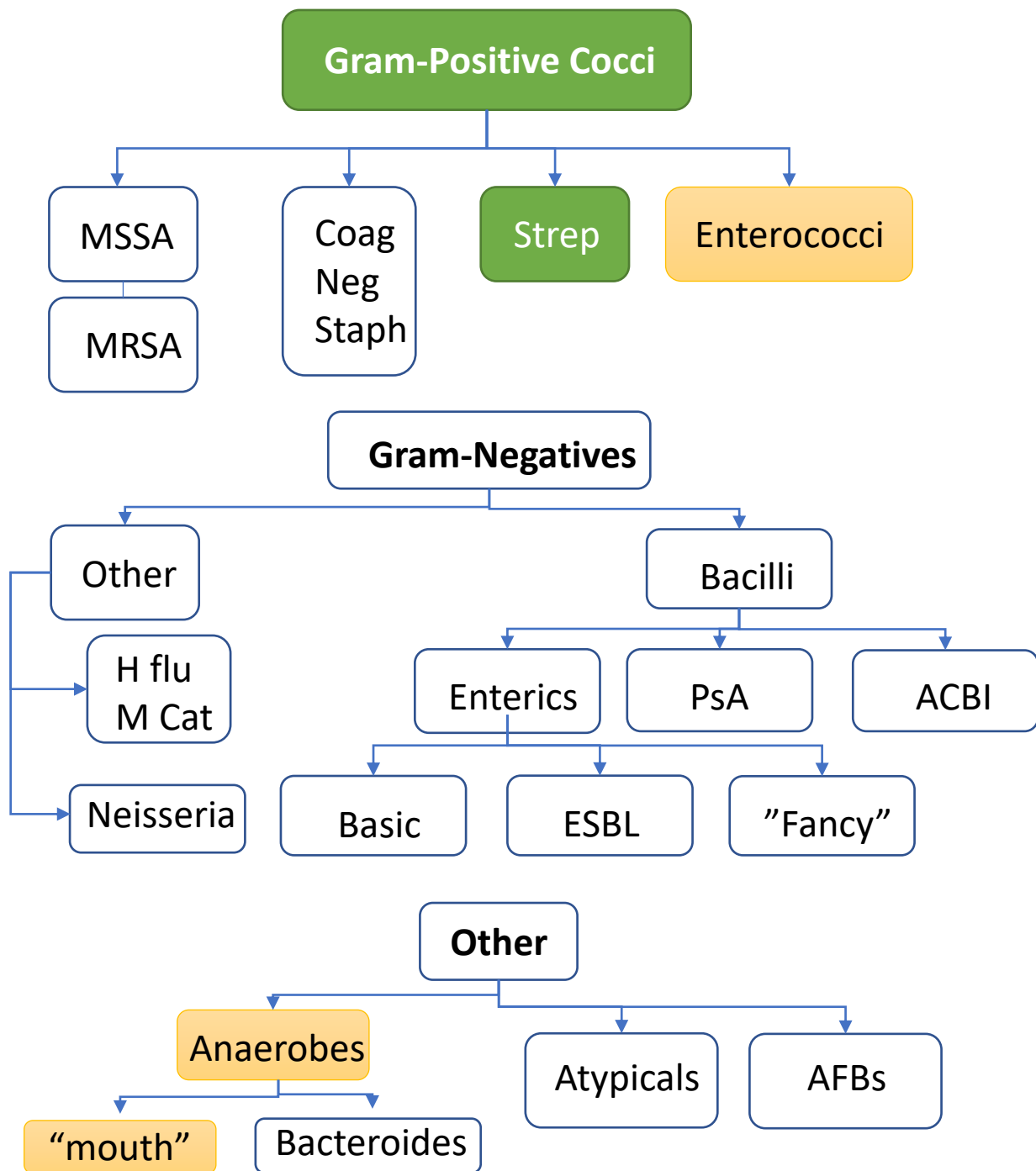


Drug Class	
Drugs	
Gram-positive highlights	
Gram-negative highlights	
Other highlights	

Good coverage. Reliable empirically unless exceptions noted.

Moderate coverage, or good in specific situations. Use empirically with caution.

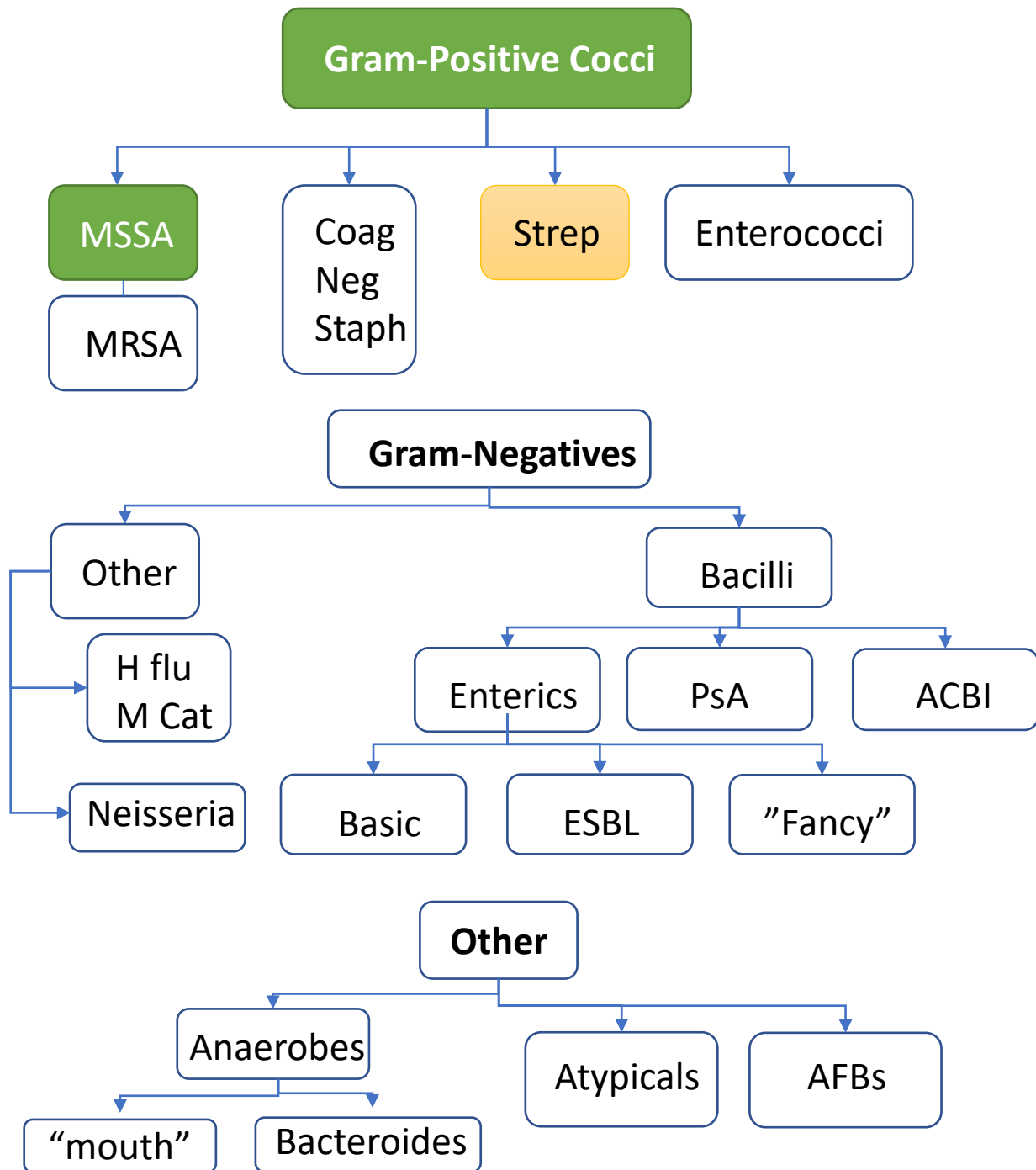
Poor/No coverage, or no data.



Penicillin	
Drugs to Remember	Penicillin G (IV) Pen VK (Oral) Benzathine Penicillin (IM)
Gram-positive highlights	Drug of choice for many Strep <i>E. faecalis</i> usually susceptible <i>E. faecium</i> , Staph usually resistant
Gram-negative highlights	Minimal activity
Other highlights	Okay for "mouth anaerobes" Also: drug of choice for <i>Treponema</i> (the spirochete that causes syphilis)

Notes on Penicillin

- Side effects:
 - Hypersensitivity reactions, anaphylaxis (estimated 10% of population)
 - Neutropenia, thrombocytopenia
 - Interstitial nephritis
 - Autoimmune hemolytic anemia

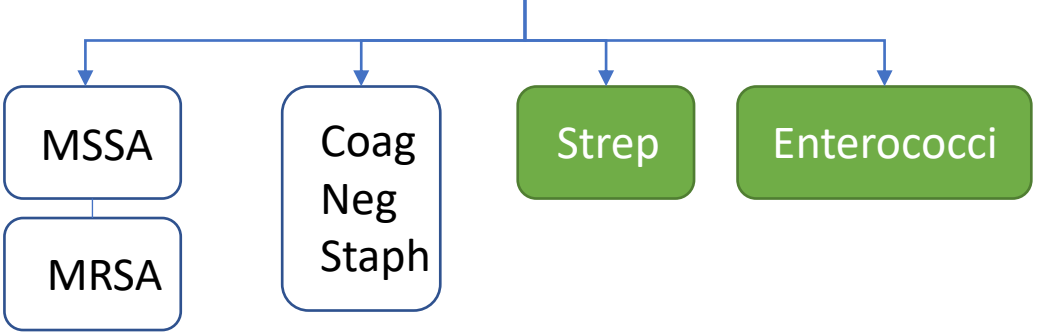


Anti-staphylococcal Penicillins	
Drugs to Remember	Nafcillin (IV) Oxacillin (IV) Dicloxacillin or Flucloxacillin (PO)
Gram-positive highlights	Excellent MSSA activity Okay Streptococcal activity, but not as strong as some other penicillins NO enterococcus, MRSA, and most Coag-negative Staph are resistant
Gram-negative highlights	Minimal
Other highlights	Minimal

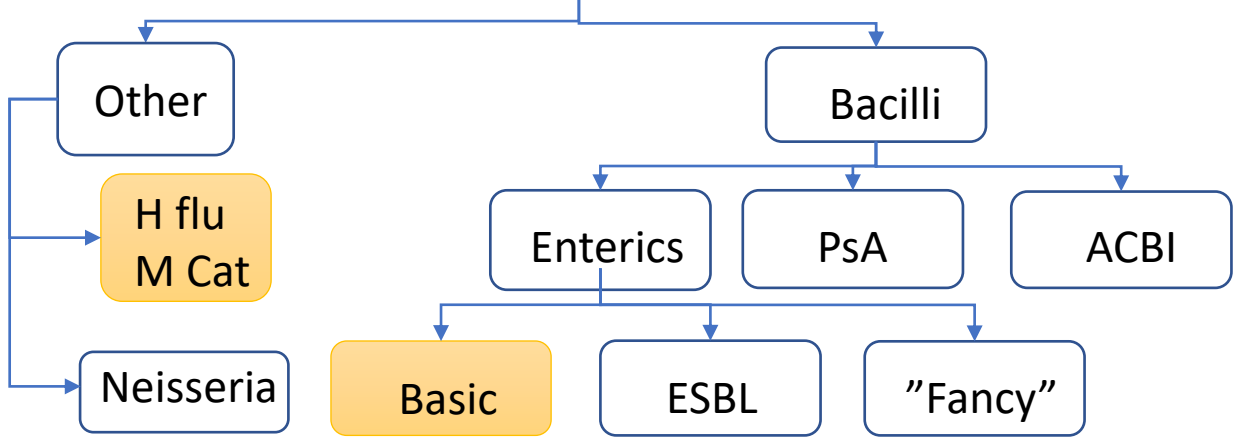
Notes on Antistaphylococcal Penicillins

- Side effects:
 - Hypersensitivity reactions, anaphylaxis
 - Neutropenia, thrombocytopenia
 - Interstitial nephritis
 - Autoimmune hemolytic anemia

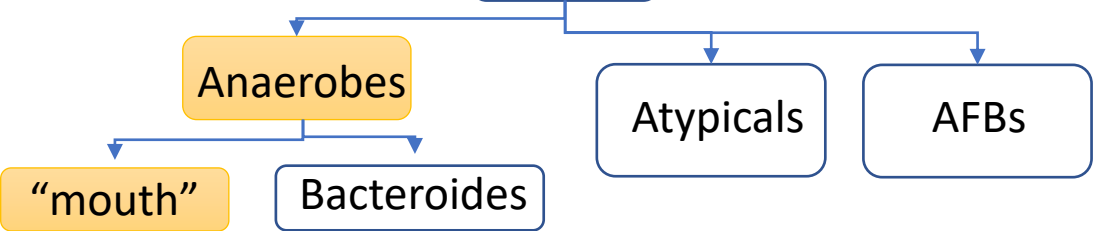
Gram-Positive Cocci



Gram-Negatives



Other

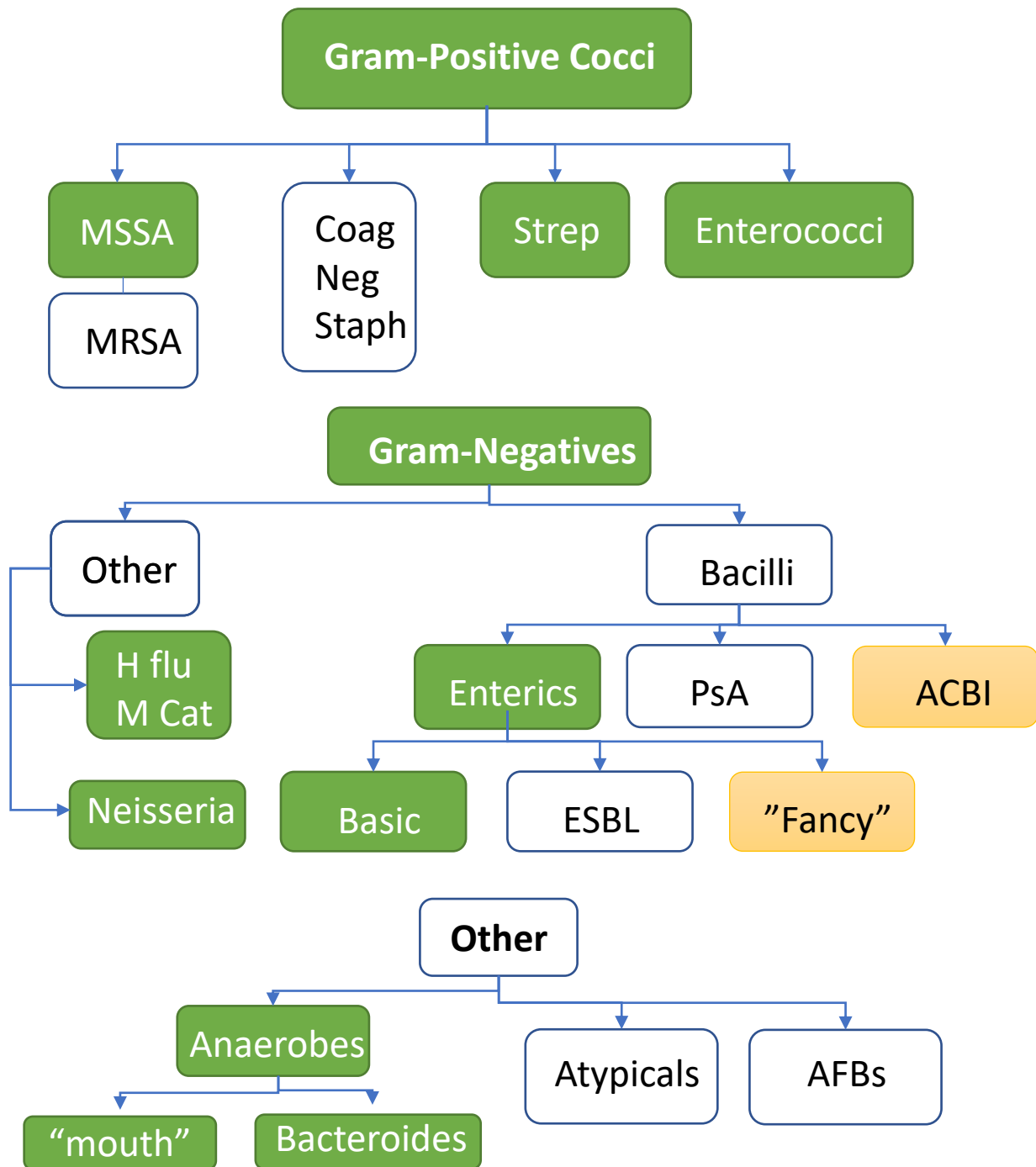


Aminopenicillins

Drugs to Remember	Ampicillin (IV, PO) Amoxicillin (PO)
Gram-positive highlights	Great for strep, <i>E faecalis</i> * <i>E faecium</i> are often resistant Very poor staphylococcus coverage
Gram-negative highlights	Some, but poor activity against <i>H influenzae</i> , <i>Proteus</i> spp., <i>E coli</i> NOT active against <i>Klebsiella</i> spp., other GNBs
Other highlights	Ampicillin is good for <i>Listeria</i> spp. (a Gram-positive organism) Some anaerobic activity as penicillin

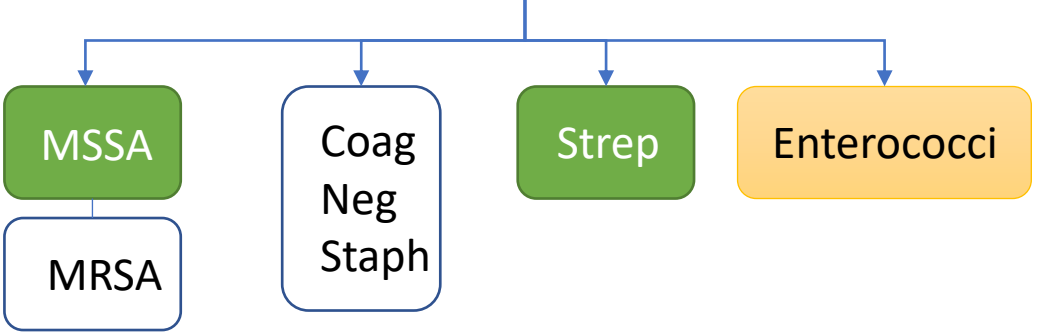
Notes on Aminopenicillins

- Side effects:
 - Gastrointestinal distress

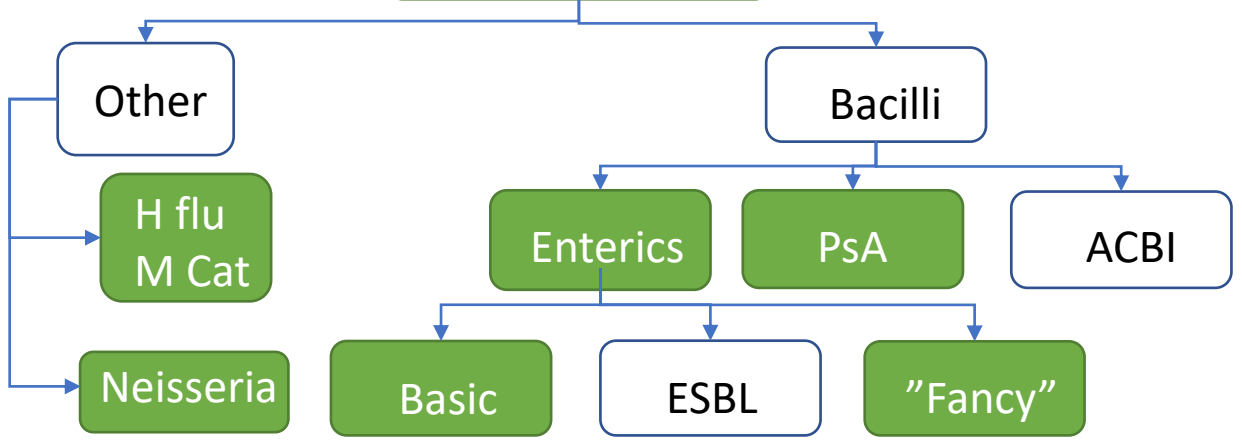


AminoPCN + BL inhibitor	
Drugs to Remember	Amoxicillin/clavulanate (PO) Ampicillin/sulbactam (IV) (Enterococcal activity same as ampicillin or amoxicillin)
Gram-positive highlights	Adds MSSA coverage The rest is the same as aminopenicillins
Gram-negative highlights	Covers <i>Neisseria</i> spp., <i>H influenzae</i> , <i>Moraxella catarrhalis</i> , basic enterics, some "fancy" enterics. SULBACTAM covers ACBI
Other highlights	Broad anaerobic coverage

Gram-Positive Cocci



Gram-Negatives



Other

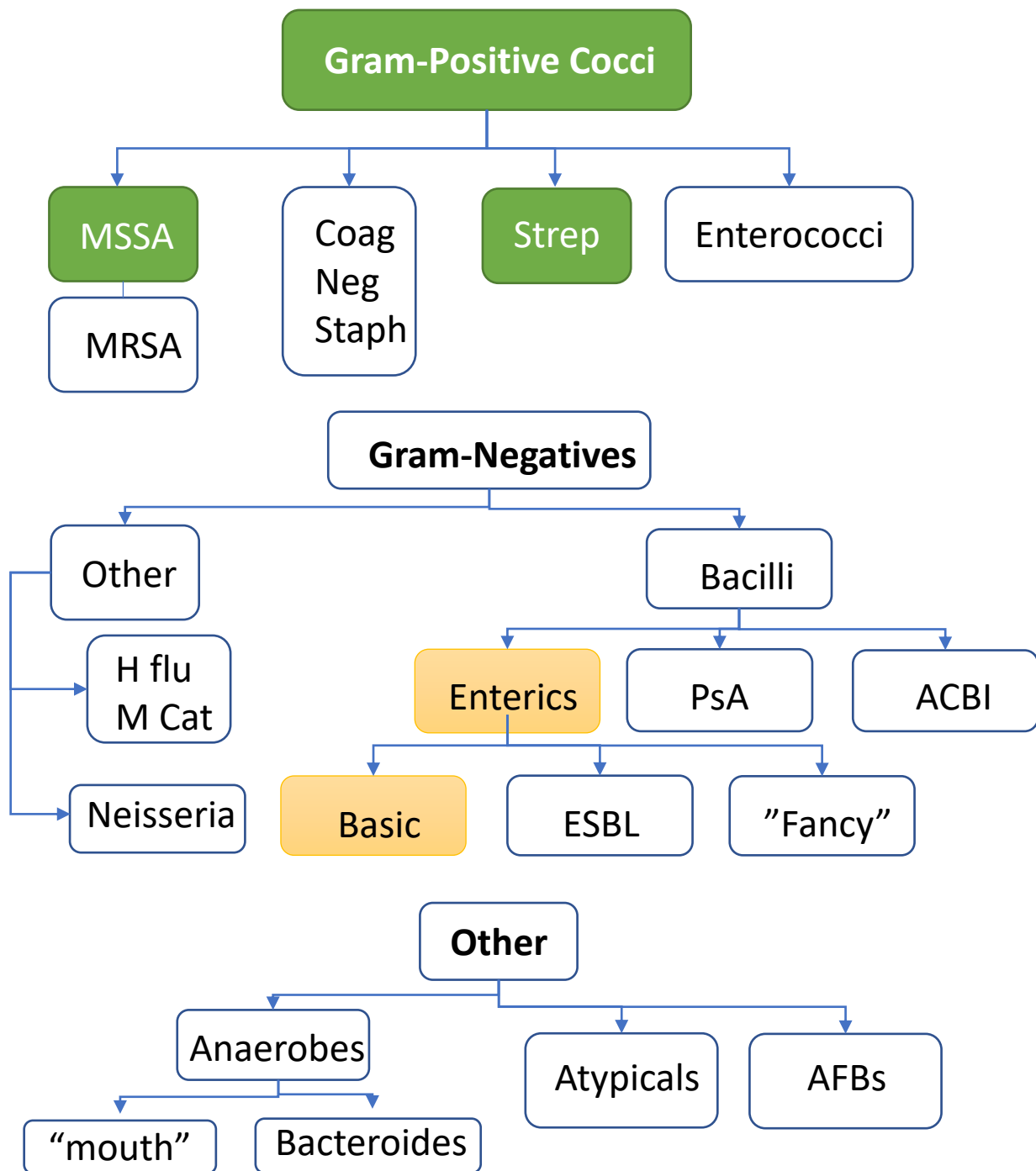


Other PCN + BLI Combos

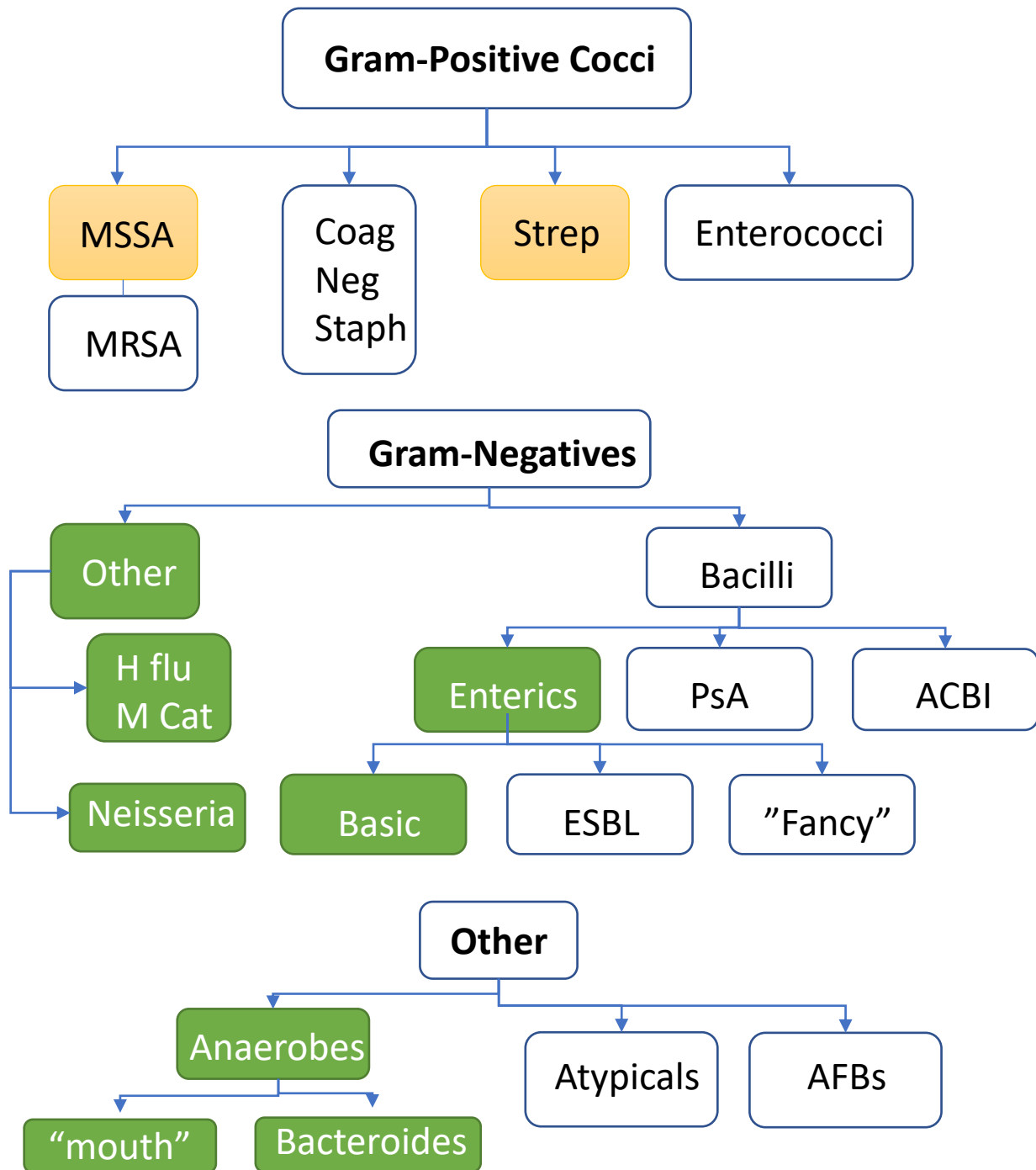
Drugs to Remember	Piperacillin/tazobactam (IV) (ticarcillin/clavulanate is no longer available)
Gram-positive highlights	Similar to aminopenicillin/BLI combos
Gram-negative highlights	Broad Gram-negative coverage Adds PsA coverage Does NOT cover ACBI
Other highlights	Broad anaerobic coverage

Notes on BLI's

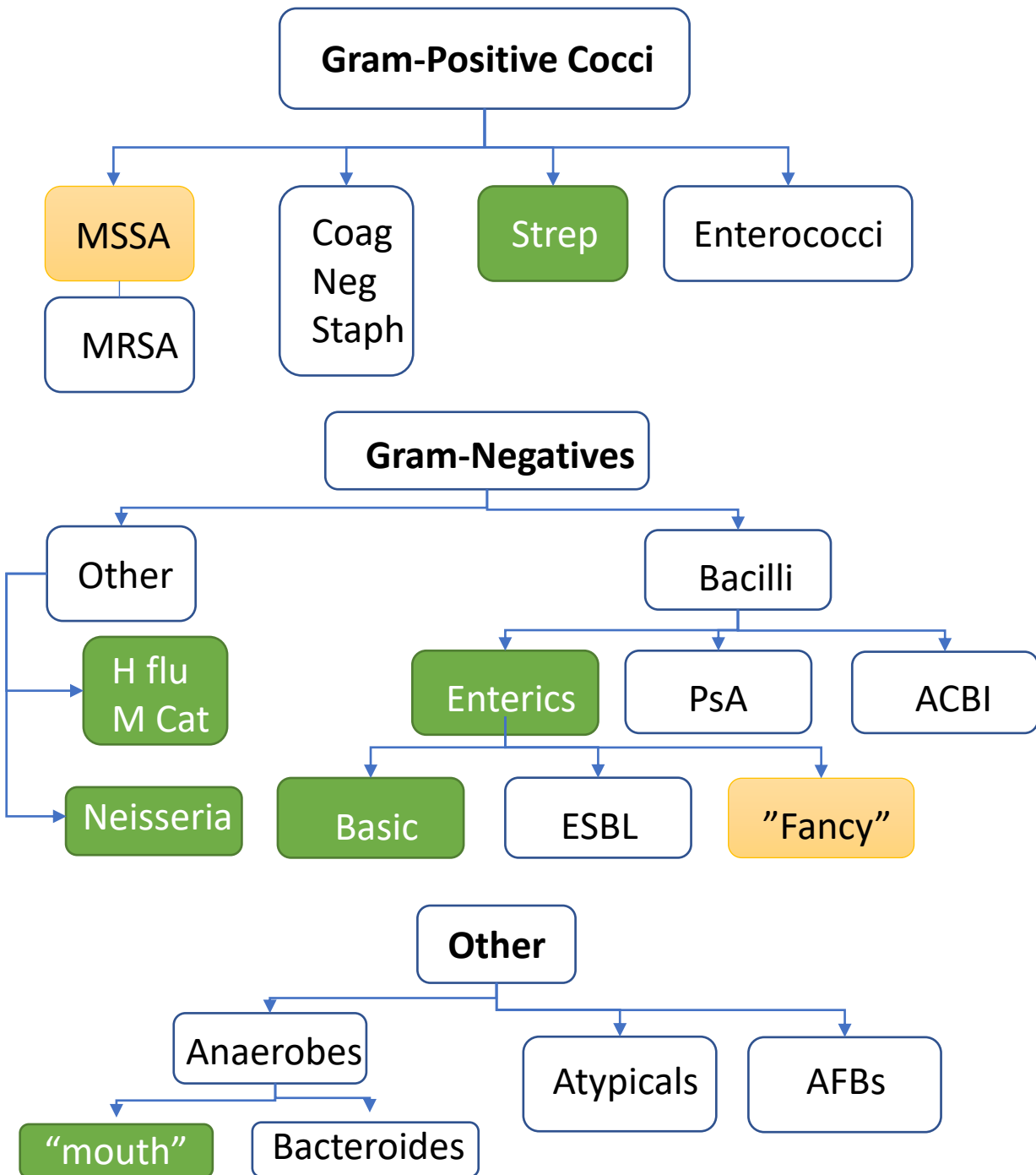
- Side effects:
 - Gastrointestinal distress (dose-dependent reaction)



1 st Gen Cephalosporins	
Drugs to Remember	Cefazolin (IV) Cephalexin (PO) Cefadroxil (PO)
Gram-positive highlights	Good MSSA, strep No enterococcus, no MRSA CoNS frequently resistant
Gram-negative highlights	Covers basic enterics, <i>Proteus</i> spp.
Other highlights	Minimal

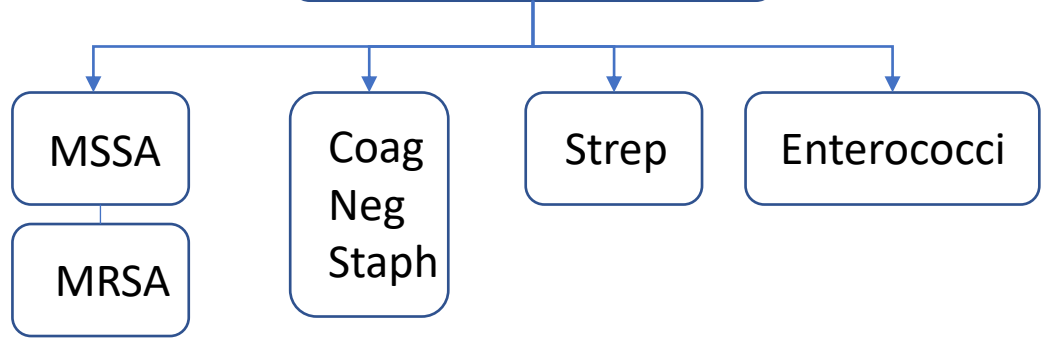


2 nd Gen Cephalosporins	
Drugs to Remember	Cefotetan, Cefoxitin (IV)- "cephamycins" Cefuroxime (IV/PO) Cefclor, Cefprozil (PO)
Gram-positive highlights	Moderate streptococcal and staphylococcal activity
Gram-negative highlights	Covers enterics, <i>H influenzae</i> , some <i>Neisseria</i> spp.
Other highlights	Cephamycins have anaerobic activity, others do not

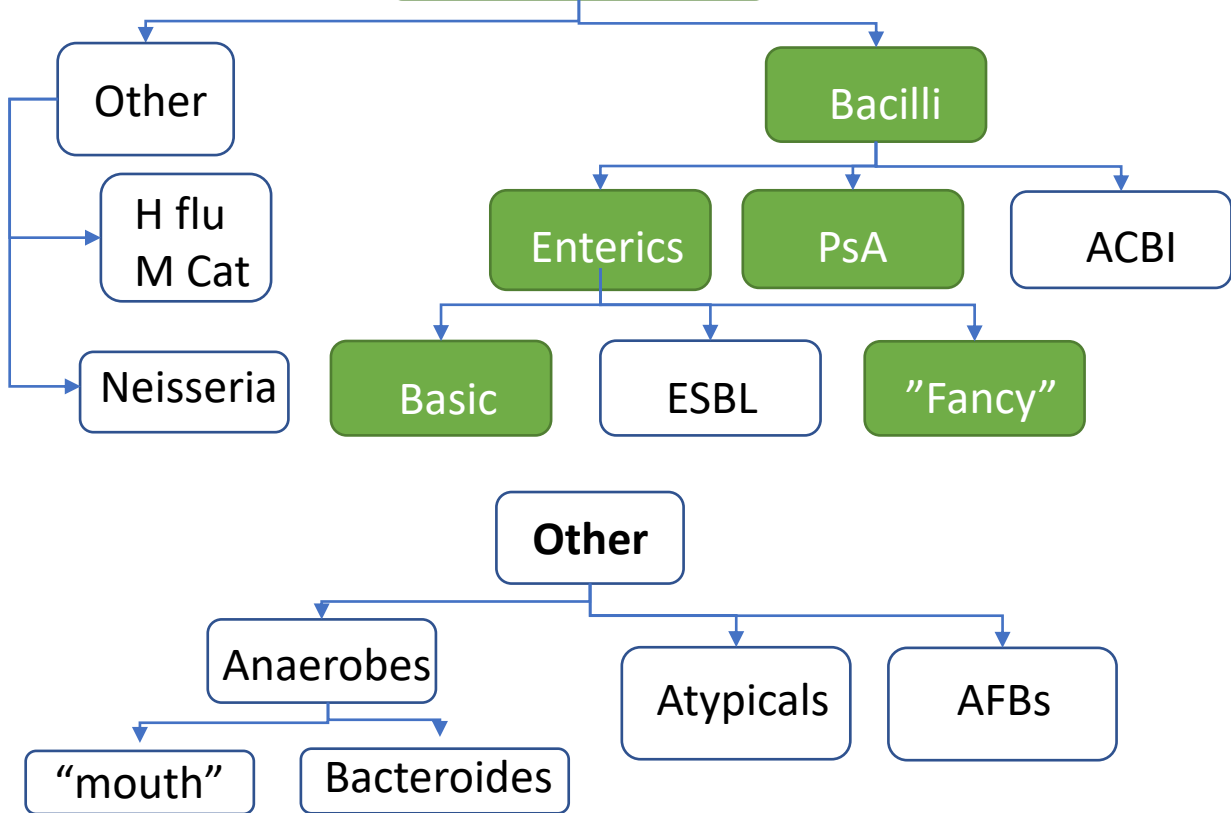


3 rd Gen Cephalosporins	
Drugs to Remember	Ceftriaxone, Cefotaxime (IV) Ceftazidime (IV). This one is different and gets it's own slide. Cefixime, cefdinir, cefpodoxime, ceftibuten, cefditoren (PO)
Gram-positive highlights	Good strep Some MSSA coverage, but UNRELIABLE No MRSA or enterococcus activity
Gram-negative highlights	Good vs. "respiratory" GN coccobacilli Good vs <i>Neisseria</i> spp. Good vs basic Enterobacterales "Fancy" enterics may display inducible resistance (e.g. AmpC) NO ESBL, PsA, ACBI
Other highlights	Adequate "mouth anaerobe" coverage

Gram-Positive Cocci



Gram-Negatives



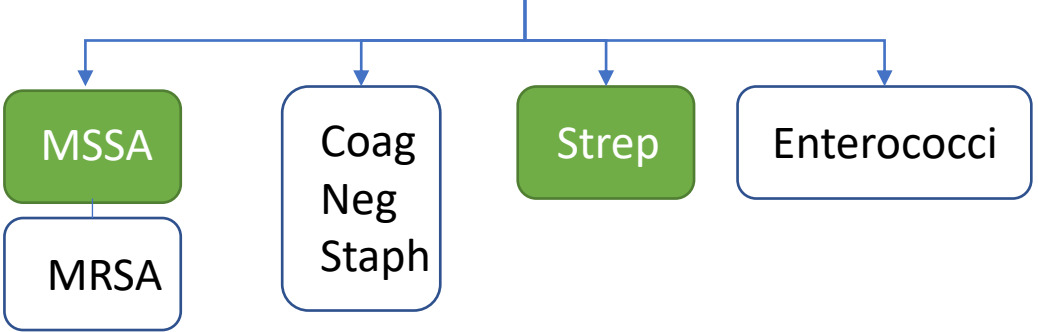
Odd 3rd Gen Ceph- CEFTAZIDIME

Gram-positive highlights	Not great
Gram-negative highlights	Broad, including PsA NO ESBLs "Fancy" enterics may display inducible resistance (e.g. AmpC)
Other highlights	None

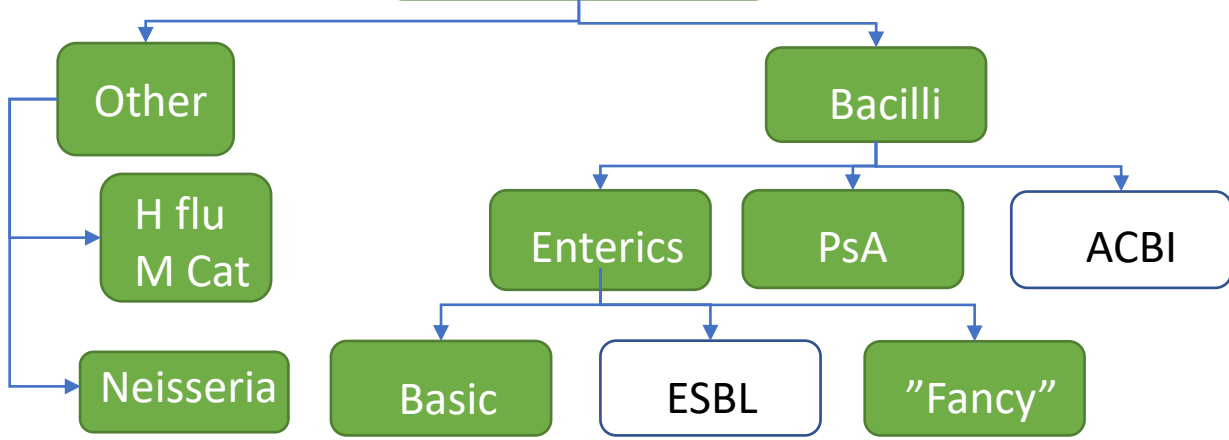
Monobactams - Aztreonam

Gram-positive highlights	None
Gram-negative highlights	Broad, including PsA NO ESBLs
Other highlights	None

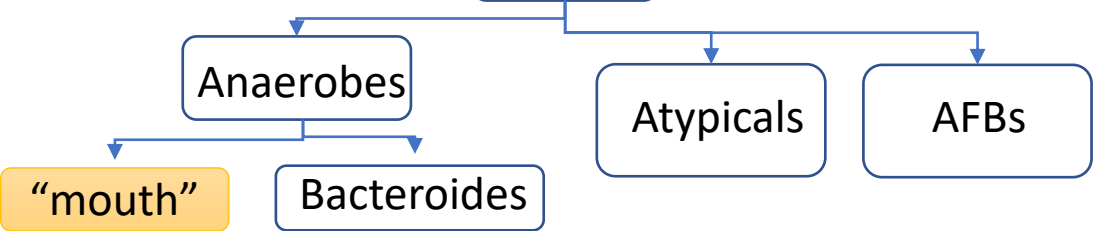
Gram-Positive Cocci



Gram-Negatives

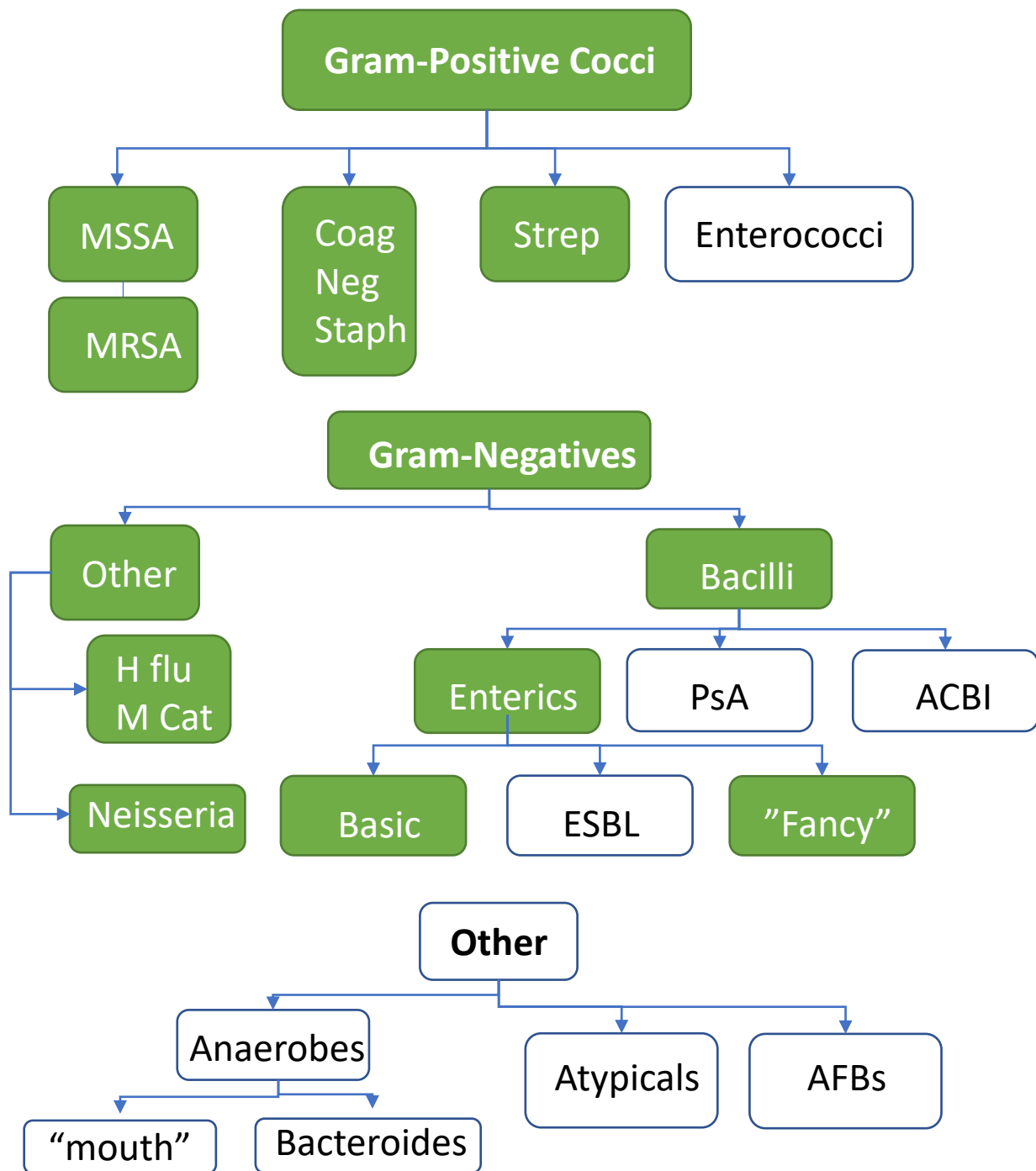


Other



4th Gen Cephalosporins

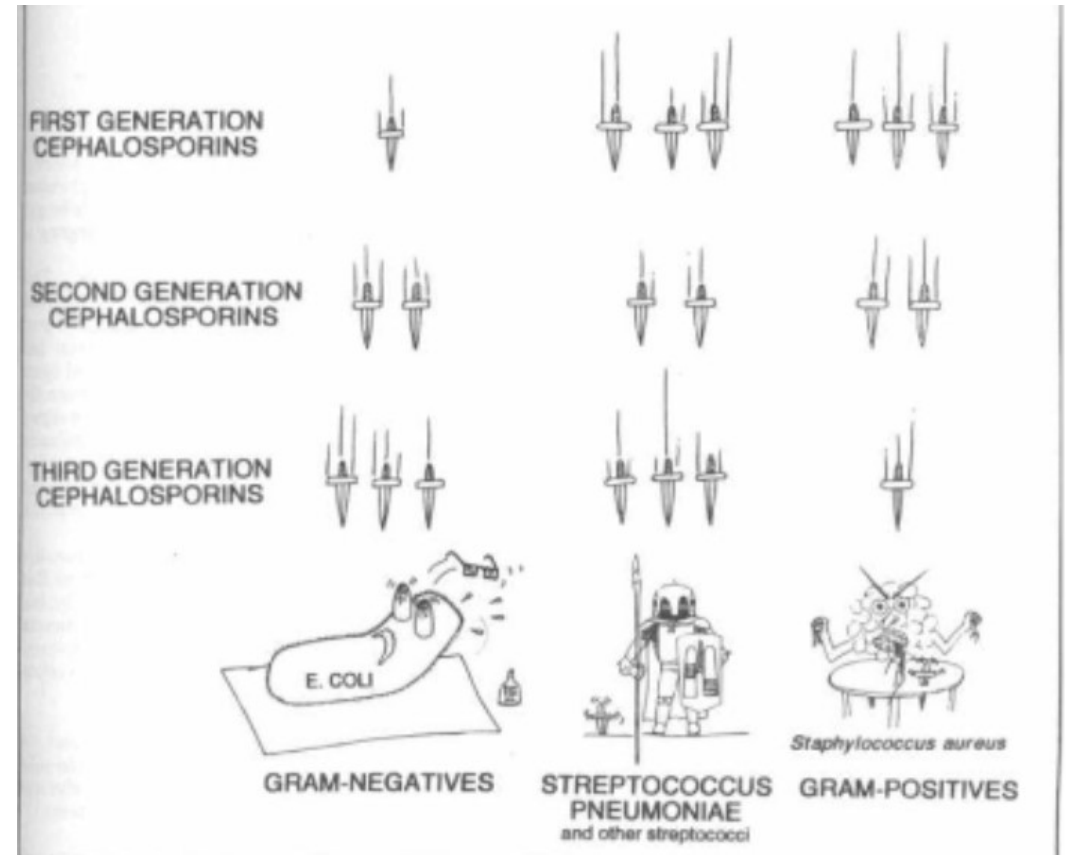
Drugs to Remember	Cefepime
Gram-positive highlights	Good strep, MSSA NO Enterococcus
Gram-negative highlights	Broad, including PsA and "fancy" enterics NO ESBLs (controversial)
Other highlights	Adequate mouth anaerobe

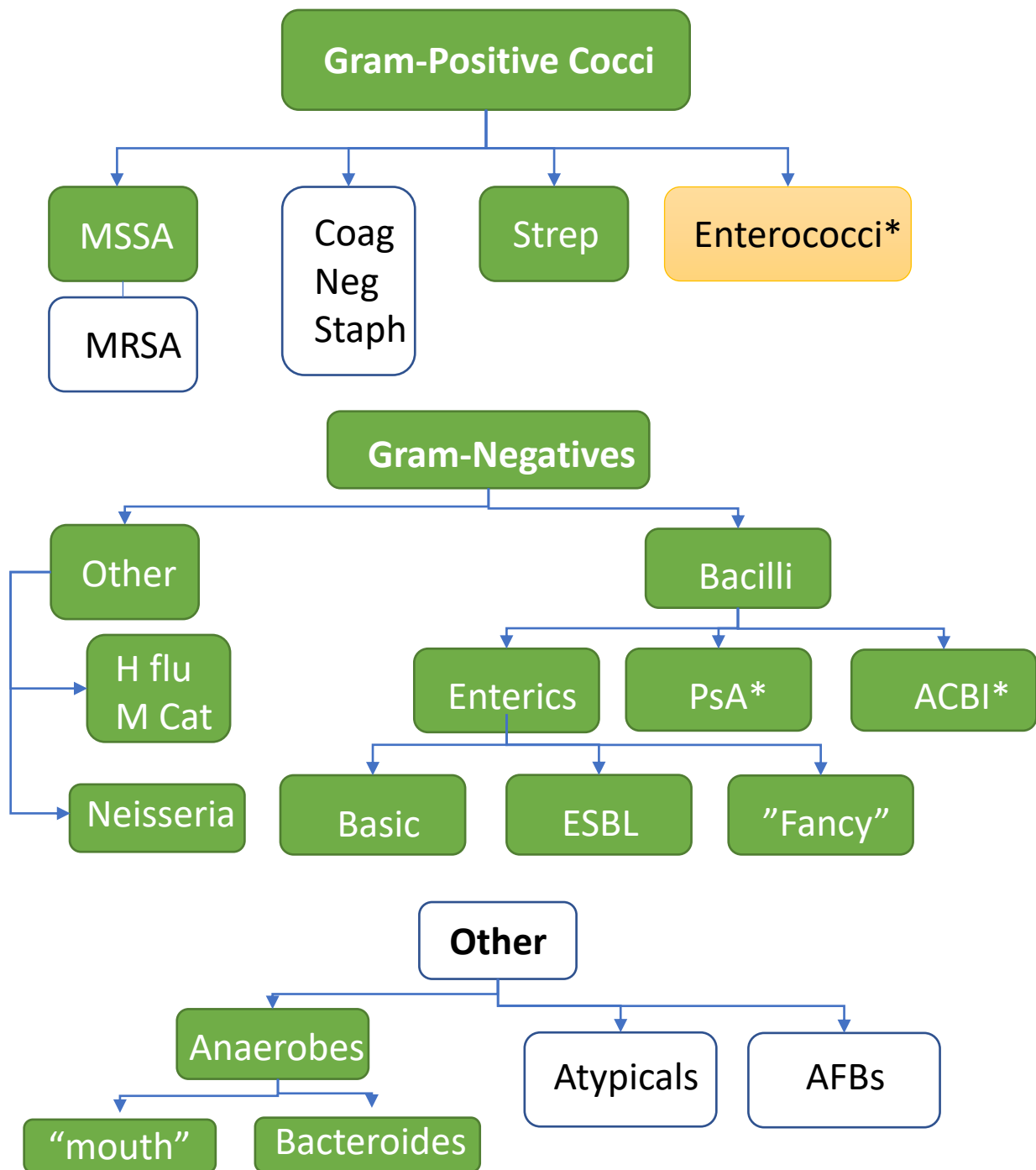


Advanced Gen Cephalosporins	
Drug to Remember	Ceftaroline
Gram-positive highlights	MRSA Good Strep, Staph May cover some <i>E faecalis</i>
Gram-negative highlights	Broad vs. Enterobacterales No PsA, ACBI, or ESBL
Other highlights	None
Misc	"Ceftriaxone plus MRSA coverage" <u>Others BL/BLIC</u> Ceftolozane-tazobactam – MDR PSA drug Ceftazidime-avibactam – CRE drug

Notes on Cephalosporins

- Side effects:
 - Cefepime can be associated with altered sensorium
 - Ceftaroline carries a potential risk for hemolytic anemia
- Caution in neonates due to risk for biliary obstruction, kernicterus



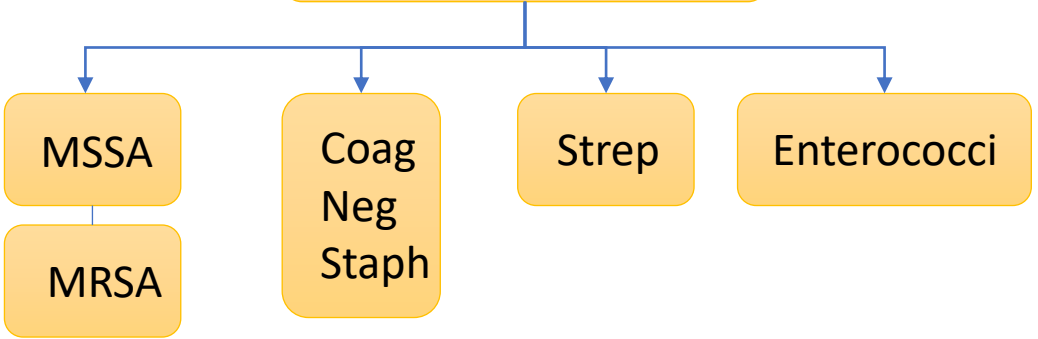


Carbapenems	
Drugs to Remember	Ertapenem- slightly different spectrum Imipenem/cilastatin Meropenem Doripenem
Gram-positive highlights	Broad (Streptococci, MSSA, <i>E faecalis</i>) No MRSA, most CoNS are resistant <i>E. Faecium</i> usually resistant (similar to ampicillin spectrum) Ertapenem does <u>not</u> cover enterococci
Gram-negative highlights	Very Broad. Includes EBSLs, PsA, ACBI <u>Exception:</u> Ertapenem does not cover ACBI or PsA
Other highlights	BROAD anaerobic coverage Meropenem-vaborbactam- KPC drug

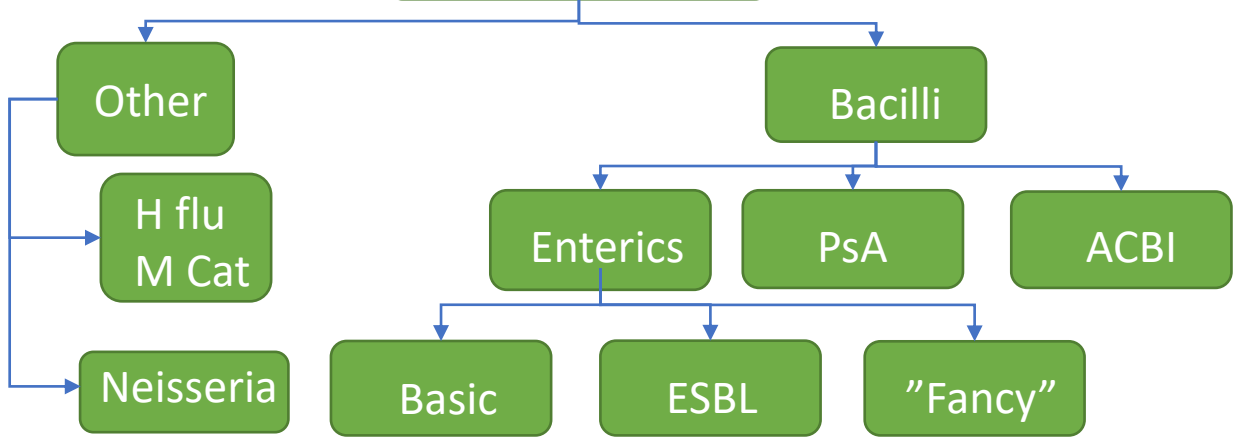
Notes on Carbapenems

- Side effects:
 - Imipenem – seizures
 - Gastrointestinal distress
- Ertapenem, compared to meropenem, does not cover APE
 - *Acinetobacter baumannii*
 - *Pseudomonas* sp
 - *Enterococcus* sp

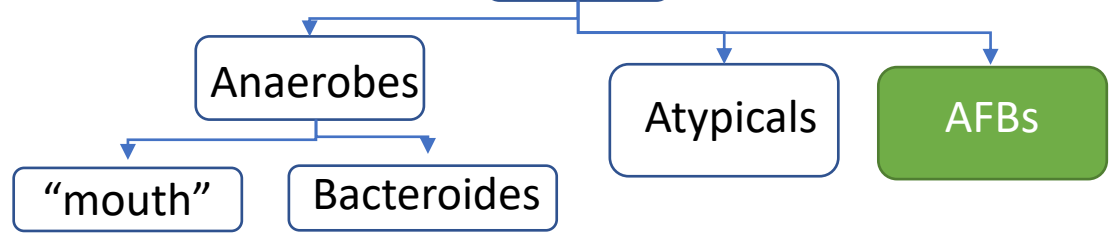
Gram-Positive Cocci



Gram-Negatives



Other

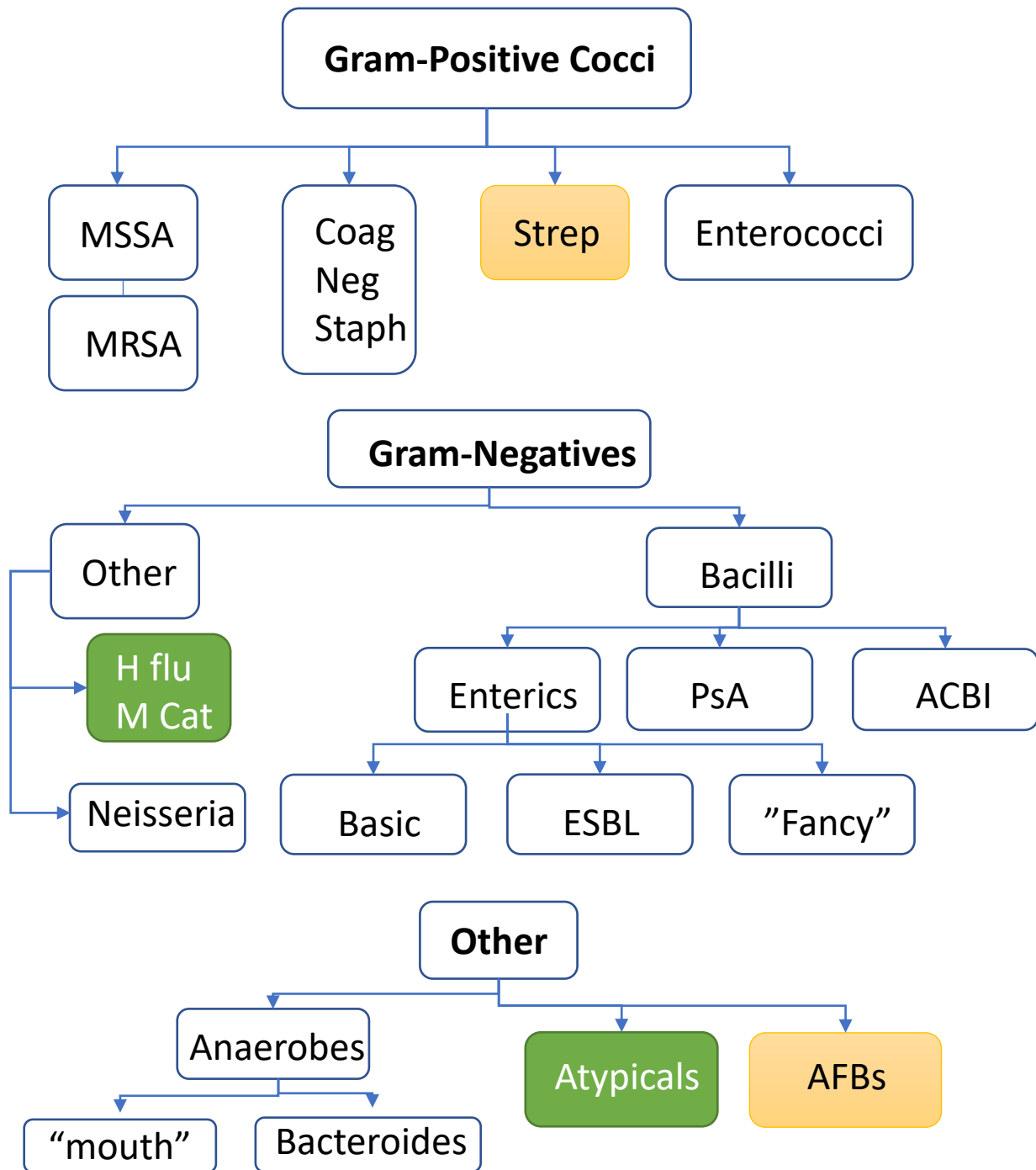


Aminoglycosides

Drugs to Remember	Gentamicin, Tobramycin, Amikacin (IV or Inhaled)
Gram-positive highlights	Synergy when added to beta-lactams or glycopeptides NOT AS MONOTHERAPY
Gram-negative highlights	Very broad Generally would not use as monotherapy outside of UTIs
Other highlights	Mycobacteria (Streptomycin)

Notes on Aminoglycosides

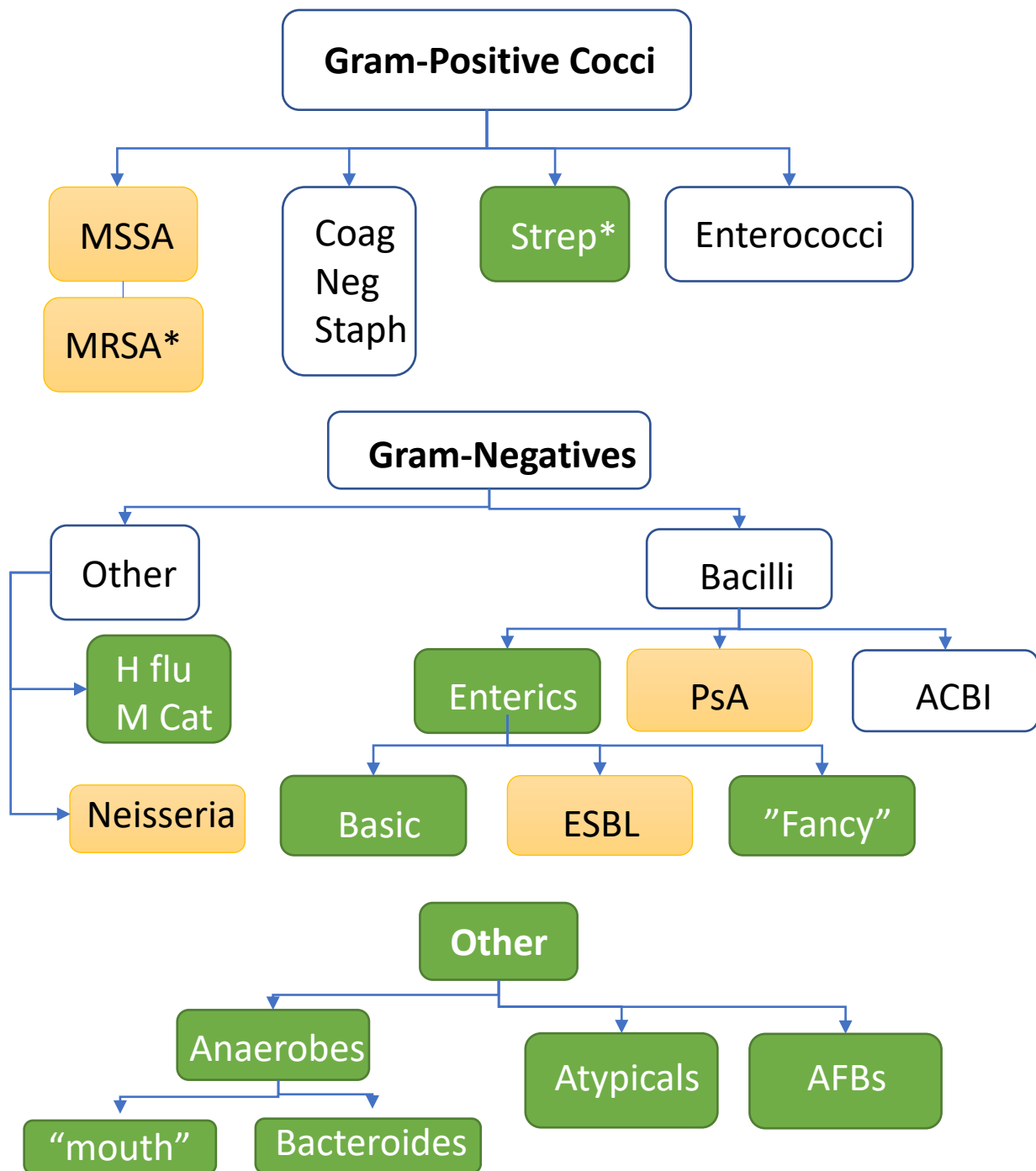
- Side effects:
 - Nephrotoxicity (~25% of patients within 7 days)
 - Vestibular and auditory toxicity (irreversible)
- Poor CNS penetration



Macrolides	
Drugs to Remember	Azithromycin Clarithromycin Erythromycin
Gram-positive highlights	Moderately good <i>S. pneumoniae</i> and <i>S. pyogenes</i> Little to no Staph No Enterococci
Gram-negative highlights	Good "respiratory" Gram-negative coccobacilli (<i>H influenzae</i> , <i>M catarrhalis</i>)
Other highlights	Atypicals <i>H pylori</i> <i>Mycobacterium avium</i>

Notes on Macrolides

- Side effects:
 - QT prolongation
 - Gastrointestinal distress
 - Hearing loss
- Long half life

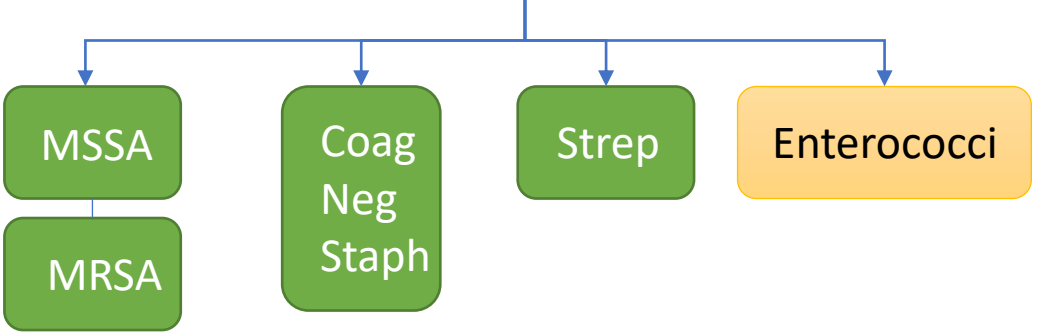


Quinolones	
Drugs to Remember	Moxifloxacin Levofloxacin Ciprofloxacin Delafloxacin
Gram-positive highlights	Strep (Moxi > Levo >>>> Cipro) Some MSSA, minimal MRSA (Dela likely the best) Not really for Enterococcus
Gram-negative highlights	Broad- some PsA (Cipro, Levo only) NO ACBI ESBLs are often resistant <i>Neisseria</i> spp. often resistant
Other highlights	Atypicals AFBs Moxi has strong anaerobic coverage, cannot be used for UTI

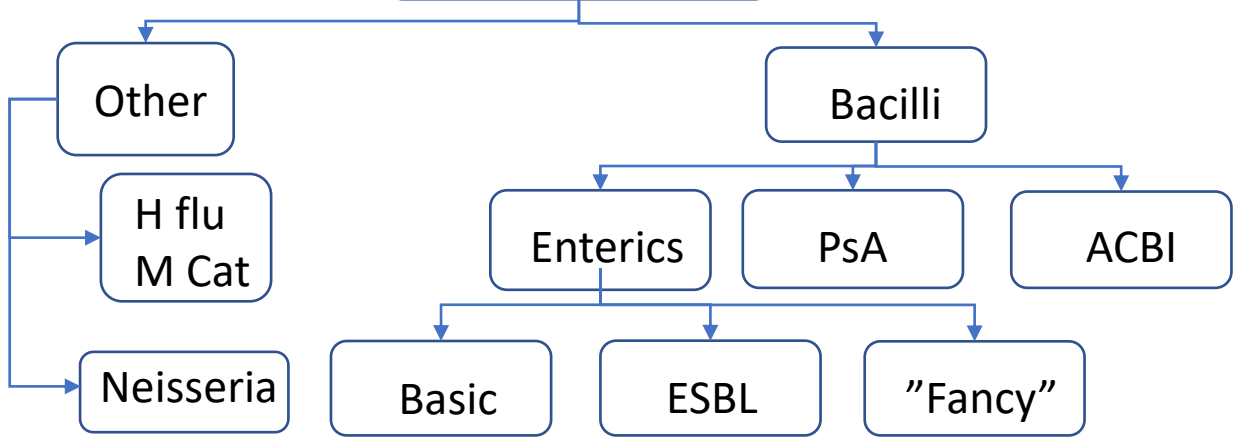
Notes on Quinolones

- Side effects:
 - Tendinopathies and tendon rupture
 - QT prolongation
 - Confusion in the elderly
- Avoid in patients with aneurysms due to risk for rupture
- Excellent bioavailability and tissue penetration
- Avoid taking with multivitamins

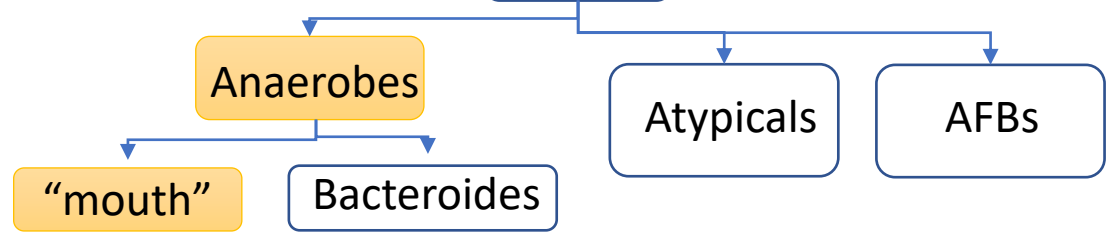
Gram-Positive Cocci



Gram-Negatives



Other



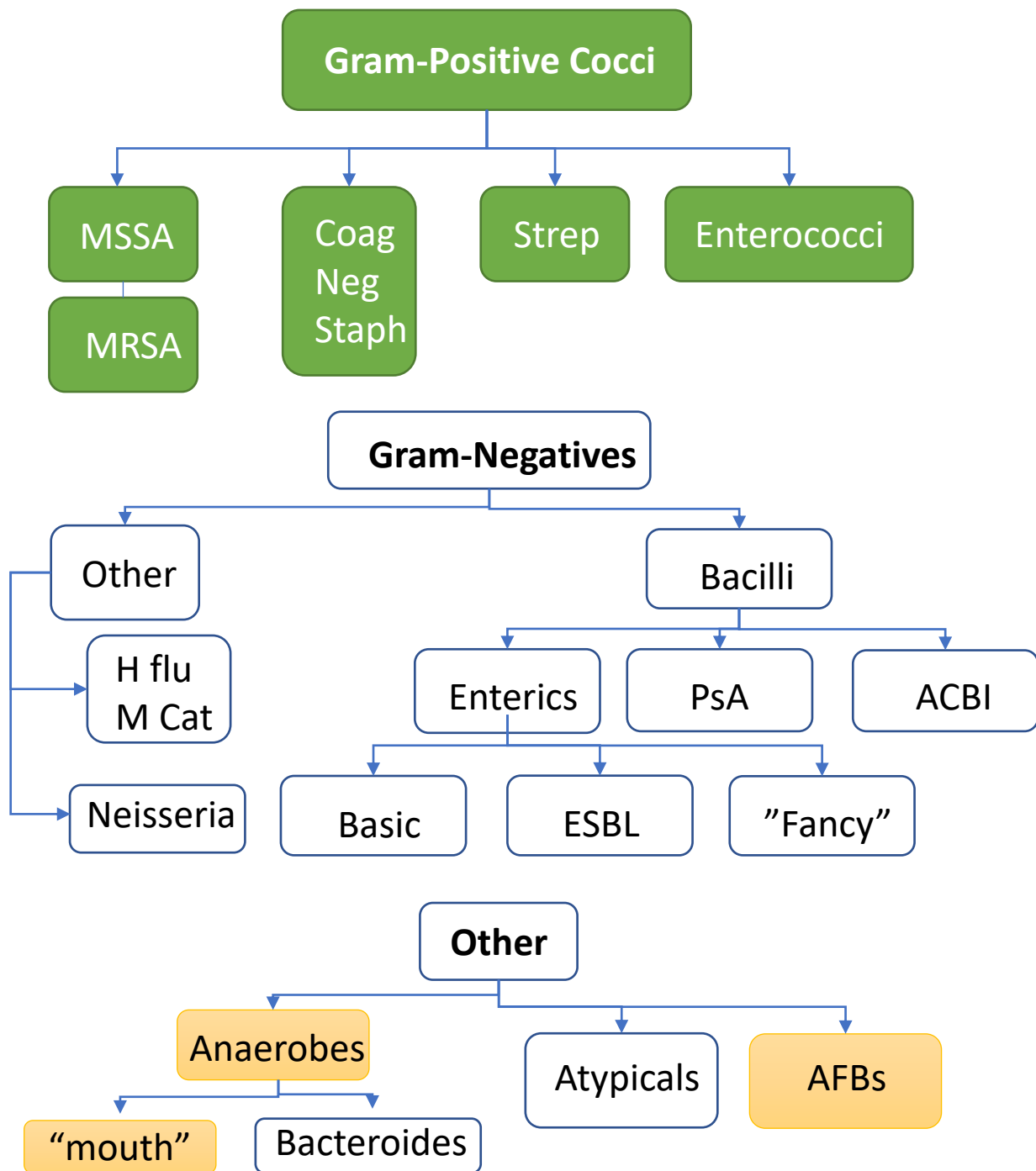
Glycopeptides

Drugs to Remember	Vancomycin Dalbavancin, Oritavancin, Telavancin
Gram-positive highlights	BROAD, including MRSA VRE- others MAY be active
Gram-negative highlights	None
Other highlights	Gram-positives "mouth" anaerobes Oral vancomycin – <i>C. difficile</i>

Notes on Vancomycin

- Side effects:
 - Red Man Syndrome
- Oral is *only* for C difficile infections

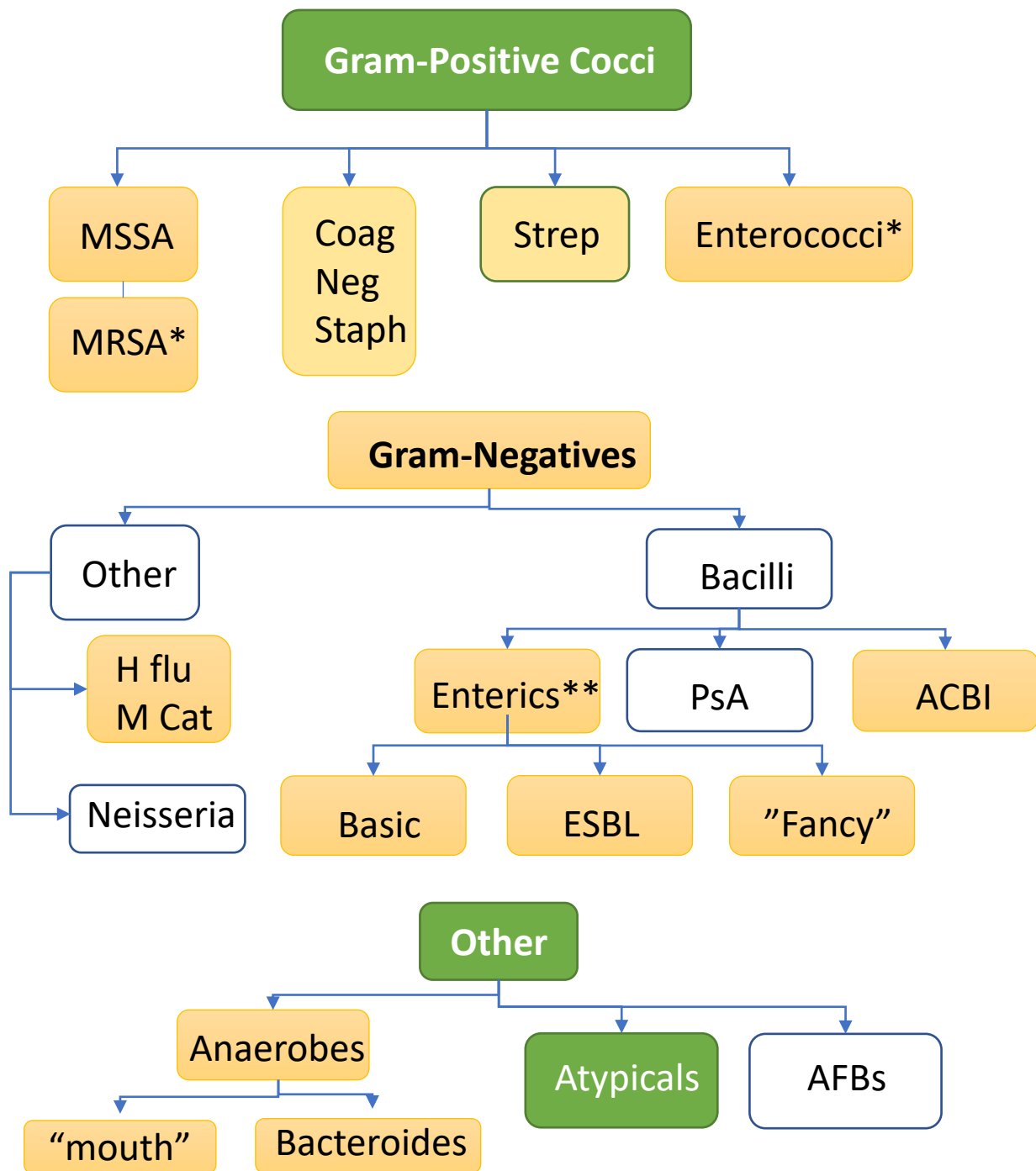




Misc Gram-positive Agents	
Drugs to Remember	<p><u>Oxazolidinones</u> Linezolid</p> <p><u>Lipopeptides</u> Daptomycin</p> <p><u>Streptogramins</u> Quinupristin/dalfopristin</p>
Gram-positive highlights	VERY broad, including MRSA and VRE **Streptogramins do NOT cover <i>E. faecalis</i>
Gram-negative highlights	None
Other highlights	Gram-positive "mouth anaerobes" Linezolid – AFB, <i>Nocardia</i> spp., some atypicals

Notes on These Drugs

- Linezolid:
 - Associated with thrombocytopenia, serotonin syndrome (when combined with other serotonergic drugs), optic neuritis, peripheral neuropathy, lactic acidosis due to mitochondrial toxicity
- Daptomycin:
 - Associated with skeletal muscle toxicity, elevated CK, and rhabdomyolysis (particularly when combined with statins), eosinophilic pneumonia
- Quinupristin/Dalfopristin
 - Associated with myalgias without elevation in creatine kinase, elevated LFTs

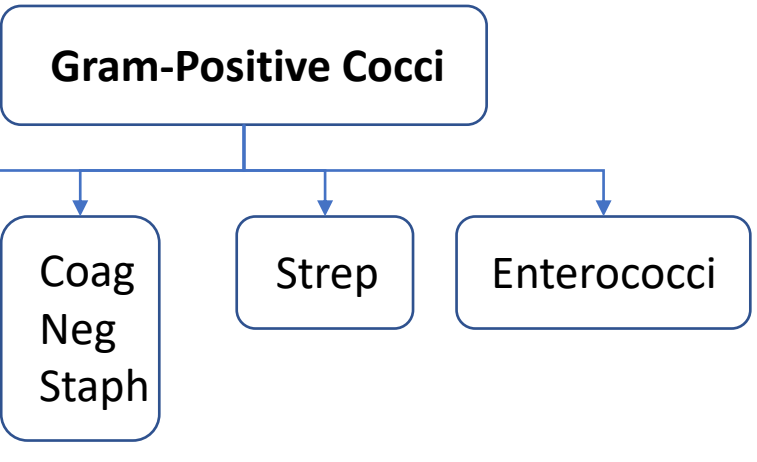


Tetracyclines, Glycylcyclines	
Drugs to Remember	Tetracycline, Doxycycline, Minocycline Tigecycline (broadest)
Gram-positive highlights	Pretty broad *Tigecycline more potent than the others ("good" coverage)
Gram-negative highlights	Tigecycline is broader/more potent than others **May include ESBLs but does not cover "MP3" organisms: <i>Morganella</i> , <i>Pseudomonas</i> , <i>Proteus</i> , <i>Providencia</i>
Other highlights	Some anaerobic coverage (tigecycline more than others) Atypicals Interestingly: <i>Rickettsia</i> spp., <i>B burgdorferi</i> , <i>H pylori</i> , <i>Plasmodium</i> spp.

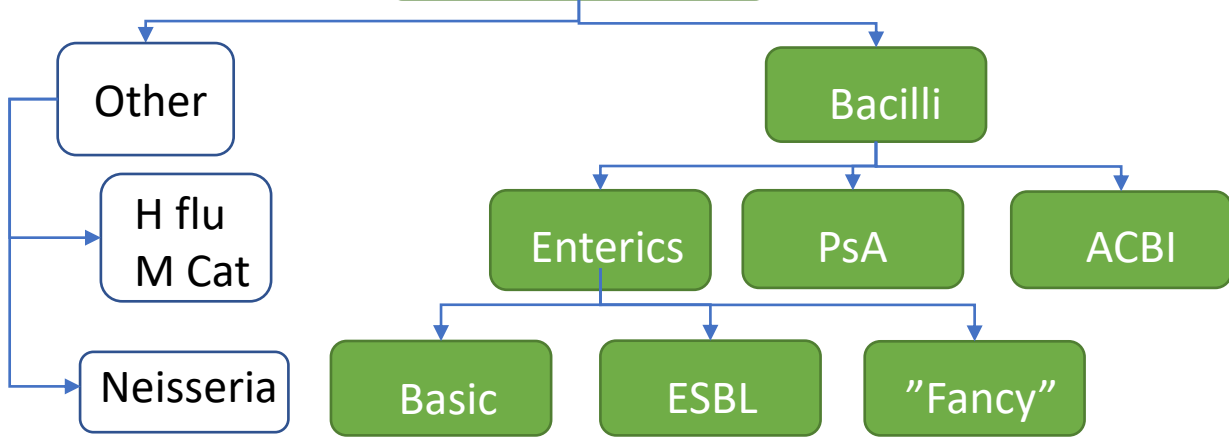
Notes on Tetracyclines

- Side effects:
 - Phototoxicity
 - Pill-esophagitis
- Cannot be used in pregnancy
- Should not be used in children < 8 years old
- Should be taken on empty stomach to enhance absorption, avoid taking with multivitamins

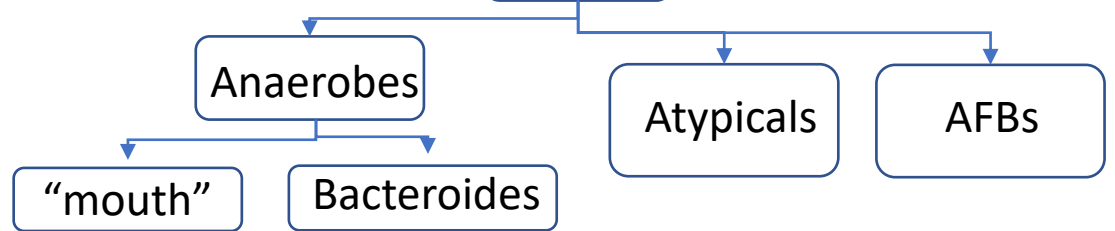




Gram-Negatives



Other

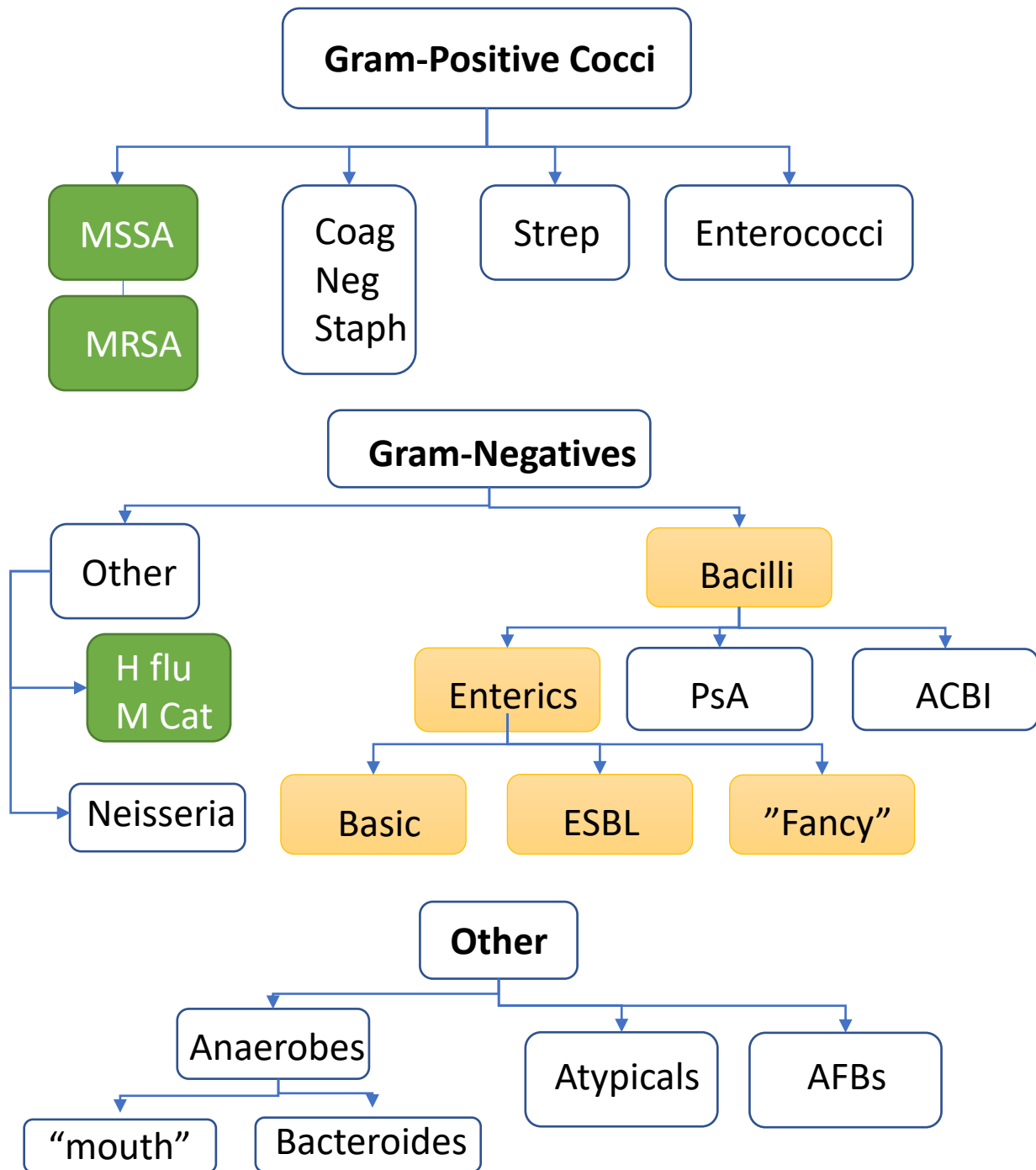


Polymyxins

Drugs to Remember	Colistin (polymyxin E) Polymyxin B
Gram-positive highlights	None
Gram-negative highlights	VERY BROAD, including MDRO POOR vs. <i>Proteus, Providencia, Serratia</i>
Other highlights	None

Notes on Polymyxins

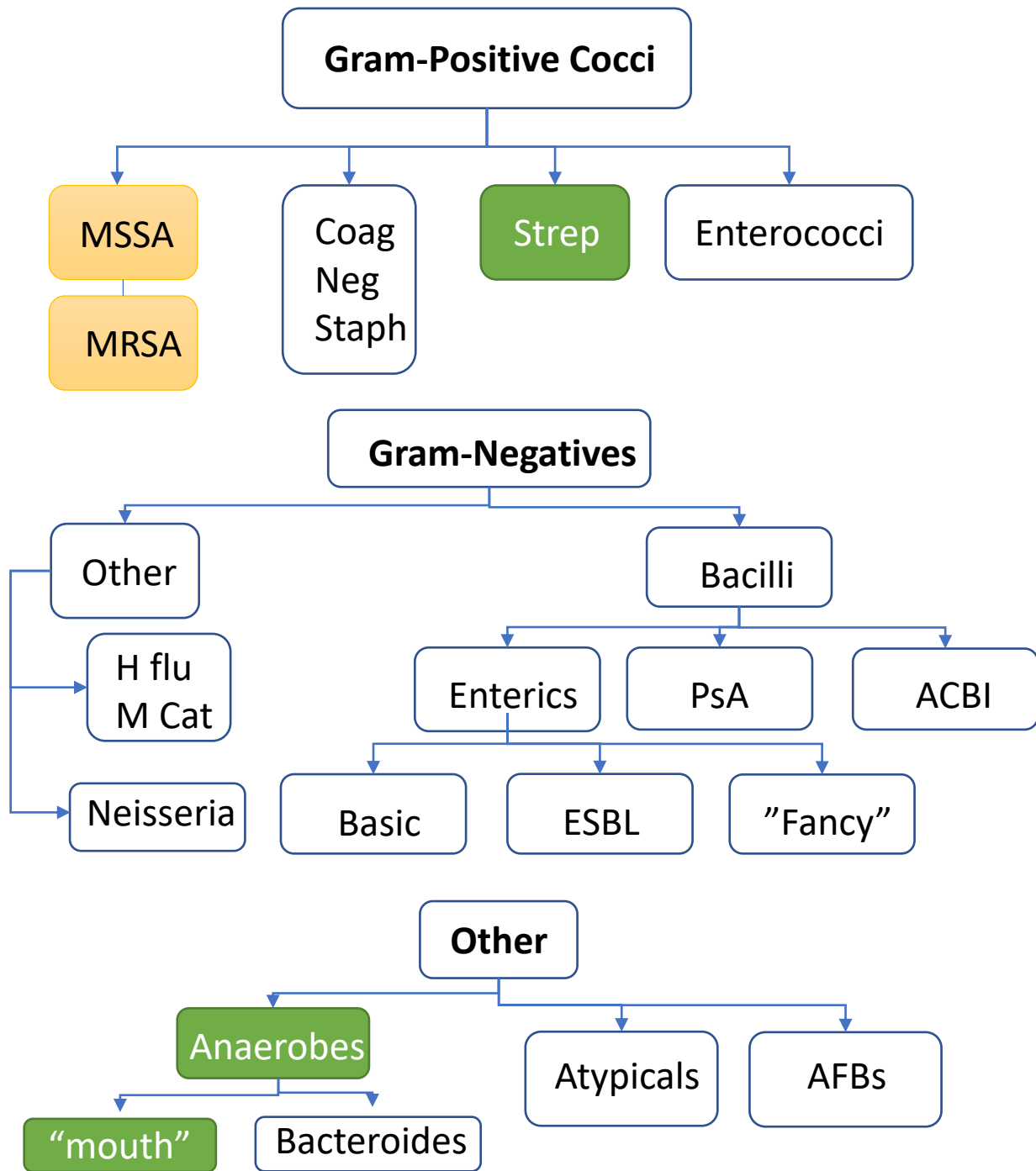
- Side effects:
 - Nephrotoxic
 - Neurotoxic
- Adjunctive therapy, monotherapy associated with increased resistance



Trimethoprim-Sulfamethoxazole	
Gram-positive highlights	Good <i>S. aureus</i> activity, including MRSA (but many CoNS are resistant) Low streptococcal activity No enterococcal activity
Gram-negative highlights	Reasonable activity against basic Enterobacterales as well as FEW ESBLs and "fancy" enterics NO PsA or ACBI
Other highlights	Has some activity against interesting pathogens like <i>Listeria</i> , <i>Shigella</i> , <i>Salmonella</i> , <i>Nocardia</i> , <i>Stenotrophomonas maltophilia</i> (a GNB), and other opportunistic pathogens like <i>Pneumocystis</i> and <i>Toxoplasma</i> spp.

Notes on Trimethoprim/Sulfamethoxazole

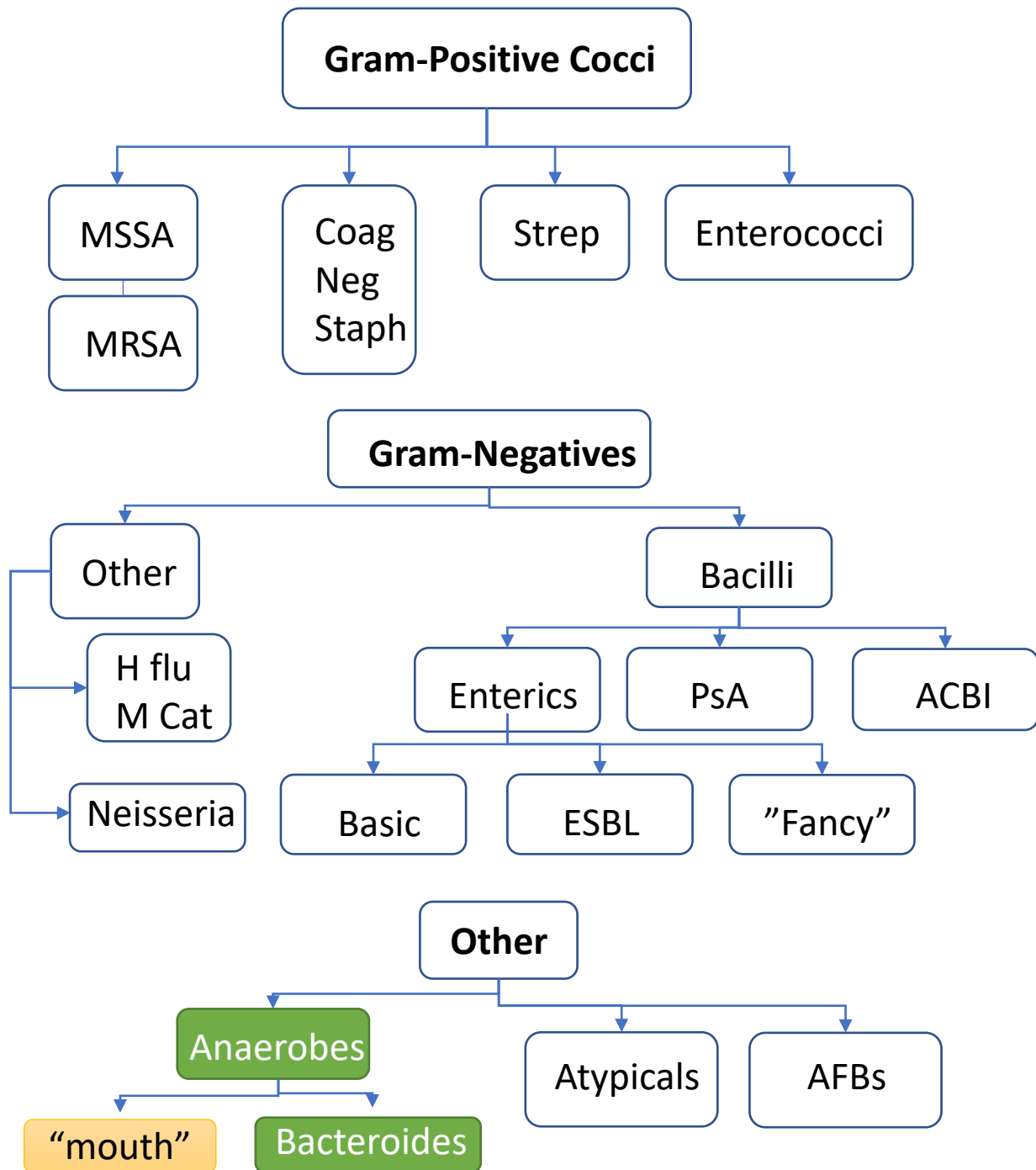
- Side effects:
 - Bone marrow suppression (dose dependent)
 - Aseptic meningitis
 - Hyperkalemia
 - Crystalluria
- Do not use in patients with sulfa allergies and G6PD deficiency



Clindamycin	
Gram-positive highlights	Moderate <i>S. aureus</i> activity, can be resistant Great for <i>S. pyogenes</i>
Gram-negative highlights	None
Other highlights	Good anaerobic activity, Gram-positives No activity vs. Gram-negative anaerobes Also covers: Actinomyces, Chlamydia, Plasmodium, Pneumocystis, Toxoplasma

Notes on Clindamycin

- Side effects:
 - Strong association with *C difficile* colitis
- Good bone penetration, bad CNS penetration
- Increasing resistance to *Bacteroides* sp

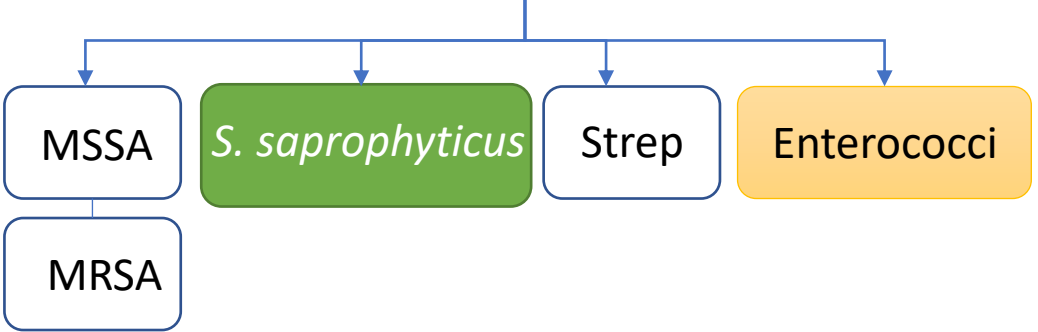


Metronidazole	
Gram-positive highlights	No aerobes
Gram-negative highlights	No aerobes
Other highlights	Great vs. wide range of anaerobes Not great vs. "mouth anaerobes" Also: Protozoa, trichomonas, entamoeba, Giardia

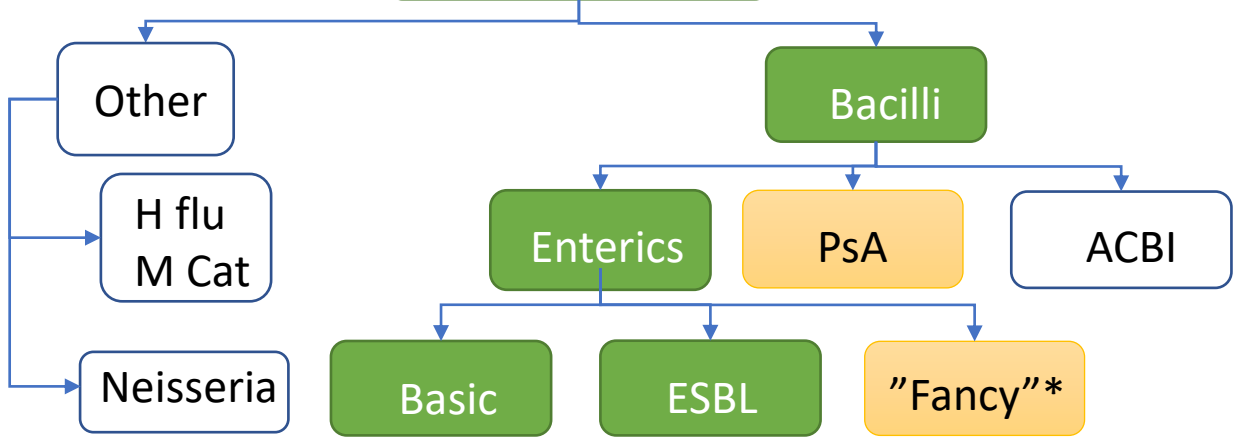
Notes on Metronidazole

- Side effects:
 - Metallic taste
 - Peripheral neuropathy
 - Disulfiram-like reaction with alcohol

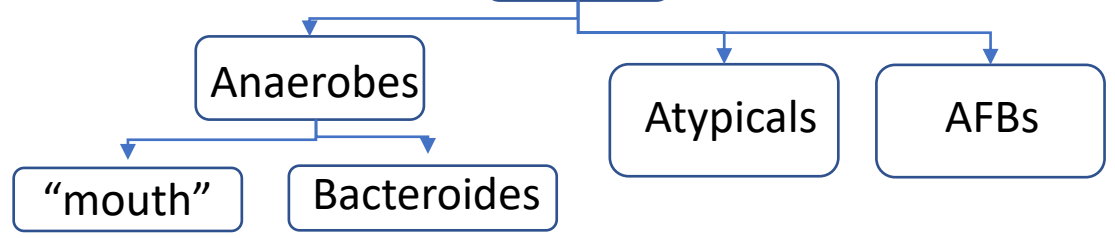
Gram-Positive Cocci



Gram-Negatives



Other



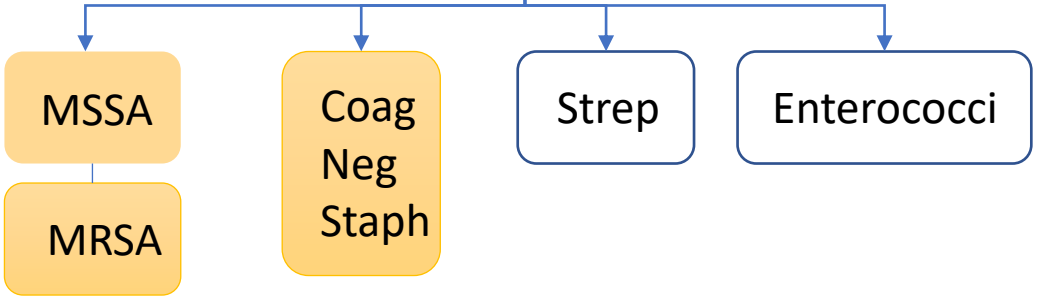
Misc UTI Drugs

Drugs to Remember	Nitrofurantoin Fosfomycin (different class, similar spectrum)
Gram-positive highlights	<i>S. Saprophyticus</i> Moderate Enterococcus
Gram-negative highlights	Enteric GNBs, including ESBLs *Moderate PsA, <i>Serratia</i> spp. (fosfomycin only)

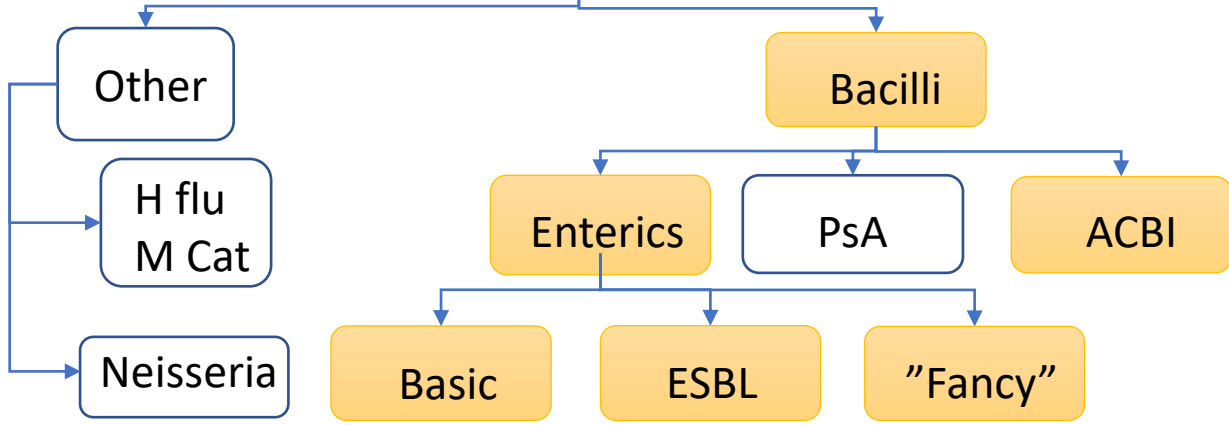
Notes on Nitrofurantoin & Fosfomycin

- Side effects:
 - Nitrofurantoin – peripheral neuropathy, pulmonary fibrosis
- Concentrates in the urinary bladder only
 - NOT to be used for systemic infections

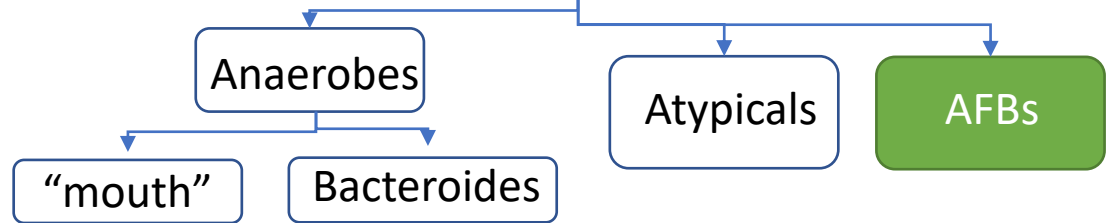
Gram-Positive Cocci



Gram-Negatives



Other



Rifamycins

Drugs	Rifampin
Gram-positive highlights	Staphylococci
Gram-negative highlights	ACBI (with synergy) and other Gram-negative bacilli, except Pseudomonas
Other highlights	Tuberculosis and other mycobacteria Bio-film producing infections in Gram-positive bacteria

Notes on Rifamycins

- Side effects:
 - Red-tinged bodily fluids
 - Gastrointestinal distress
- Major inhibitor of CYT P450 3A4
 - Significant drug-drug interactions



Case Based Question

Case

- 45 YO M with SOB, right-sided chest pain, fever. He took two doses of doxycycline and one dose of cefazolin that he had in his medicine cabinet. He has a history of a penicillin allergy. (rash, age 14) You diagnose him with pneumonia. What antibiotic will you initiate?
 - Amoxicillin/sulbactam
 - Piperacillin/tazobactam
 - Vancomycin
 - Ceftriaxone
 - Cefazolin

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Additional Resource

- <https://www.who.int/publications/m/item/the-who-essential-medicines-list-antibiotic-book-infographics>
- See handout

Integrated Activities and Tools for Antimicrobial Stewardship

