ANTIBIOTICS

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Cape Cod Vet Specialists

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Outline

- **Definitions**
- Bacteria review
- How to choose an antibiotic
- How to decide on a dose
- What could go wrong?
- Types of antibiotics

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Definitions

- Antibiotic: natural chemical produced by organisms to suppress other organisms
- Antimicrobial: any compound that suppresses microbial growth
- Antibacterial: targets bacteria
- Microbe: includes bacteria, fungi, other non-viral organisms
- Aerobic: generate ATP using oxygen
- Obligate aerobes: require oxygen
- Facultative anaerobe: prefers oxygen, but can use fermentation without oxygen
- Obligate anaerobe: cannot tolerate oxygen
- Microaerophilic bacteria: require a low concentration of oxygen to live
- Aerotolerant: live with or without oxygen
- Organism: refers to genus or genus and species
- Strain: different versions of an organism
- Isolate: one colony-forming unit of the resident population of an organism
- Inoculum: resident population
- Commensal: normal flora that neither harm nor help the host
- Opportunistic: commensal that becomes pathogenic
- Pathogen: causes host damage

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Bacteria Review

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Structure

- Bacteria are prokaryotes - no organelles
- Flagellae provide motility and fimbriae (pili) allow for adherence to structures
- Polysaccharide layer - “capsule” if tightly integrated, “slime layer” if loosely associated
    - Adhere to host cells and surfaces (biofilm), prevent phagocytosis, prevent dessication
- Surface structures
    - Cell wall - determines cell shape
        - Mycoplasmas - no cell wall (obligate intracellular pathogen)
        - Gram negative - murein is only building block
        - Gram positive - murein and techoic acid are building blocks
        - Archaea - cells walls without murein or no cell wall

Structure

- Surface structures (cont.)
  - S-layer - protein/glycoprotein layer on surface (except Mycoplasmas)
    - Thought to protect from toxins, help with adherence, phage receptor, help maintain morphology, bind extracellular enzymes
    - Comprises 5-10% of cellular protein
  - Outer membrane - present in Gram negative bacteria
    - Outer leaflet of lipopolysaccharide (LPS), inner leaflet of phospholipids
    - Provides barrier to lysozyme, hydrolytic enzymes, surfactants, bile salts, and **hydrophobic antibiotics**

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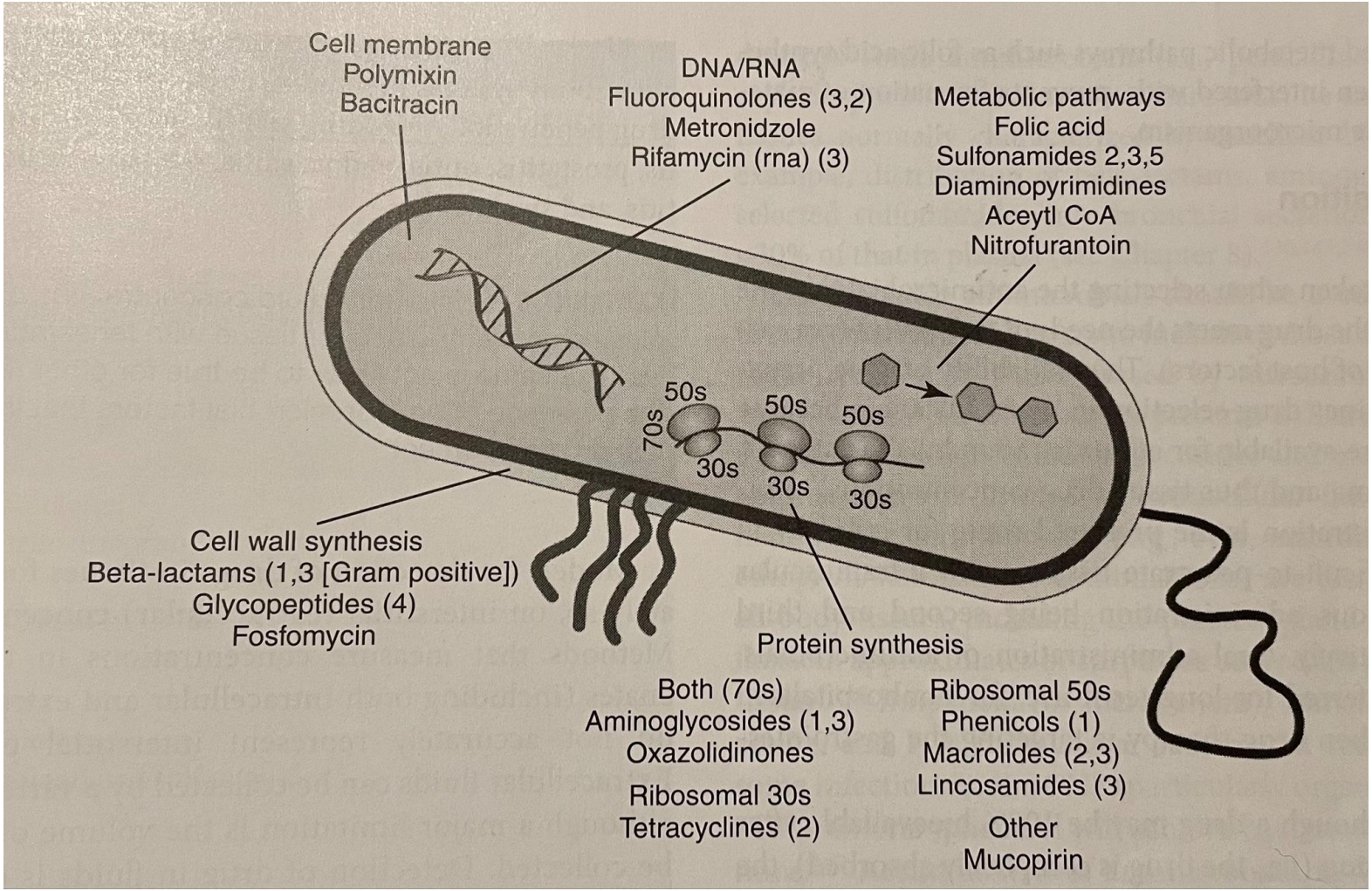
Structure

- Cell membrane - phospholipid and protein
  - Responsible for solute transport, oxidative phosphorylation, photosynthetic electron transport, electrochemical gradient maintenance, ATP synthesis, motility, signal transduction, synthesis of cell surface structures, protein secretion
- Cytoplasm - contains DNA, ribosomes, protein, RNA, salts, and metabolites
  - Ribosomes - have 70S size
    - Large subunit - 50S size
    - Small subunit - 30S size

Structure

- Genetic material
  - Single chromosome, tightly wound around proteins to form nucleoid
  - Small circular pieces of DNA - plasmids
- Gaining new genetic material
  - Spontaneous genetic mutations
  - Horizontal gene transfer
    - Conjugation - passage of genetic material via direct contact
    - Transduction - passage of genetic material via bacteriophage
    - Transformation - uptake of naked DNA from environment


Cell membrane
Polymixin
Bacitracin
DNA/RNA
Fluoroquinolones (3,2)
Metronidzole
Rifamycin (rna) (3)
Metabolic pathways
Folic acid
Sulfonamides 2,3,5
Diaminopyrimidines
Aceytl CoA
Nitrofurantoin
70s
50s
30s
50s
30s
50s
30s
Cell wall synthesis
Beta-lactams (1,3 [Gram positive])
Glycopeptides (4)
Fosfomycin
Protein synthesis
Both (70s)
Aminoglycosides (1,3)
Oxazolidinones
Ribosomal 30s
Tetracyclines (2)
Ribosomal 50s
Phenicols (1)
Macrolides (2,3)
Lincosamides (3)
Other
Mucopirin

How to avoid antibiotic use

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How to avoid antibiotic use

- Prevent disease
  - Teach good husbandry
  - Advocate for preventative medicine
  - Institute infection control measures in hospitals and where animals live
- Reduce antimicrobial use
  - Infection may be secondary to an underlying disease - treat the underlying disease and infection will likely resolve
  - Incision and drainage of abscesses
  - Local therapy instead of systemic
- Improve use of antimicrobials when able
  - Identify the bacteria and treat with narrow spectrum drug based on C&S results

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How to Choose an Antibiotic

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How to choose an antibiotic?

Do you need to treat?

1. **Confirm the presence of infection, if able**
2. Identify the underlying cause of infection (bacterial, fungal, etc)
3. Determine need for treatment of the infection
4. Determine whether antimicrobials need to be utilized

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Confirm the Infection

- Infection-specific clinical signs
- Location of infection (is it accessible for sampling)
- Supportive changes
  - Fever, inflammation, organ dysfunction
  - Structural changes on imaging
  - Molecular diagnostics (i.e. PCR) - may not indicate cause/effect
- Cytology showing WBC phagocytosis of an organism
- Growth on culture and sensitivity (C&S)

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How to choose an antibiotic?

1. Do you need to treat?
   a. Confirm the presence of infection, if able
   b. Identify the underlying cause of infection (bacterial, fungal, etc)
   c. Determine need for treatment of the infection
   d. Determine whether antimicrobials need to be utilized

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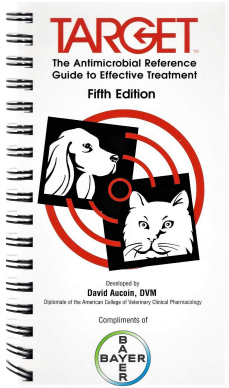
Identify the underlying cause

- Location of infection
  - Genitourinary tract - likely gram- aerobes
  - Intraabdominal - likely gram- aerobes initially, followed by anaerobes several days later
  - Skin - likely S. *intermedius* group
  - Abscesses - likely anaerobes, *Pasteurella*
  - Critically ill patients - likely translocation from the gut or nosocomial infection
- Location does not impart susceptibility information
- Target book/app
- Speciation on C&S



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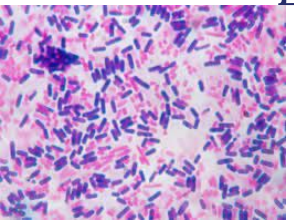
Identify the underlying cause

- Gram staining
  - Gram positive organisms have a thicker cell wall and lack outer LPS covering
    - Crystal violet dye enters cell, complexes with iodine, cannot leave cell during solvent wash
    - Appears purple on microscopic exam
  - Gram negative organisms have a thinner cell wall and an outer LPS covering
    - Crystal violet dye enters cell, but LPS layer is removed during solvent wash and dye is washed away
    - Appears pink on microscopic exam (following counterstain)



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Identify the underlying cause

- Gram positive organisms (generally)
  - Clustered cocci = Staphylococcus
  - Cocci in chains = Streptococcus
  - Thick bacilli = Clostridium
  - Thin bacilli = Listeria
  - Branched bacilli = Nocardia or Actinomyces
- Gram negative organisms (generally)
  - Thin bacilli = Enterobacteriaceae (e.g. E. coli)
- Gram variable organisms (generally)
  - Curved = Vibrio or Campylobacter

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Quick note on Diff-Quik

- Diff-Quik is NOT a Gram stain
  - Does not differentiate between Gram positive and negative
    - All bacteria appear dark blue, regardless of genus
  - Useful for an initial screening to determine if bacteria are present

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Identify the underlying cause

Culture and susceptibility testing

- Identifies the pathogen
- Provides susceptibility data for that particular pathogen
- Provides some information for deciding on antibiotic dosing
- Provides input from a microbiologist

C&S is especially useful if patient has seen antibiotics in prior 3 months

Identify the underlying cause

In-clinic C&S testing

- Kits are available
- USE CAUTION
  - Risk of propagating drug-resistant bacteria
    - Exposure to staff, patients, and clients
  - Risk of isolating bacteria that require biosafety rooms/practices (i.e. *Brucella* spp.)
  - Risk of isolating pathogenic fungi
- Limitations in specificity and accuracy of results

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How to choose an antibiotic

1. Do you need to treat?
   a. Confirm the presence of infection, if able
   b. Identify the underlying cause of infection (bacterial, fungal, etc)
   c. Determine need for treatment of the infection
   d. Determine whether antimicrobials need to be utilized

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Determine need for treatment

- Source control (i.e. abscess drainage) in an animal that is not lethargic, febrile, anorexic, etc may be all the therapy that is required
- Local therapy with biocides (i.e. chlorhexidine baths)
- Treatment of underlying conditions may resolve superficial infections
- Worsening state of a critically ill animal does not always necessitate escalation of antimicrobial therapy

How to choose an antibiotic

- If bacteria is present, considered likely the cause of the clinical signs, and patient is showing signs of systemic illness
- Choose an antibiotic that covers the bacteria of concern
  - Use Gram staining and location of infection while C&S pending
- Chosen antibiotic must be able to penetrate into tissue of concern at appropriate concentration
- Choose the drug with the most narrow spectrum for the bacteria of concern
- Avoid later generation drugs as “first line” therapies
  - Resistance has been shown within 10-20 years of an antibiotic being put into practice

1,3,6

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How to choose an antibiotic

- Determine if the drug is bactericidal or bacteriostatic
  - Bactericidal drugs kill bacteria
    - Consider using with severely ill and immunocompromised patients
  - Bacteriostatic drugs stop growth of bacteria
    - Primarily rely on host immune system to clear the infection
- Use caution if combining a bacteriostatic drug with a bactericidal drug
  - Slowing the growth may decrease the efficacy of the bactericidal drug

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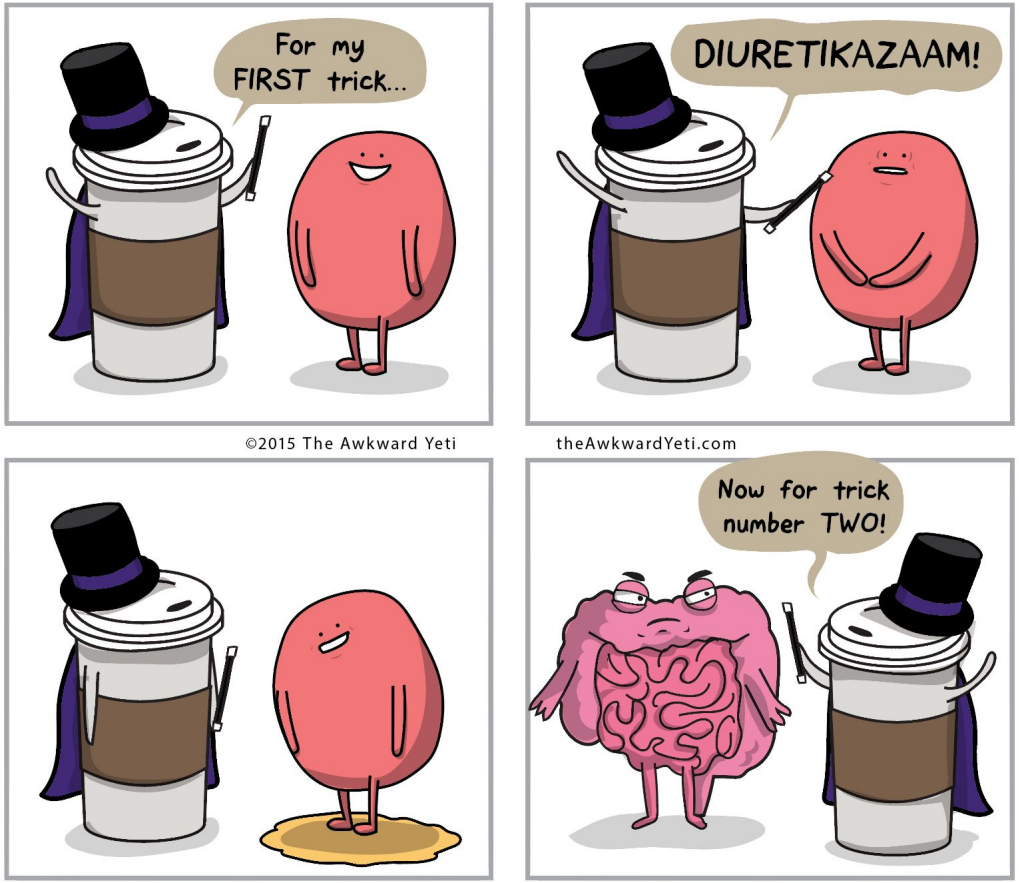

theAwkwardYeti.com

How to choose a dose

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How to choose a dose

- Determine the minimum inhibitory concentration (MIC) of the chosen drug
  - Reported on C&S, can be found in Target, +/- product insert
- Determine if your chosen antibiotic is time-dependent or concentration-dependent
  - For most time-dependent antibiotics, goal is to have plasma concentration above MIC for >50% of the dose interval
  - Concentration-dependent antibiotics should have peak plasma concentration 8-10x MIC

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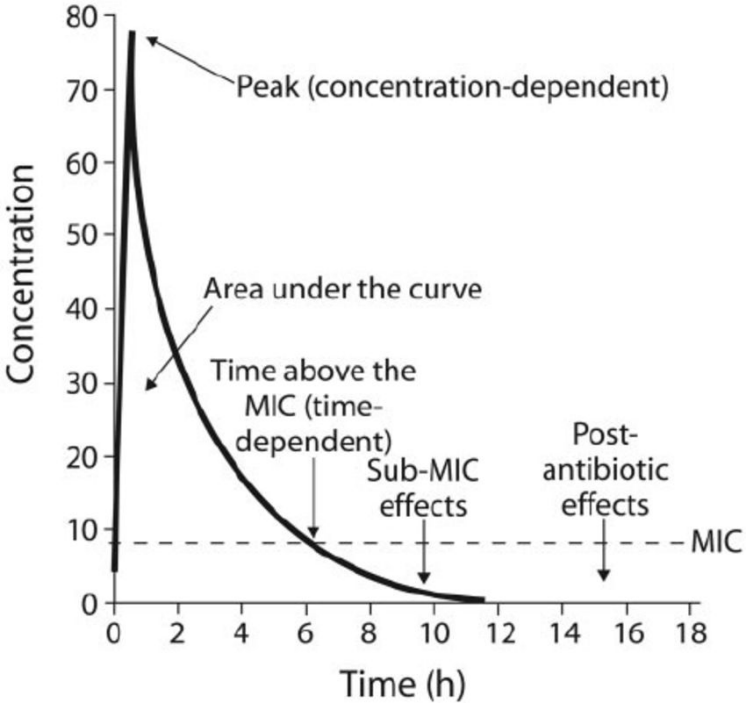
How to choose a dose

Time-dependent antibiotics

- T0: administration
- T6: plasma conc. = MIC
- Ideally, would give this antibiotic at this dose every 8-12 hours to maintain plasma concentration > MIC more than 50% of the dosing interval



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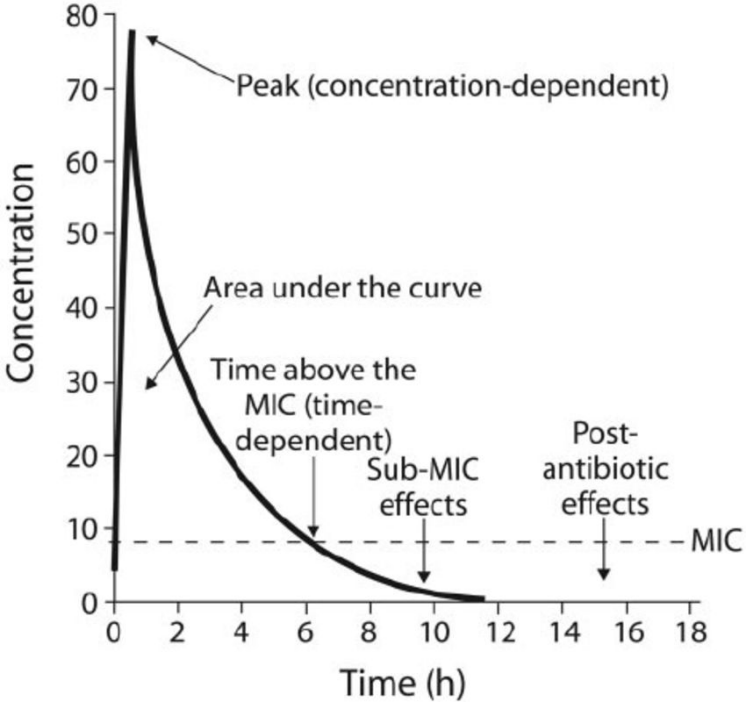
How to choose a dose

Concentration-dependent antibiotics

- T0: administration
- T1: peak plasma concentration (Cmax) = 80 ng/dL
- MIC = 10 ng/dL
- Goal is to have Cmax/MIC ≥ 8-10
  - Also called I/Q
- This dose is appropriate, as 80/10 = 8
- Generally dosed 1-2x per day



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Case Examples

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7y MN Beagle

- Presented for acute onset ventral neck swelling
- No history of trauma, considered previously healthy, no current medications
- Firm swelling/mass on midline, drooling, temp 103.5, remainder of PE unremarkable
- Primary concern is for cervical abscess

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7y MN Beagle

Confirm presence of infection

- Infection-specific clinical signs: cervical swelling
- Is it accessible for sampling?: Yes
- Supportive changes: Fever
- Cytology showing WBC phagocytosis of an organism (Diff-Quik)
- Submit C&S

Identify the underlying cause

- Location of infection: abscess likely to have anaerobes, *Pasteurella*
- Gram stain (if available)
- Target book (next slide)

Need to treat?

- Source control (lance) AND antibiotic (fever)

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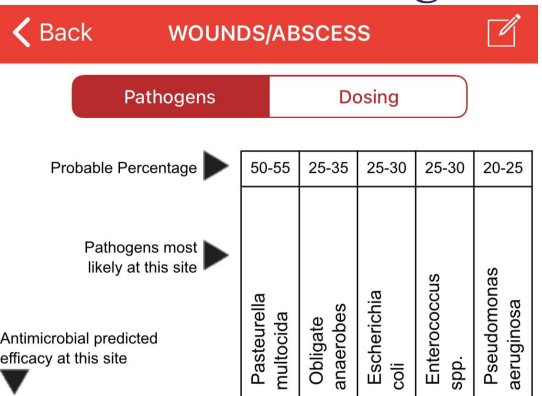
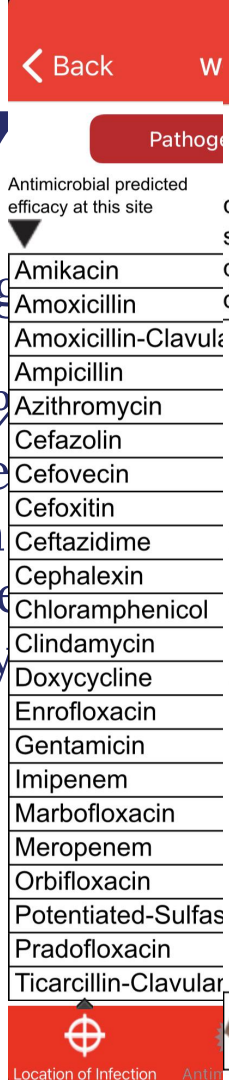
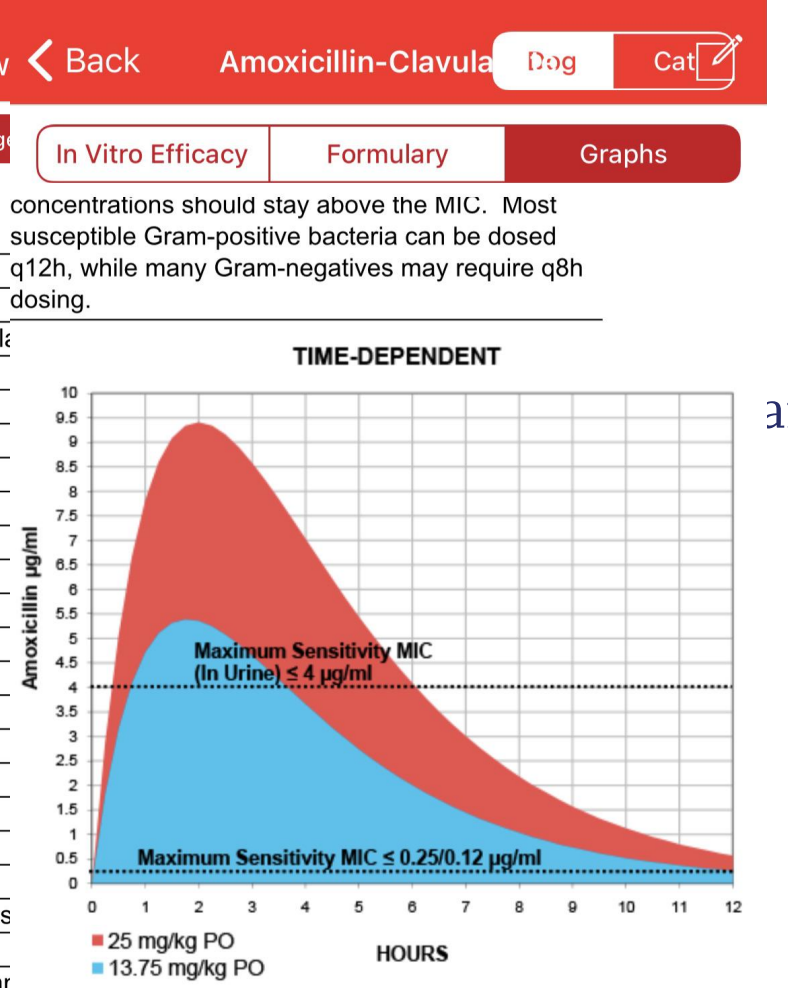
Identify the underlying

- Target
  - Target: 50-55% anaerobe
  - Excellent cove
    cephalosporin
    - We choose
  - Dosing: Ideally







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14y FS DSH

- Presented for general malaise, vomiting, anorexia x72 hrs
- No history of trauma, indoor only cat, no known dietary indiscretions
- Owner has been noticing increased thirst for the past month
- Laterally recumbent, dull, temp 98.4, HR 150
- Kidneys palpate small, patient is uncomfortable on palpation
- Primary concern is for renal injury with possible SIRS/sepsis
    - Bradycardia, dull mentation, hypothermia concerning for shock

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14y FS DSH

Confirm presence of infection

- Infection-specific clinical signs: concern for shock, no clear indication of infection
- Is it accessible for sampling?: Cannot sample kidneys, could consider urine cytology and C&S

Identify the underlying cause

- Location of infection: UTI likely gram- aerobes
- Gram stain (if available)
- Target book (next slide)

Need to treat?

- Systemic antibiotics AND resuscitation for shock!

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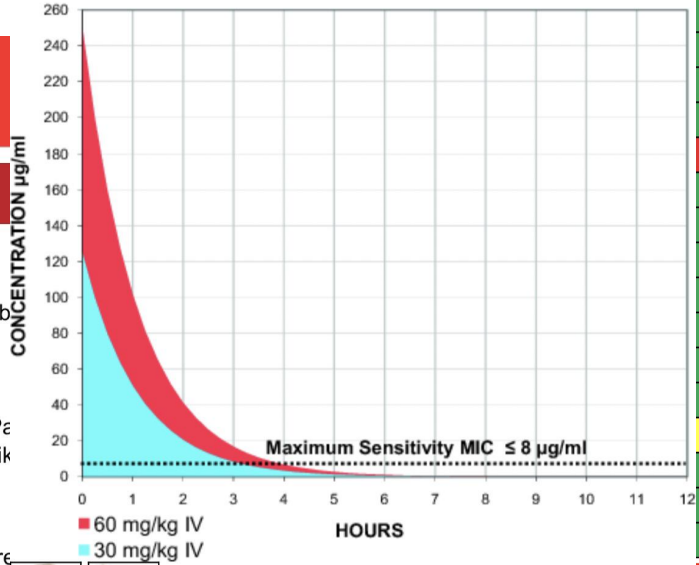
Ceftazidime

In Vitro Efficacy | Formulary | Graphs

correlating best with T> MIC (Time above MIC). The best clinical response is obtained if serum concentrations stay above the MIC for > 40-50% of the dosing interval. The more immunosuppressed the patient, the greater the time serum concentrations should stay above the MIC. Most susceptible Gram-negative bacteria including *P.aeruginosa*, should be be dosed q8h by this route .

TIME-DEPENDENT



Staph pseudi	Klebs pneum
E	E
G	N
G	P
G	N
G	N
G	G
G	G
G	E
G	G
G	F
E	G
G	N
G	G
G	G
G	E
G	E
G	G
G	E
F	G
G	G
G	E
G	G

More

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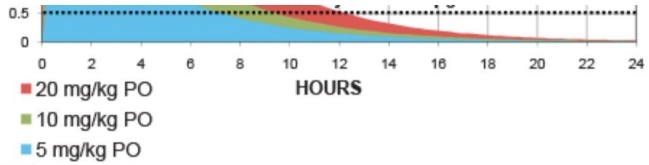
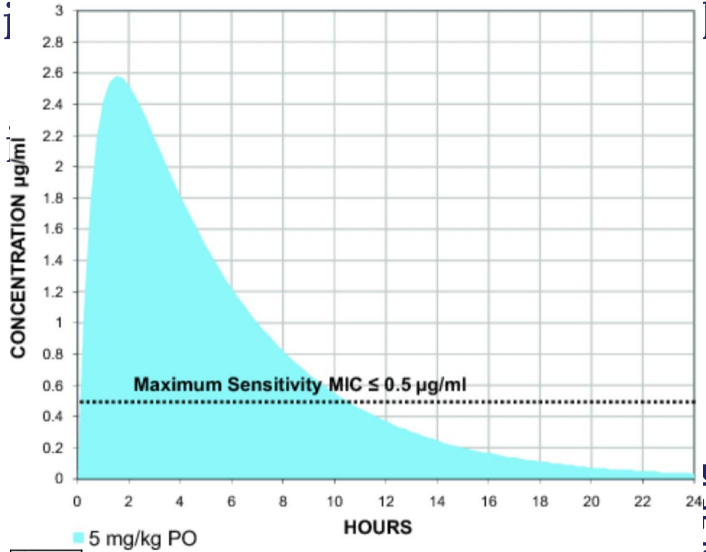
Enrofloxacin

In Vitro Efficacy | Formulary | Graphs



DOSE-DEPENDENT



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What could go wrong?

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What could go wrong?

- Toxicity
  - Antibiotics are not benign drugs
- Increased cost of diagnosis and treatment
  - Repeated antibiotic courses due to treatment failure can ultimately result in higher cost in the long run
  - Resistant bacteria may require more expensive antibiotics and/or prolonged courses
- Resistance

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What could go wrong?

Resistance

- Developed through spontaneous mutation or horizontal gene transfer
  - Normally 1 mutation per million basees per cell division
    - Most harmful to the organism, some confer resistance
- Constitutive resistance: lack of mechanisms required for antimicrobial action (lack of penicillin binding protein), slow growth rate (beta-lactams), anaerobic resistance to aminoglycosides
- Acquired resistance: drug inactivation, drug modification, production of competitive metabolites, target mutation/substitution/modification, decreased permeability, active efflux, failure to metabolize to active form

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What could go wrong?

Resistance

- Genes can be on plasmids
  - Plasmid can be lost when selective pressure is gone
  - Genes for resistance to different antibiotics can be linked
    - Exposure to one antimicrobial inadvertently selects for resistance to the other
- Genes can transfer to bacteria of different species or genera
- If maintaining resistance genes is not harmful, do not assume that it will resolve when selection pressure removed

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What could go wrong?

Resistance

- The more often a population of bacteria are exposed to an antibiotic, the more likely they are to develop resistance

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“Even experienced practitioners may not realize that giving a patient antibiotics affects not just that patient, but also their environment, and all the other people that come into contact with that environment.”

- Dancer

Minimize environmental exposure

- Encourage owners to follow recommendations
  - There is no such thing as “extra” or “left over” antibiotics
- If a prescription is changed, consider asking owners to bring remainder of initial prescription back to the clinic for proper disposal
- Develop evidence-based practice guidelines
  - Can prevent “big guns” from being employed as first line
  - Can be tailored to the individual clinic
- Consider grouping drugs as primary, secondary, tertiary
  - Start with primary, don’t escalate unless therapeutic failure or C&S results dictate change
  - Increase barrier precautions and cleaning when using secondary or tertiary drugs

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Ethics of Antimicrobial Drug Use and Resistance

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“Therefore, if an animal with a medical condition can be reasonable expected to improve as a result of treatment with antimicrobial drugs, and the animal is under a veterinarian’s care with a [VCPR], then the veterinarian has an obligation to offer antimicrobial treatment…”

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“However, to protect public health, the veterinarian also has an obligation to actively promote disease prevention efforts, treat as conservatively as possible, and explain the potential consequences associated with antimicrobial treatment…including the possibility of promoting selection of resistant bacteria.”

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Types of Antibiotics

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Target Cell Wall

Beta-lactam antibiotics

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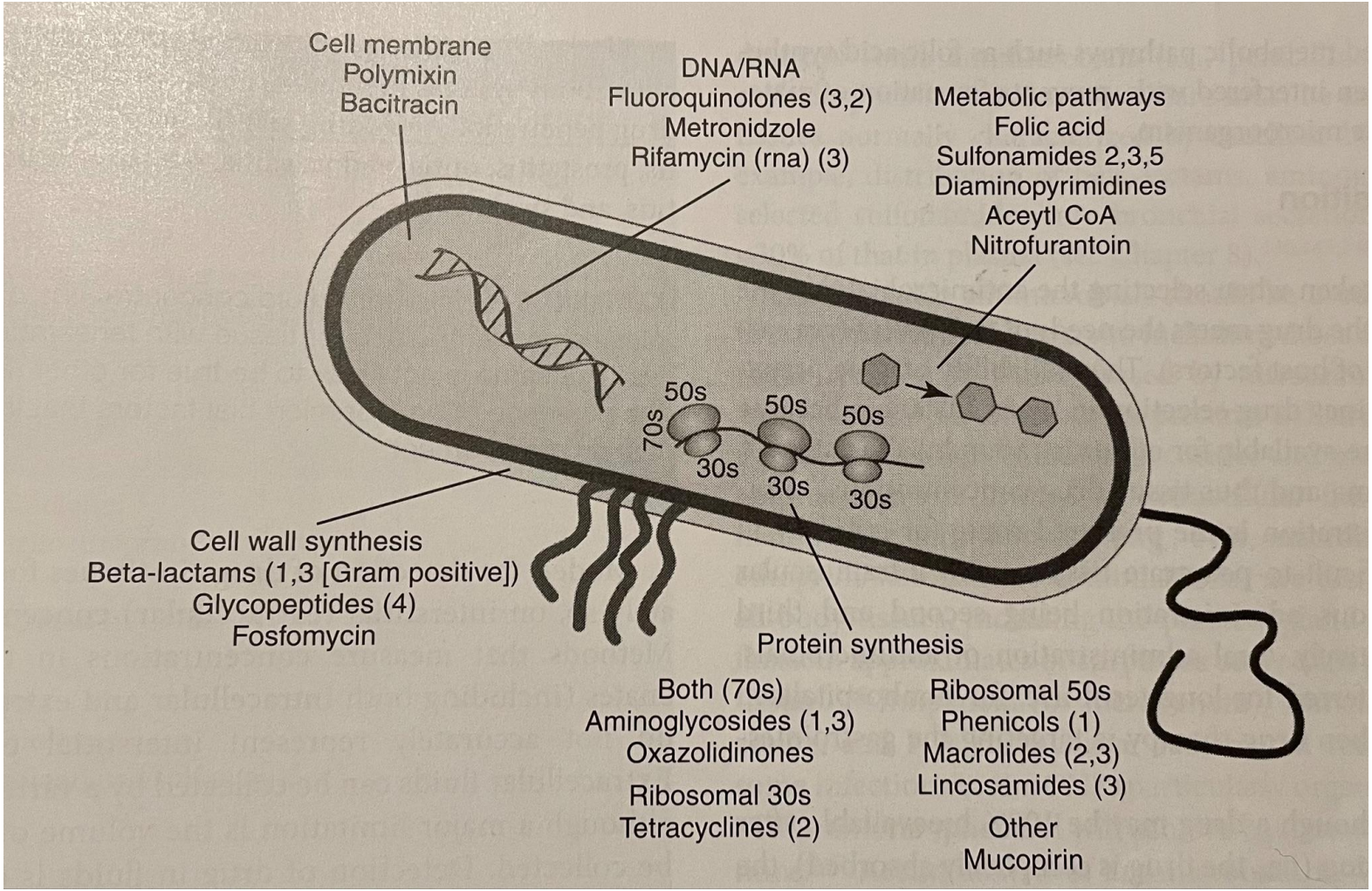
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30s
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30s
50s
30s
Cell wall synthesis
Beta-lactams (1,3 [Gram positive])
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Protein synthesis
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Aminoglycosides (1,3)
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Ribosomal 30s
Tetracyclines (2)
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Phenicols (1)
Macrolides (2,3)
Lincosamides (3)
Other
Mucopirin

Beta Lactam Antibiotics

- Cephalosporins
  - First generation most susceptible to beta-lactamase destruction
- Penicillins
  - Aminopenicillins (ampicillin, amoxicillin)
  - Extended-spectrum (carbenicillin, ticarcillin, piperacillin)
- Carbapenems
  - Imipenem, meropenem
- Monobactams
  - Aztreonam

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Beta Lactam Antibiotics

Mechanism of Action

- Interferes with cell wall synthesis by binding to the terminus of a peptidoglycan strand and preventing cross-linking by the transpeptidase enzyme
- As transpeptidase substrate builds up, autolysins start to degrade cell wall
- Influx of fluid results in osmotic lysis
- Considered **time-dependent**, as cell walls are continuously being constructed

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Beta Lactam Antibiotics

Spectrum of activity

- Variable, depending on the specific antibiotic
- Pen-G: select gram+ cocci, gram+ and gram- anaerobes, *Pasteurella*
  - Beta-lactamase sensitive
- Aminopenicillins: Pen-G plus enterococci and gram- (*E. coli*, *Salmonella*, *Pasteurella*, others)
  - Considered broad spectrum, but resistance patterns have made potentiation necessary (clavulanic acid or sulbactam)
  - *Enterococcus faecium* often resistant

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Beta Lactam Antibiotics

Spectrum of activity

- Extended-spectrum penicillins: increased activity against gram-
  - Beta-lactamase sensitive
- Carbapenems: broadest spectrum, including *Pseudomonas*
  - An extended beta-lactamase enzyme has been reported
- Monobactams: particularly effective against gram- aerobes; ineffective against gram+ organisms and anaerobes

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Beta Lactam Antibiotics

Spectrum of activity

- Cephalosporins - consult package insert for the particular drug, as spectrum is widely variable within this drug class
  - Generally ineffective against enterococci
  - Generally more resistant to beta-lactamases than penicillins
- First generation: aerobic spectrum similar to aminopenicillins; gram+ and gram- organisms (*E. coli*, *K. pneumoniae*, *P. mirabilis*); anaerobic spectrum fair, but less than aminopenicillins

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Beta Lactam Antibiotics

Spectrum of activity

- Second generation: better activity against *Enterobacter*, some *Proteus*, *E. coli*, and *Klebsiella*
  - Cefoxitin - excellent anaerobic spectrum, less good with gram+
- Third and fourth generation: generally reserved for serious gram+ or gram- infections

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Beta Lactam Antibiotics

Resistance

- Altered penicillin-binding proteins
  - Responsible for MRSA and vancomycin-resistant enterococci (VRE)
- Efflux through drug-specific pumps
- Loss/change of porins
- Inactivation by beta-lactamases (most common)
  - Occurs in both gram+ and gram-

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Target Ribosomes

- Aminoglycosides
- Tetracyclines
- Phenicols
- Lincosamides
- Macrolides/Azalides

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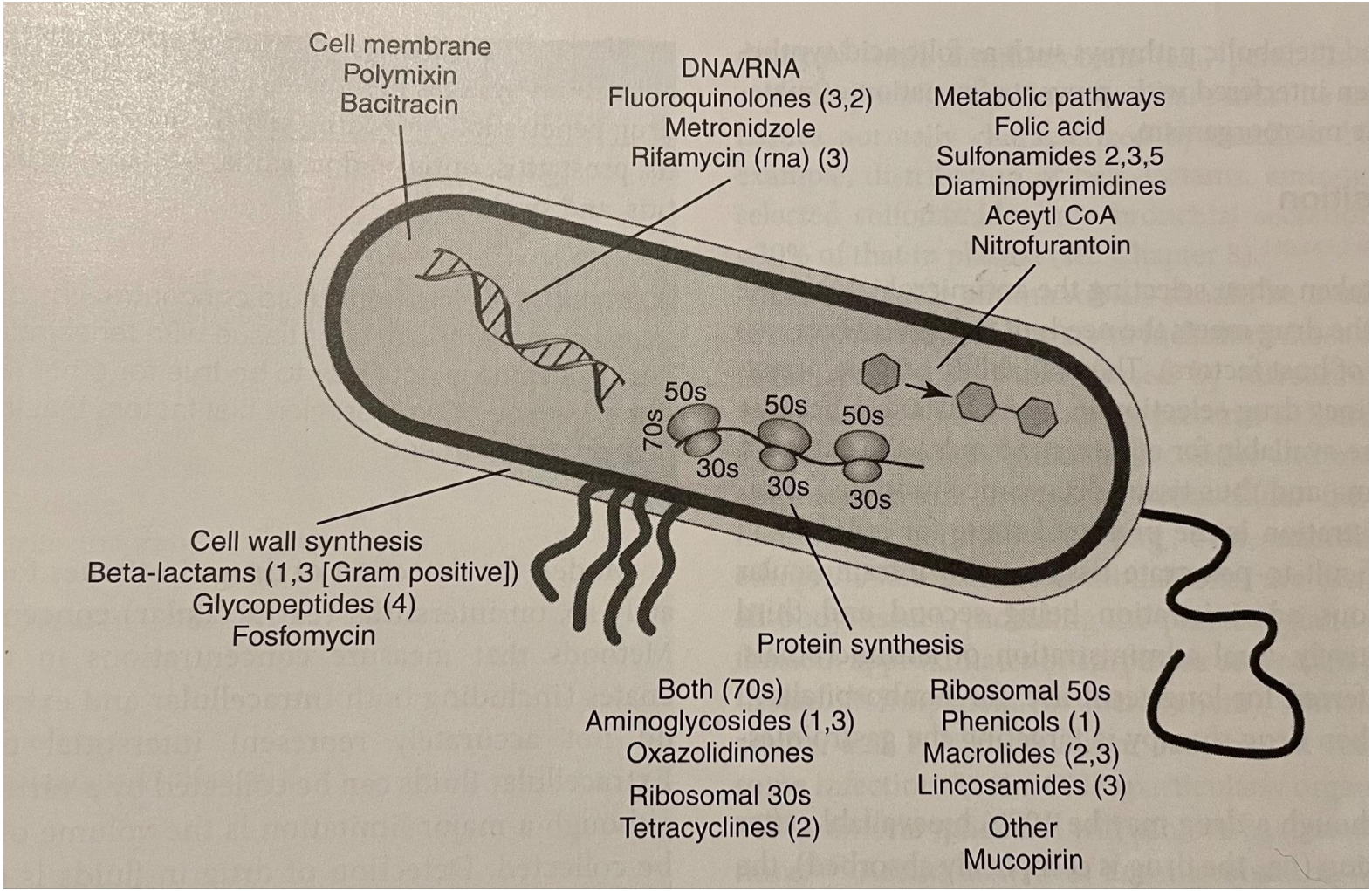
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Diaminopyrimidines
Aceytl CoA
Nitrofurantoin
70s
50s
30s
50s
30s
50s
30s
Cell wall synthesis
Beta-lactams (1,3 [Gram positive])
Glycopeptides (4)
Fosfomycin
Protein synthesis
Both (70s)
Aminoglycosides (1,3)
Oxazolidinones
Ribosomal 30s
Tetracyclines (2)
Ribosomal 50s
Phenicols (1)
Macrolides (2,3)
Lincosamides (3)
Other
Mucopirin

Aminoglycosides

- Neomycin
- Gentamicin
- Amikacin
- Netilimicin
- Streptomycin
- Tobramycin

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Aminoglycosides

Mechanism of Action

- Target bacterial ribosomes
  - 30S subunit is initiator of protein synthesis
    - Likely to achieve **bactericidal** activity
  - Irreversible saturation of ribosomes - **concentration dependent**
- Enter gram- organisms through porins in LPS layer, then active transport across cell membrane via respiratory protein
  - Inherent resistance in anaerobic bacteria and facultative anaerobes

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Aminoglycosides

Spectrum of Activity

- Most aerobic gram- bacteria (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Proteus*, and *Serratia*)
- Synergism against gram+ when combined with penicillins or vancomycin
- Amikacin is generally most effective against *Pseudomonas*

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Aminoglycosides

Resistance

- Inherent resistance of anaerobic organisms
- Decreased cell entry
- Altered ribosomal structure (*Enterococcus*)
- Destruction by microbial enzymes within the cell (most important clinically)

Adverse Effects

- Glomerular and tubular nephrotoxicity

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Tetracyclines

Short acting

- Oxytetracycline
- Tetracycline

Intermediate acting

- Demethylchlortetracycline
- Methacycline

Long acting

- Minocycline
- Doxycycline

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Tetracyclines

Mechanism of Action

- Bind the 16S portion of the 30S subunit of bacterial ribosomes and inhibit protein synthesis
  - **Bacteriostatic**
  - **Time dependent**

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Tetracyclines

Spectrum of Activity

- Enter through porins or active transport
- Considered broad spectrum - effective against gram+, gram- anaerobic organisms
- Effective against cell wall deficient organisms and rickettsial organisms
- *P. aeruginosa* generally resistant, though may be listed as susceptible on C&S testing - use caution

Resistance

- Decreased influx or increased transport
- Altered binding site
- Enzymatic destruction

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Tetracyclines

Adverse Effects

- Hepatotoxicity
- Collapse following rapid IV administration
- Erythema of skin and mucous membranes
- Anemia
- Brown/gray discoloration of teeth
- Drug fever (cats)
- Antianabolic effect
- Fanconi-like syndrome
- Esophageal erosions (cats and humans)

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Phenicols

- Chloramphenicol
- Florfenicol

Mechanism of Action

- Binds 50S subunit of bacterial ribosome - inhibits peptidyl transferase
- **Bacteriostatic**
- **Time dependent**

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Phenicols

Spectrum of Activity

- Broad spectrum: gram+, gram-, and anaerobic organisms
- *P. aeruginosa* generally not included
- Does include *Chlamydia*, *Mycoplasma*, *Rickettsia*, and *Hemobartonella*

Resistance

- Destruction via microbial enzymes

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Phenicols

Adverse Effects

- Reversible dose-dependent (humans and animals) and irreversible dose-independent bone marrow suppression (humans)

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Lincosamides

- Lincomysin
- Clindamycin

Mechanism of Action

- Inhibit 50S subunit at a distinct site from that of macrolides or phenicols
- **Bacteriostatic**
  - Clindamycin can be bactericidal in some tissues
- **Time dependent**

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Lincosamides

Spectrum of activity

- Clindamycin is more effective against susceptible bacteria than lincomysin and has better anaerobic activity
- Aerobic gram+ cocci, *Nocardia*, anaerobes
- Cell wall deficient organisms (e.g. *Mycoplasma*)

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Macrolides/Azalides

- Erythromycin
- Clarithromycin
- Azithromycin
- Tylosin

Mechanism of Action

- Inhibit bacterial ribosomes by binding to the 50S subunit
- Bacteriostatic in vitro, **bactericidal** against susceptible organisms
- Accumulate in phagocytic white blood cells
- **Time or concentration dependent** (depends on organism)

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Macrolides/Azalides

Spectrum of Activity

- Erythromycin: gram+ organisms; *P. multocida*, *B. pertussis*, and *Mycoplasma*; anaerobes except *Bacterioides*
- Generally effective against *Campylobacter*
- Clarithromycin and azithromycin have increased gram- coverage, but require higher doses for gram+

Resistance

- Drug efflux, altered ribosomal targets

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Target Nucleic Acids

- Fluoroquinolones
- Rifamycins
- Nitroimidazoles

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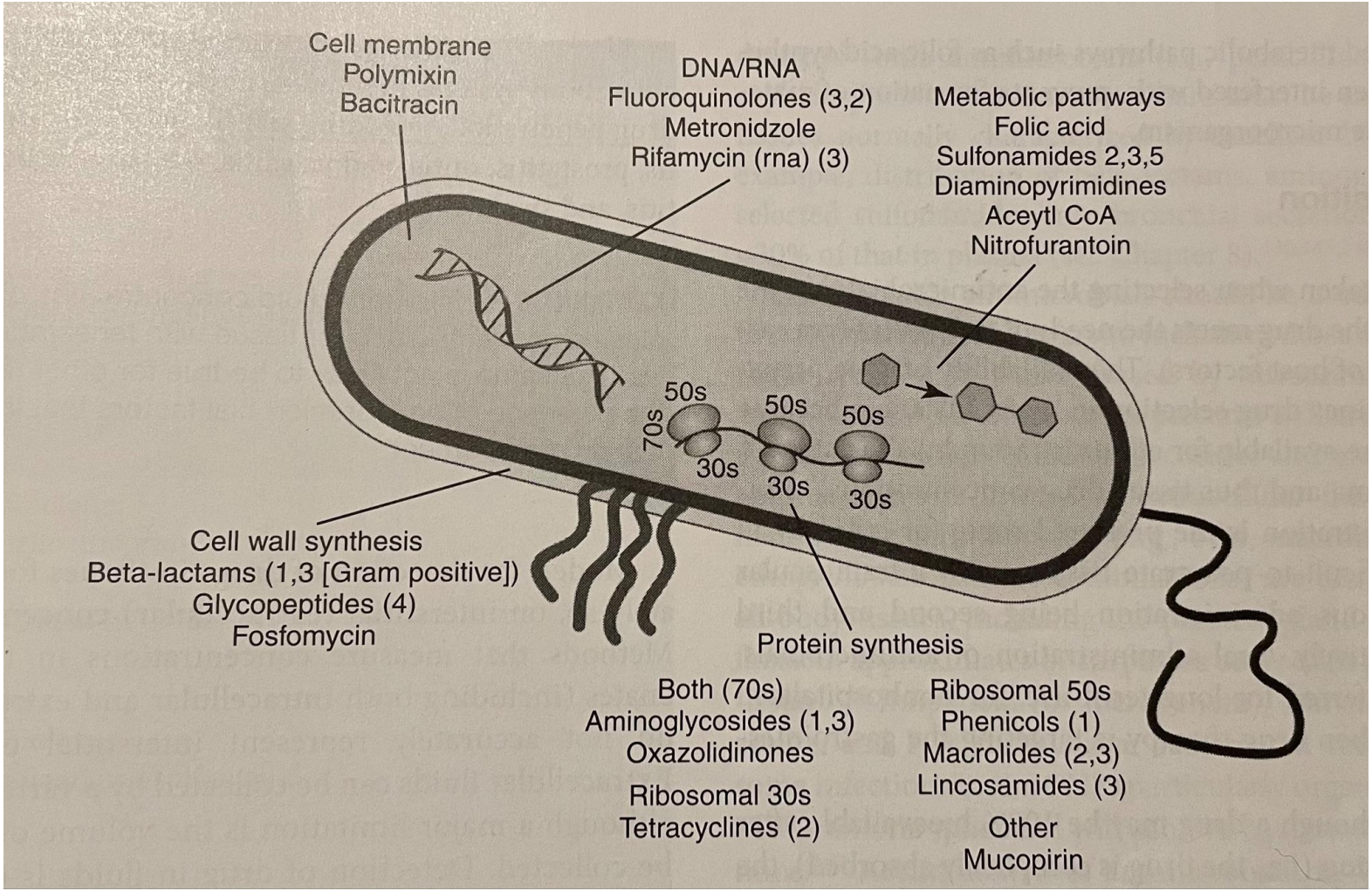
Cell membrane
Polymixin
Bacitracin
DNA/RNA
Fluoroquinolones (3,2)
Metronidzole
Rifamycin (rna) (3)
Metabolic pathways
Folic acid
Sulfonamides 2,3,5
Diaminopyrimidines
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Fluoroquinolones

- Enrofloxacin
- Orbifloxacin
- Difloxacin
- Marbofloxacin
- Pradofloxacin

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Fluoroquinolones

Mechanism of Action

- Directly inhibit DNA synthesis by targeting DNA gyrase and topoisomerase IV
    - Binds irreversibly - **concentration dependent** and **bactericidal**

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Fluoroquinolones

Spectrum of Activity

- Broad gram- and less broad gram+
- Not effective against anaerobes
- Effective against cell wall deficient microbes and mycobacteria
- Particularly effective against *Pasteurella*, *E. coli*, *Klebsiella*, *E. cloacae*, *P. mirabilis*, *Citrobacter freundii*, *S. marcascens*

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Fluoroquinolones

Resistance

- Genetic mutations in topoisomerase enzymes
- Resistance is emerging the longer the drugs are on the market

Adverse Effects

- Cartilage deformities and tendon repair
- Seizures, CNS disorders
- Retinal degeneration

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Rifamycins

Macrocyclic antibiotics

- Rifampin

Mechanism of Action

- Inhibits DNA dependent RNA polymerase - suppresses RNA synthesis
- **Concentration dependent** for mycobacterium, unclear for others

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Rifamycins

Spectrum of Activity

- Gram+
- *Mycobacterium*, *Neisseria*, and *Chlamydia*
- Has been used to treat *Clostridium* and *Bacterioides*

Resistance

- Develops rapidly (2 days) - prevent with combination therapy
    - Erythromycin, most beta-lactams, chloramphenicol, doxycycline, select aminoglycosides

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Nitroimidazoles

- Metronidazole
- Outside the US: tinidazole, benznidazole

Mechanism of Action

- Impairs microbial RNA and DNA synthesis
- Prodrug: metronidazole accepts electron generated by electron-generating pathways in anaerobic bacteria, creating highly reactive nitro radical ion that targets DNA - **bactericidal**
  - Only effective in anaerobes
  - Regenerated on cell death

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Nitroimidazoles

Spectrum of Activity

- All gram- and most gram+ anaerobic bacilli
- Microaerophilic microbes (*Helicobacter* and *Campylobacter*)
- Number of protozoa (trichomoniasis, amebiasis, giardiasis)

Resistance

- Aerobes and facultative anaerobes
- Can see rapid resistance of *Helicobacter* and increasing resistance of giardiasis

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Target Folic Acid

- Sulfonamides
- Diaminopyrimidines

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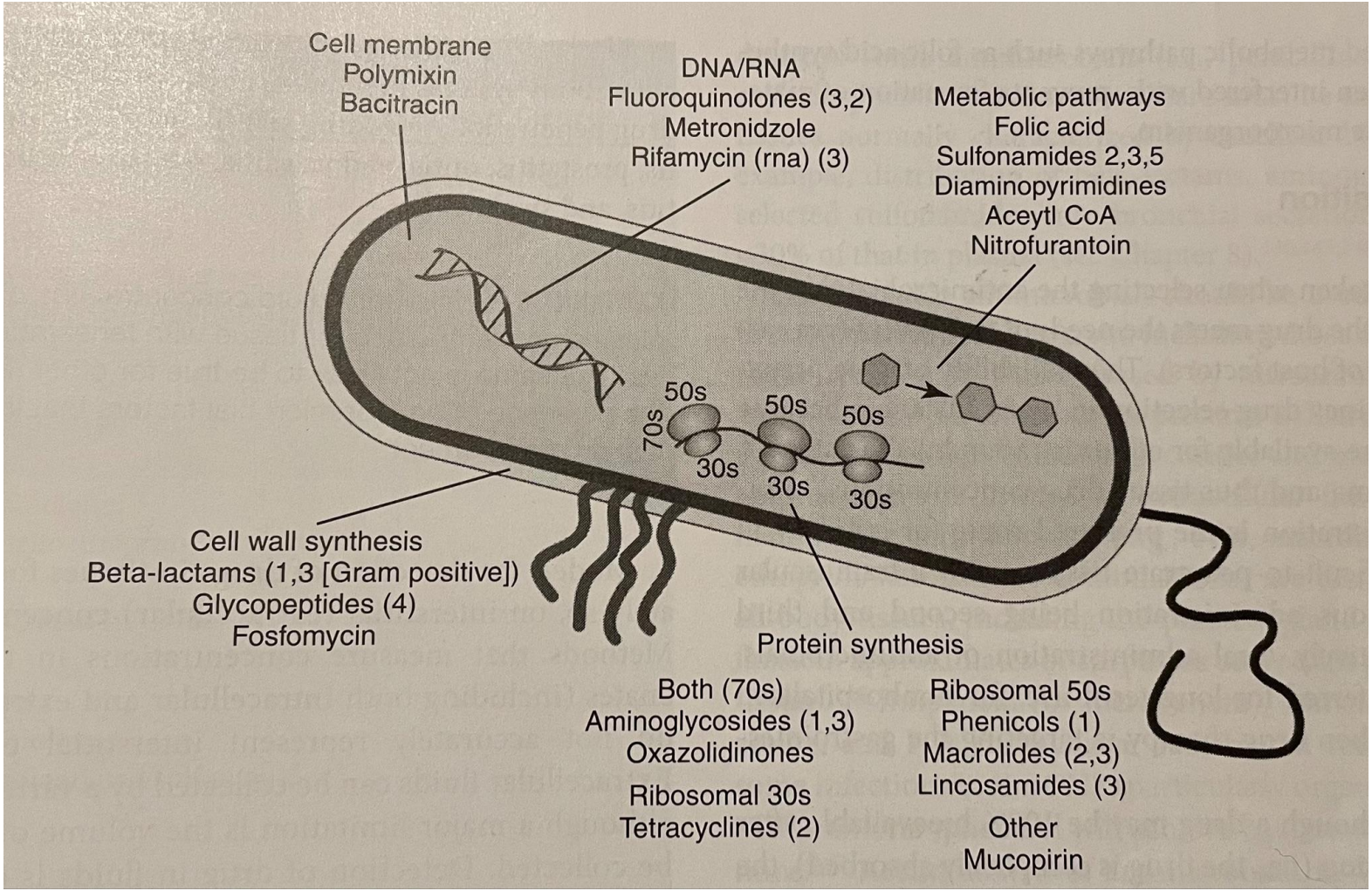
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Sulfonamides

- First commercially available antimicrobial used systemically
- Sulfadiazine
- Sulfamethoxazole
- Sulfachlorpyridazine
- Sulfadimethoxine
- Sulfasalazine

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Sulfonamides

Mechanism of Action

- Act as competitive substrates for the synthetase enzyme responsible for synthesizing folic acid
  - Folic acid is required for protein and nucleic acid metabolism
  - Inhibits bacterial growth - **bacteriostatic**

Spectrum of Activity

- Considered broad

Resistance

- Bacteria can use host folic acid
- Chromosomal resistance - impaired penetration, reduced affinity, increase bacterial production of PABA

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Sulfonamides

Adverse effects

- Thyroid gland suppression
- Aplastic anemia
- Hypersensitivity reactions
- KCS
- Toxicity: fever, thrombocytopenia, hepatopathy, neutropenia, KCS, hemolysis, arthropathy, uveitis, skin/mucosal lesions, proteinuria, facial palsy/edema, pancreatitis, pneumonitis

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Diaminopyrimidines

- Trimethoprim
- Ormetoprim

Mechanism of Action

- Impair folic acid synthesis by inhibiting the reductase enzyme - **bacteriostatic**

Combined with sulfonamides - become **bactericidal**

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QUESTIONS?

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Resources

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