Chemotherapy of infectious diseases Antimicrobials

Atnimicrobials = Antibiotics

Antibacterial agents

Antifungal agents

Antiviral agents

Antimycobacterials (Drugs for tuberculosis TB)

Antiseptics and Disinfectants

- Antimicrobial drugs should have selective toxicity towards the invading microorganism without harming the cells of the host

- Antimicrobial therapy takes advantage of the differences between microorganisms and humans

- The selective toxicity for the microorganism is usually relative, requiring careful control of the drug concentration to attack the microorganism while being tolerated by the host

- Selection of an appropriate antimicrobial agent requires knowing:

1. The microorganism
2. The organism's susceptibility to a particular agent
3. The site of infection
4. Patient factors
5. The safety of the drug
6. The cost of therapy

- Empiric treatment: Immediate administration of drugs prior to bacterial identification and susceptibility testing

Bacteriostatic vs. bactericidal drugs

- Bacteriostatic drugs arrest the growth and replication of bacteria
  - Require intact immune system

- Bactericidal drugs kill bacteria

- Minimum inhibitory concentration (MIC): the lowest concentration of antibiotic that inhibits bacterial growth

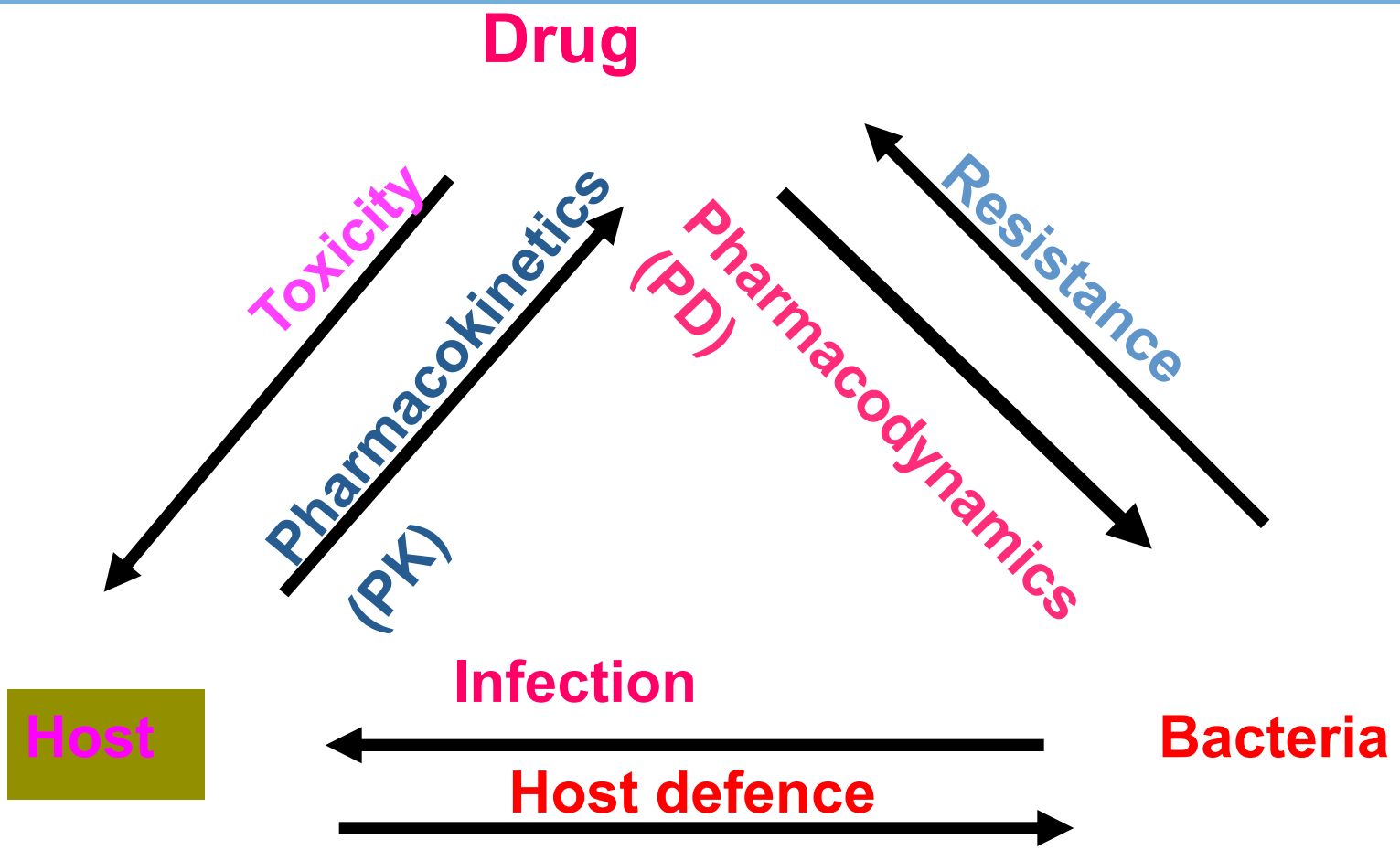
- Minimum bactericidal concentration (MBC): the minimum concentration of antibiotic that kills the bacteria under investigation

Route of administration

- Oral route is chosen for mild infections, and is favorable for outpatients
- Parenteral route is used for more serious infections, or when the anti-microbial agent of choice has poor GI absorption such as vancomycin, amphotericin B and aminoglycosides

- Concentration dependent killing
  - Rate of bacterial killing increases as the concentration increases
  - e.g. aminoglycosides like tobramycin
  - Administration by once-a-day bolus infusion achieves high peak levels, causing rapid killing of the pathogen
- Time dependent (concentration-independent) killing
  - Increasing concentration to higher multiplies of MIC does not increase the rate of killing
  - e.g. β-lactams (Penicillins, cephalosporins), glycopeptides, macrolides, clindamycin
  - Administration by extended (3-4 hours) or continuous (24 hours) infusion achieves prolonged time above MIC and kills more

There are Three in this Relationship



Agents used in bacterial infections

- Penicillins
- Cephalosporins
- Carbapenems
- Tetracyclines
- Aminoglycosides
- Macrolides
- Fluoroquinolones
- Sulfonamides
- Other

Chemotherapeutic spectra

- Narrow-spectrum antibiotics

Acting on a single or limited group

e.g. isoniazid is only active against mycobacteria

- Extended-spectrum antibiotics

Effective against gram positive organisms and also against a significant number of gram negative

e.g. ampicillin

- Broad-spectrum antibiotics

Drugs affecting a wide variety of microbial species

Can cause superinfections

e.g. tetracycline and chloramphenicol

Combinations of drug antibiotics

- It is advisable to treat patients with a single agent that is more specific to the infecting organism to reduce possibility of superinfections, decrease resistance and toxicity
- In certain situations combinations of antibiotics are needed for example treatment of tuberculosis requires the use of drug combinations

Drug resistance

- Bacteria is resistant to an antibiotic if the maximal level of the antibiotic does not stop their growth

Complications of antibiotic therapy

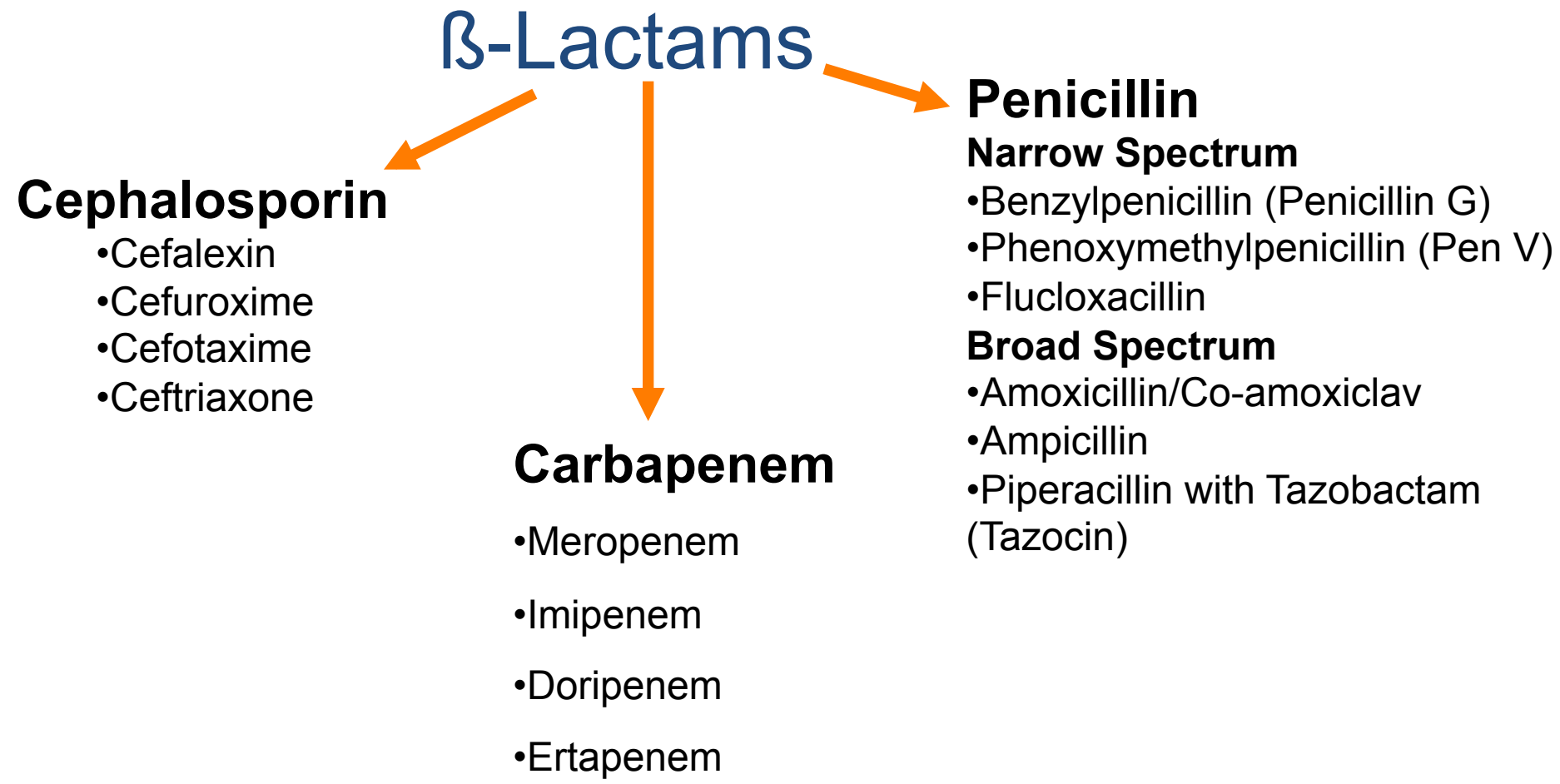
- Hypersensitivity
  - Example: Penicillins
- Direct toxicity
  - Aminoglycosides → ototoxicity
- Superinfections

ANTIBACTERIALS

Cell wall synthesis inhibitors

- Penicillins
- Cephalosporins
- Carbapenems
- Vancomycin

ß-Lactams


ß-Lactams
Cephalosporin
•Cefalexin
•Cefuroxime
•Cefotaxime
•Ceftriaxone
Carbapenem
•Meropenem
•Imipenem
•Doripenem
•Ertapenem
Penicillin
Narrow Spectrum
•Benzylpenicillin (Penicillin G)
•Phenoxymethylpenicillin (Pen V)
•Flucloxacillin
Broad Spectrum
•Amoxicillin/Co-amoxiclav
•Ampicillin
•Piperacillin with Tazobactam (Tazocin)

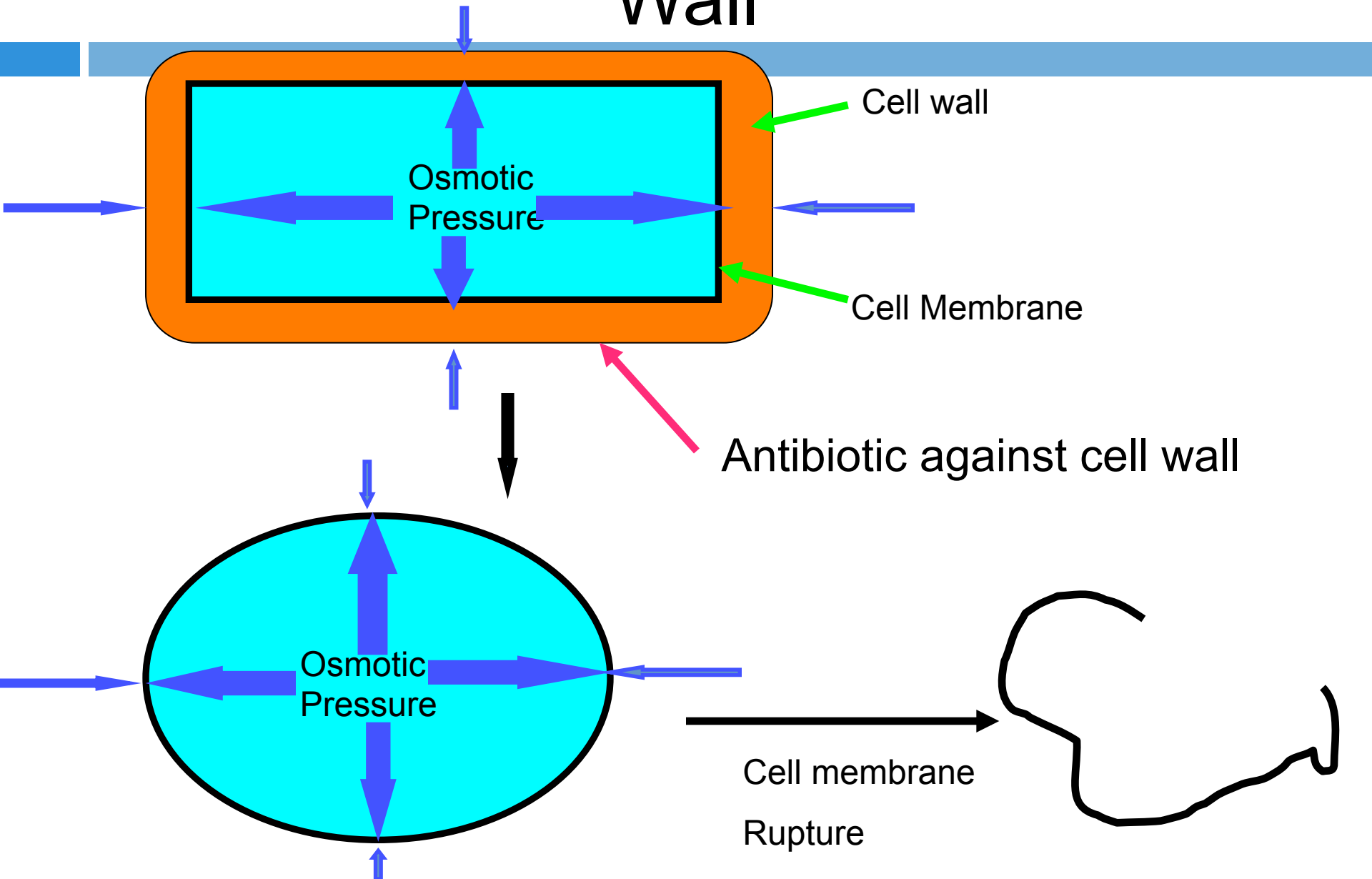
Cell wall synthesis inhibitors

- Interfere with bacterial cell wall synthesis

(Mammalian cells do not have cell wall)

- Include vancomycin, penicillins and cephalosporins, carbapenems

Beta Lactams Against Bacterial Cell Wall

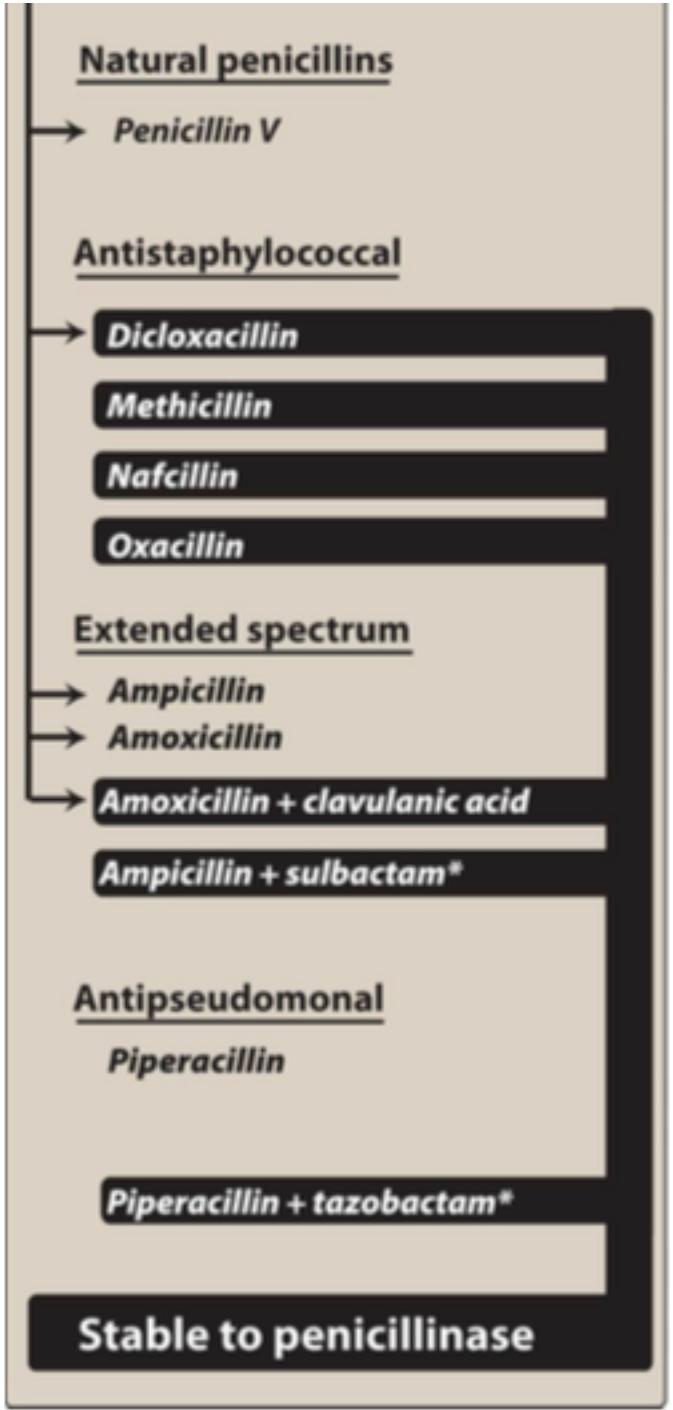


Penicillins

- Amoxicillin
- Ampicillin
- Penicillin G (Poor GI absorption, Given IV or IM)
- Penicillin V
- Dicloxacillin

- Adverse effects:

- Hypersesetivity
  - Rash
  - Anaphylaxis and death
- Diarrhea



Clavulonic acid, sulbactam are β-lactamase inhibitor

β-lactamase is an enzyme produced by bacteria which degrades penicillins causing resistance

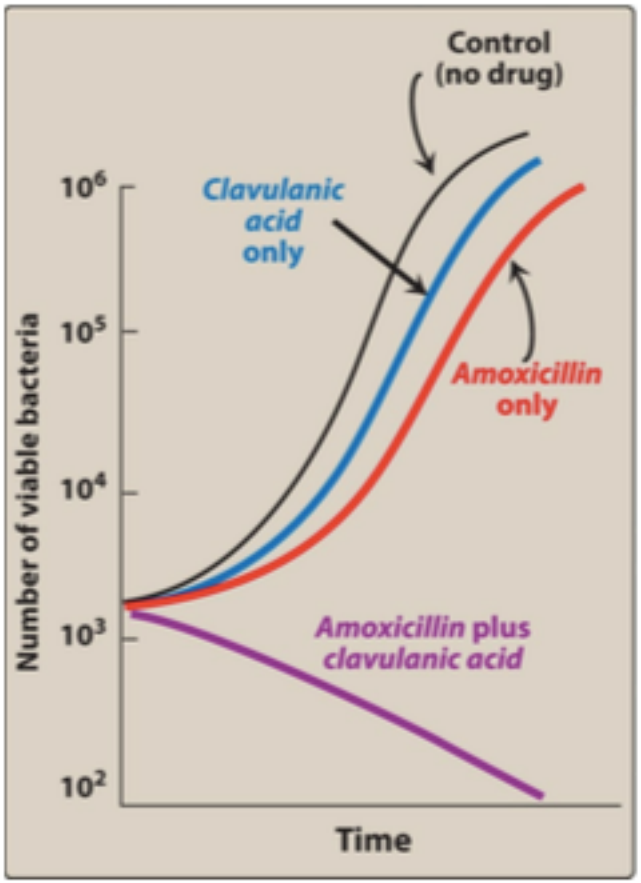
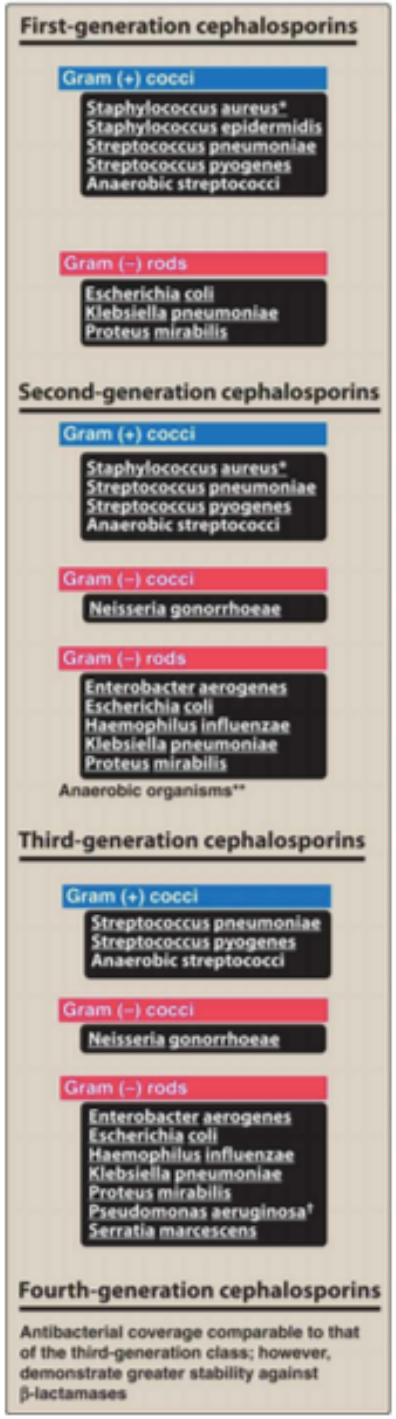


Figure 29.16 The in vitro growth of Escherichia coli in the presence of *amoxicillin*, with and without *clavulanic acid*.

Cephalosporins

- Cell wall synthesis inhibitors
- Classified based on their bacterial susceptibility
  - Firsts generation
    - Cephalexin
    - Cefadroxil
  - Second generation
    - Cefuroxime sodium (IV or IM)
    - Cefuroxime axetil (oral)
  - Third generation
    - Ceftriaxone (IV or IM)
      - Agent of choice for treatment of meningitis
    - Ceftazadime
  - Forth generation
    - Cefepime
  - Advanced generation
    - Ceftaroline (Active against MRSA)


First-generation cephalosporins
Gram (+) cocci
Staphylococcus aureus*
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci
Gram (–) rods
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Second-generation cephalosporins
Gram (+) cocci
Staphylococcus aureus*
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci
Gram (–) cocci
Neisseria gonorrhoeae
Gram (–) rods
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Anaerobic organisms**
Third-generation cephalosporins
Gram (+) cocci
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci
Gram (–) cocci
Neisseria gonorrhoeae
Gram (–) rods
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa†
Serratia marcescens
Fourth-generation cephalosporins
Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

Cephalosporines

- Adverse effects
- Generally well tolerated
  - Allergic reactions

Carbapenems

- Meropenem
- Imipenem
- Resistant to penicillinases

Monobactam

- Aztreonam
- Administered IV or IM

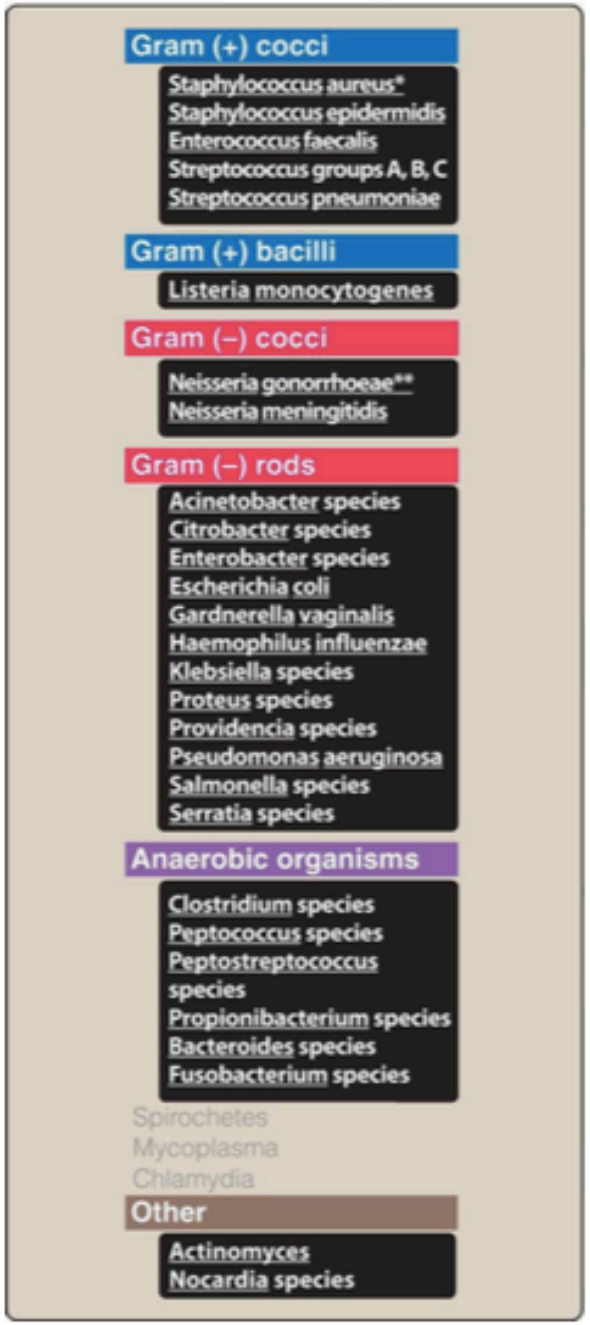


Figure 29.15 Antimicrobial spectrum of *imipenem*. **Methicillin*-resistant staphylococci are resistant. ***Includes penicillinase-producing strains.

Vancomycin

- IV vancomycin is used in individuals with prosthetic heart valves and in individuals undergoing implantation with prosthetic device
- Glycopeptide
- It is effective against aerobic and anaerobic gram positive bacteria including MRSA

Vancomycin

- Adverse effects
  - Fever
  - Phlebitis at the infusion site
  - Flushing and shock can result from a rapid infusion, due to histamine release it should be administered slowly, and with pretreatment with antihistamines in case of infusion-related reaction
  - Dose related hearing loss has occurred in individuals with renal failure who accumulate the drug
  - (Dose should be adjusted in renal impairment to prevent accumulation of drug)
  - Ototoxicity and nephrotoxicity are more common when vancomycin is coadministred with other drugs like aminoglycosides that cause these effects

Figure 29.17 Antimicrobial spectrum of *vancomycin*. *Includes *methicillin*-resistant strains. **Oral *vancomycin* only for C. difficile.

Protein synthesis inhibitors

- Antibiotics that target bacterial ribosome
  - Tetracyclines
  - Aminoglycosides
  - Macrolides
  - Chloramphenicol

Tetracyclines

- Tetracycline
- Doxycycline
- Minocycline

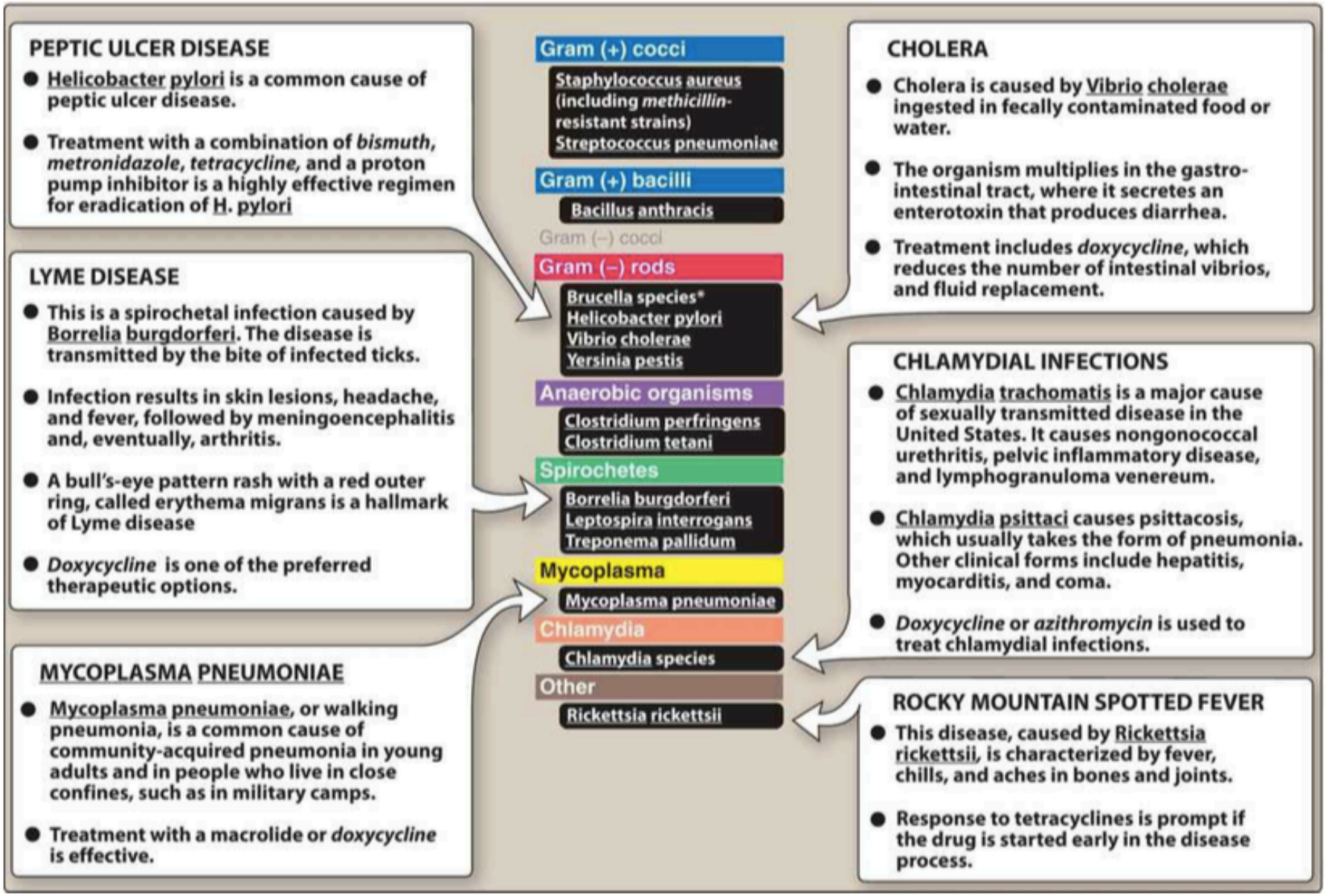
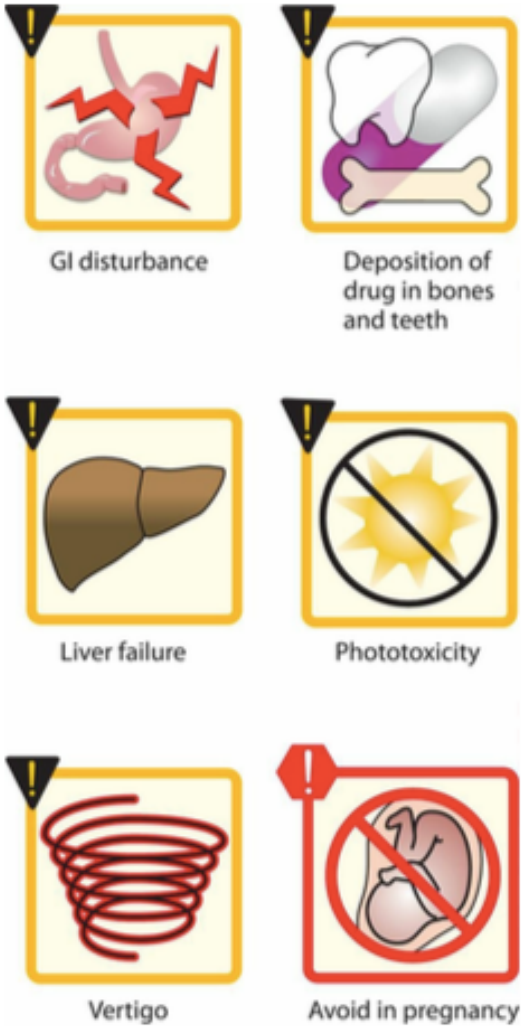


Figure 30.3 Typical therapeutic applications of tetracyclines. *A *tetracycline* + *gentamicin*.

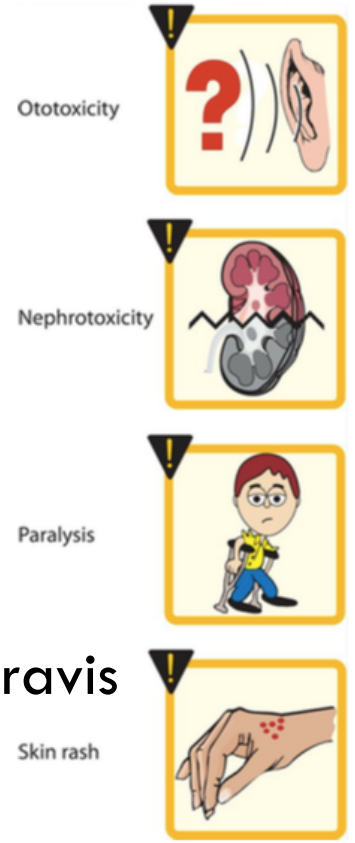
Tetracyclines

- Adverse effects
  - Gastric discomfort: drug can be taken with food to reduce discomfort (except diary)
  - Deposition in bone and primary dentition in growing children
  - Fatal hepatotoxicity
  - Phototoxicity
- Contraindicated in pregnant or breast-feeding women or in children less than 8 years of age



Aminoglycosides

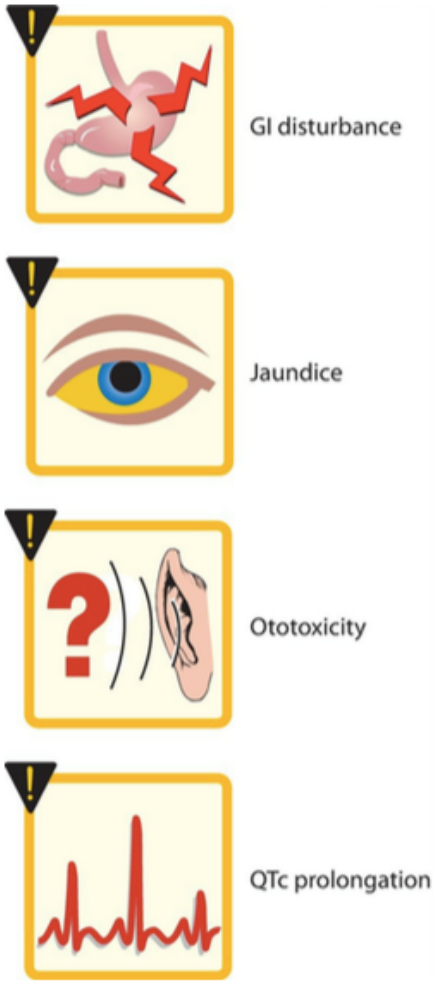
- Gentamicin
- Streptomycin
- Neomycin
- Tobramycin
- Have synergistic effect with beta-lactam antibiotics
- Adverse effects
  - Ototoxicity
  - Nephrotoxicity
  - Neuromuscular paralysis
    - with rapid IV injection especially in Myasthenia gravis
  - Allergic reactions
- Serum levels should be monitored to avoid toxicity
- Contraindicated in pregnancy



Macrolides

- Erythromycin
- Azithromycin
- Clarithromycin

- Adverse effects
  - Epigastric distress
  - Ototoxicity
  - QT prolongation



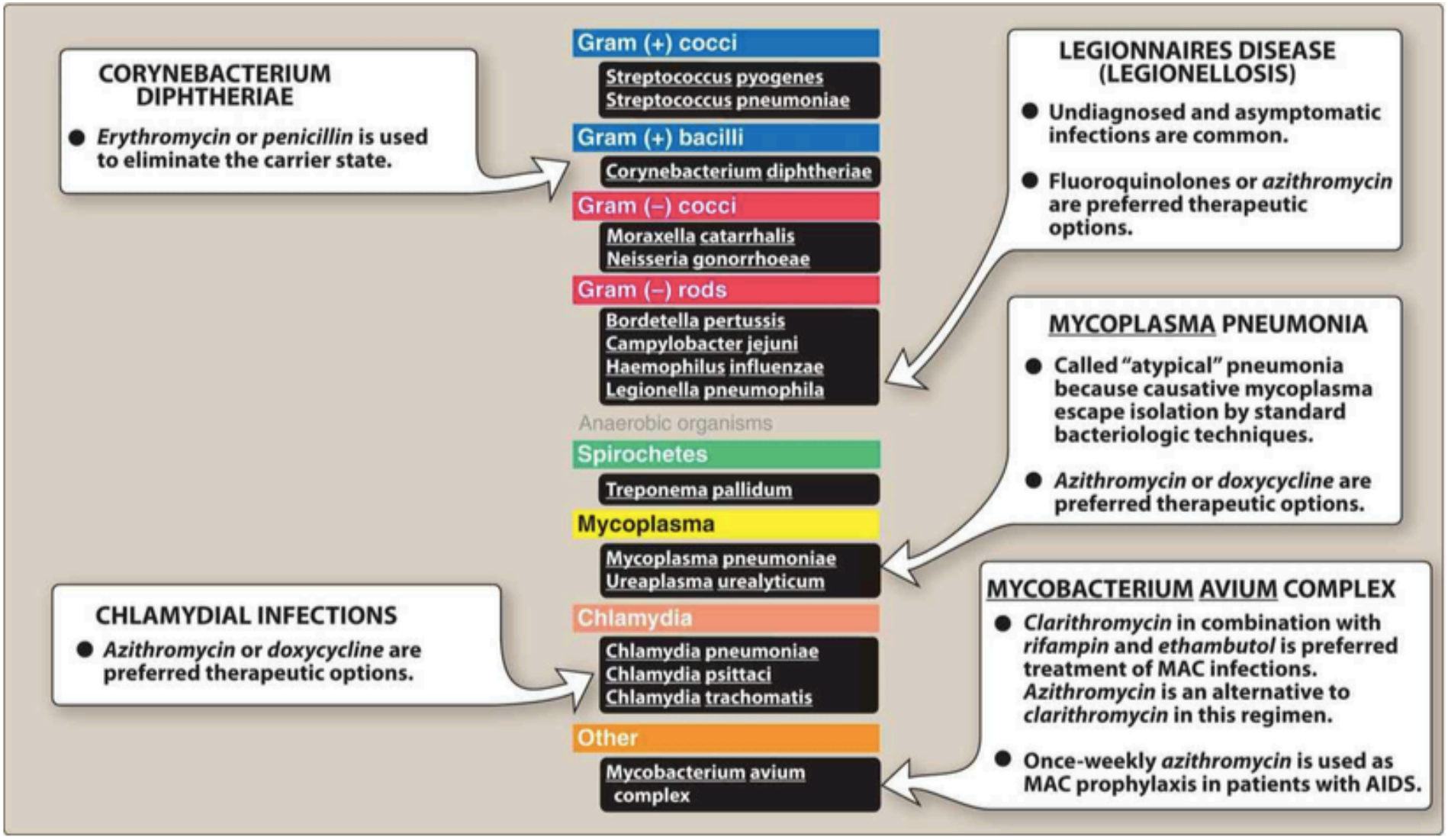


Figure 30.10 Typical therapeutic applications of macrolides.

Chloramphenicol

- Effective against a wide range of gram positive and gram negative organisms
- Use is limited due to toxicity
- Adverse effects
  - GI upsets
  - Superinfections (overgrowth of candida)
  - Anemias
  - Gray baby syndrome: occurs in neonates due to their low ability to excrete chloramphenicol, accumulation of the drug leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis and death

Fluoroquinolones

- Fluoroquinolones 1st generation
  - Nalidixic acid
- Fluoroquinolones 2nd generation
  - Ciprofloxacin
  - Norfloxacin
  - Ofloxacin
- Fluoroquinolones 3rd generation
  - Levoflaxin
- Fluoroquinolones 4th generation
  - Moxifloxacin

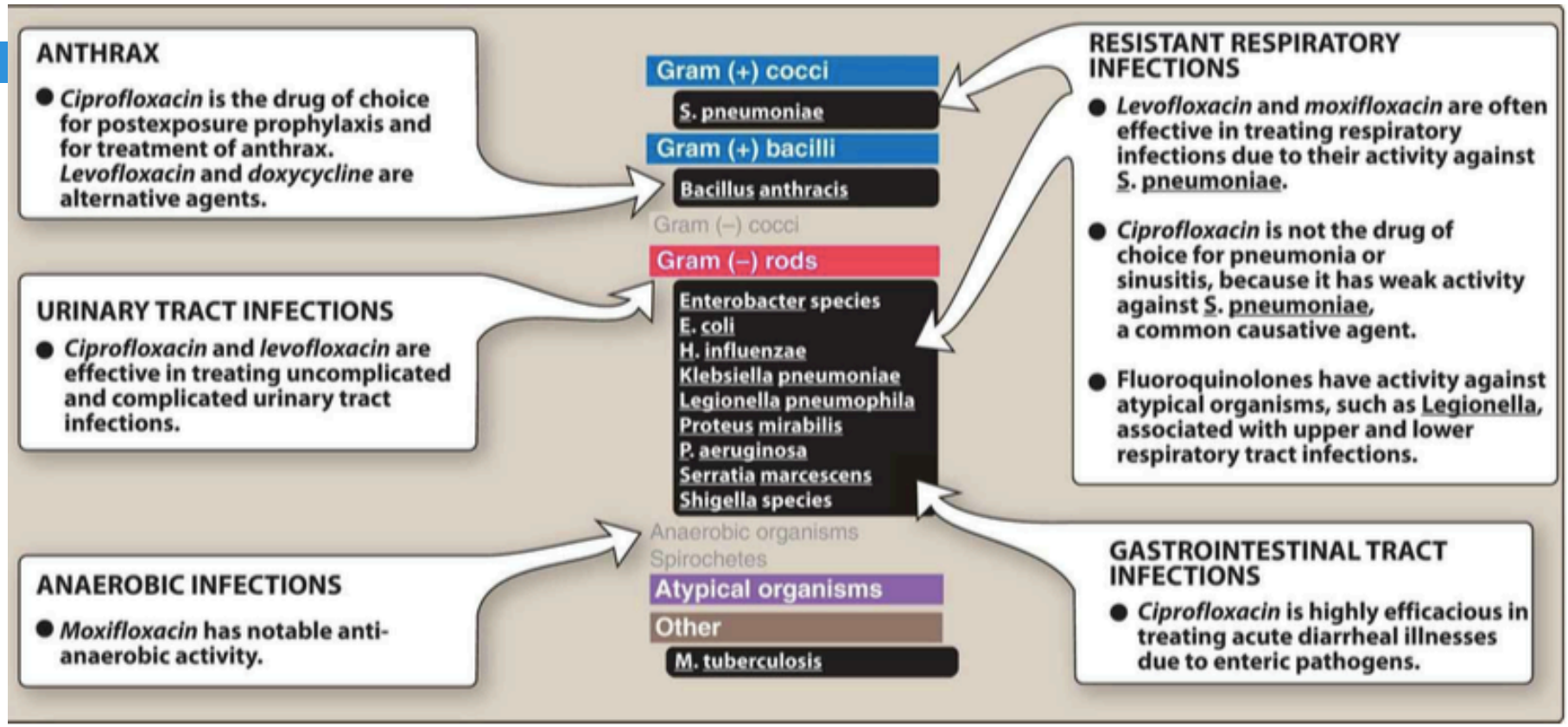


Figure 31.2 Typical therapeutic applications of fluoroquinolones.

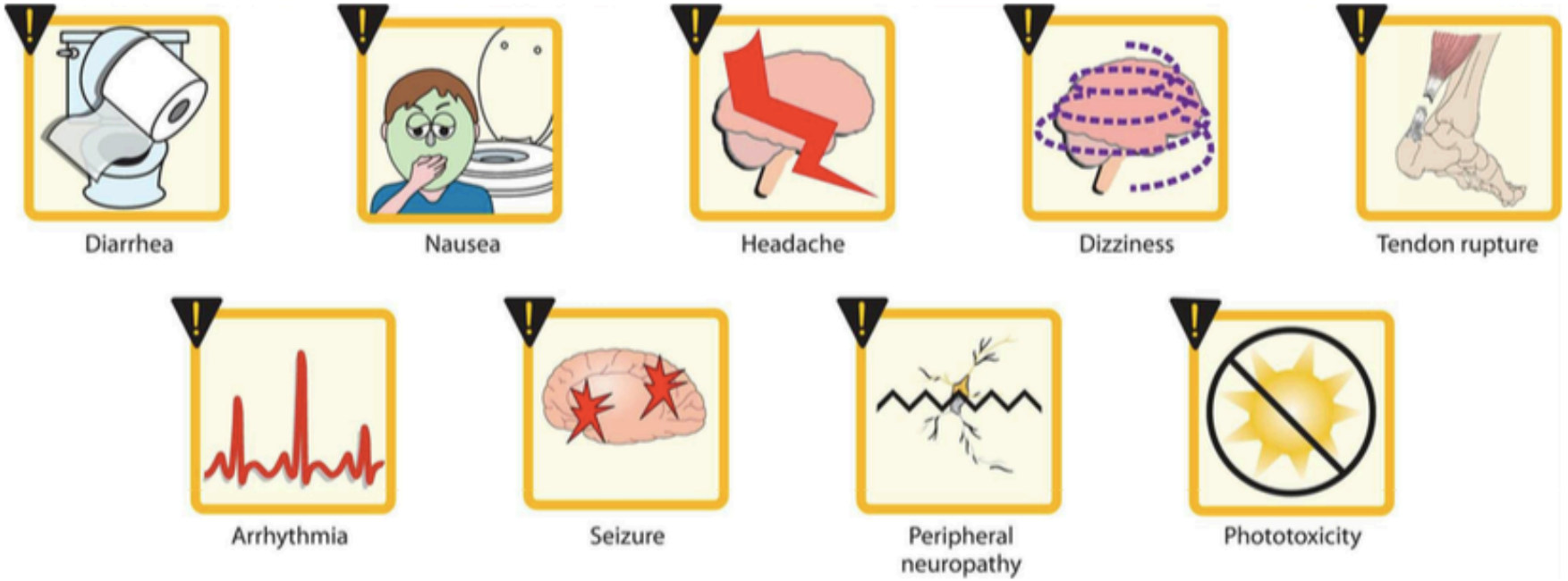


Figure 31.5 Some adverse reactions to fluoroquinolones.

Fluoroquinolones

- Adverse reactions: (well tolerated in general)
  - Nausea, vomiting and diarrhea
  - Headache and dizziness
  - Phototoxicity
  - Connective tissue problems
- Contraindications:
  - Should be avoided in pregnancy and nursing mothers and children under 18
  - Should be avoided in patients susceptible to arrhythmias; may prolong QTc interval

Cotrimoxazole (Sulfonamide)

Cotrimoxazole = Sulfamethoxazole + Trimithoprim

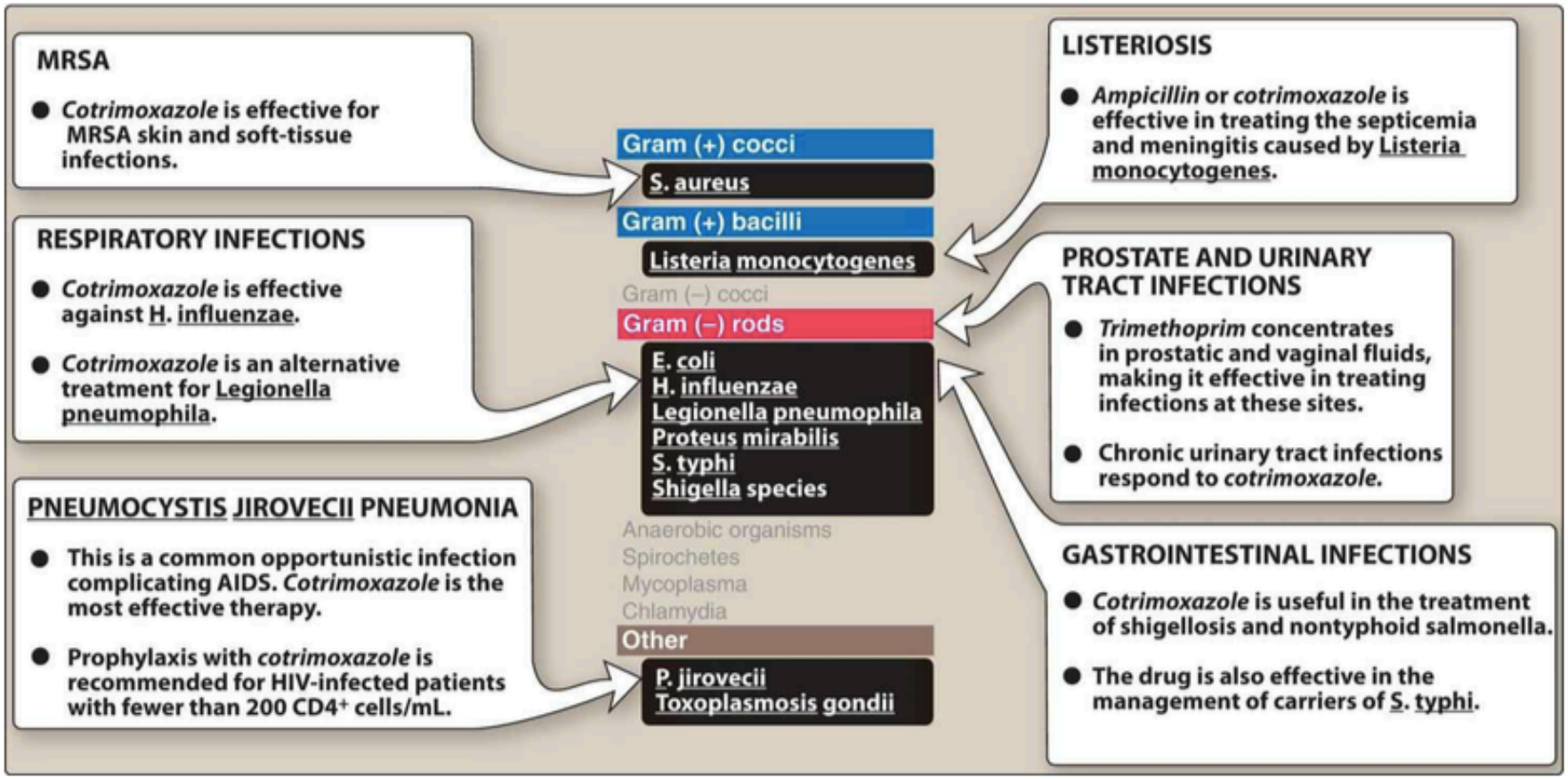


Figure 31.11 Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

Cotrimoxazole

Cotrimoxazole = Sulfamethoxazole + Trimithoprim

Adverse effects

- Crystalluria (stone formation)
  - Adequate hydration prevents the problem
- Hypersensitivity
- Hemopoietic disturbances
  - Hemolytic anemia in patients with G6PD deficiency
  - Thrombocytopenia
  - Granulocytopenia
- Kernicterus: Sulfa drugs displace bilirubin from albumin binding in newborns, bilirubin can cross the baby's BBB as it is not fully developed

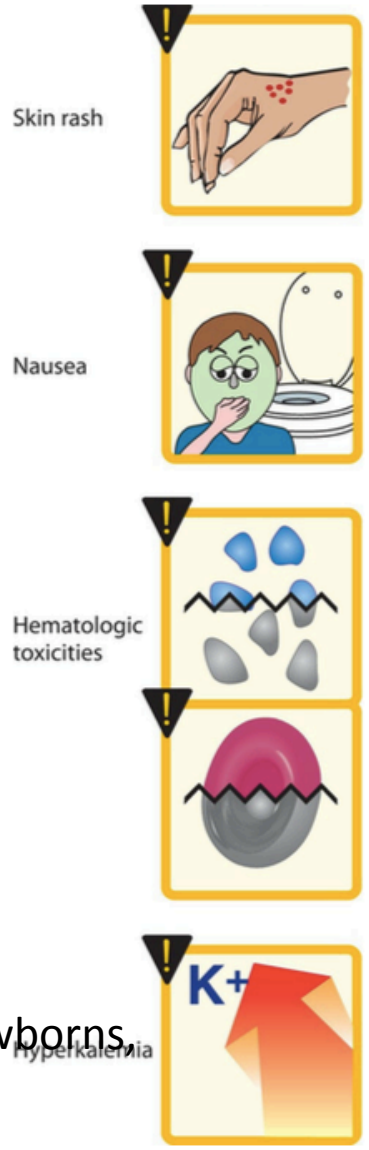


Figure 31.13 Some adverse reactions to *cotrimoxazole*.

Metronidazole (Flagyl)

Antibiotic
Amoebicide
Anti-protozoal

Adverse effects:

- Nausea, vomiting, abdominal cramps
- Unpleasant, metallic taste

Antifungal drugs

- Infections caused by fungi are called mycoses and they are often chronic
- Mycotic infections can be superficial and some involve the skin (cutaneous mycoses extending into the epidermis), but fungi may also penetrate the skin, causing subcutaneous infections, and they may cause systemic infections
- Systemic mycoses are the most difficult to treat and are often life threatening

Antifungal agents

- Amphotericin B
- Ketoconazole
- Fluconazole
- Itraconazole
- Miconazole
- Clotrimazole
- Caspofungin
- Nystatin
- Terbinafine

Antiviral agents

- Non-HIV agents
  - Acyclovir for herpes simplex and varicella zooster
  - Oseltamivir for prevention and treatment of influenza A, B and A type H5N1 (avian flu), A type H1N1 (swine flu)
  - Ribavirn for respiratory syncytial virus (RSV), also for chronic hepatitis C
  - For chronic hepatitis B inteferone alfa-2b, lamivudine

- HIV agents
  - Reverse transcriptase inhibitors
  - Protease inhibitors