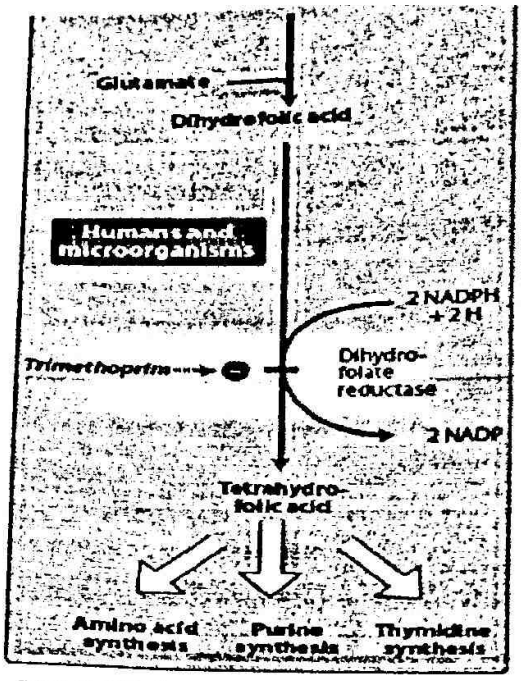


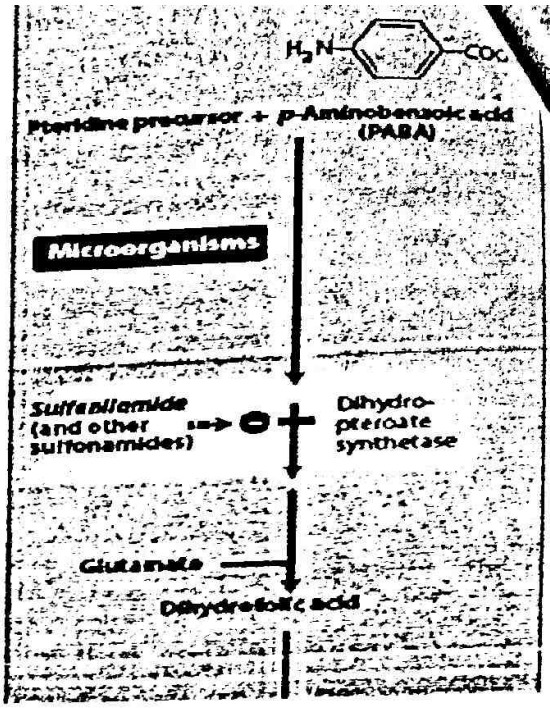


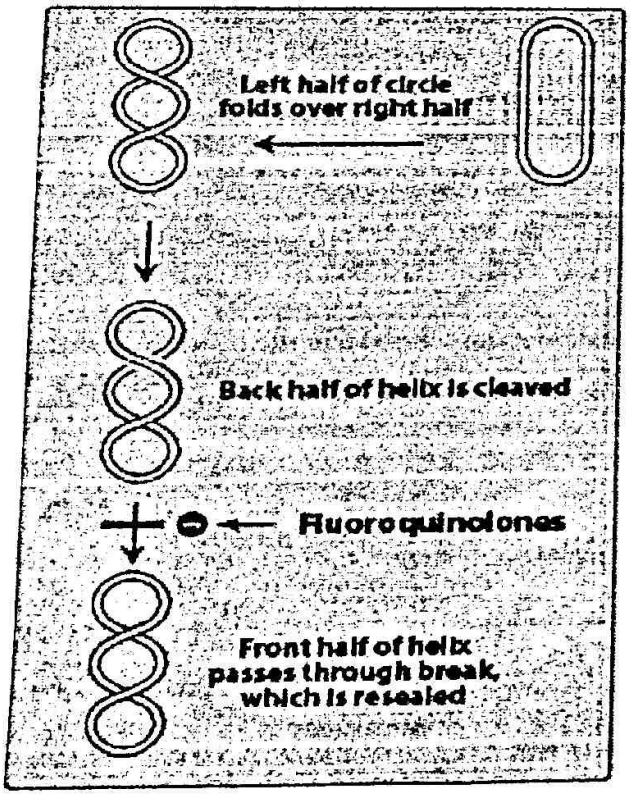
Figure 33.9
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

FLUOROQUINOLONES 1st GEN.
Nalidixic acid NEGGRAM

FLUOROQUINOLONES 2nd GEN.
Ciprofloxacin CIPRO
Norfloxacin NOROXIN
Ofloxacin FLOXIN

FLUOROQUINOLONES 3rd GEN.
Levofloxacin LEVAQUIN

FLUOROQUINOLONES 4th GEN.
Moxifloxacin AVELOX



INHIBITORS OF FOLATE SYNTHESIS
Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE
Sulfasalazine AZULFIDINE
Sulfisoxazole GANTRISIN

INHIBITORS OF FOLATE REDUCTION
Pyrimethamine DARAPRIM
Trimethoprim PROLOPRIM

COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION
Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM

URINARY TRACT ANTISEPTICS
Methenamine MANDELAMINE, HIPREX
Nitrofurantoin MACROBID

Figure 33.2

Resistance

Only organisms that synthesize their folate requirements de novo are sensitive to the sulfonamides. Thus, humans, who synthesize folate cofactors from dietary folic acid, are not affected, and bacteria that can obtain folates from their environment are naturally resistant to these drugs.

Resistance is due to 1) an altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA.

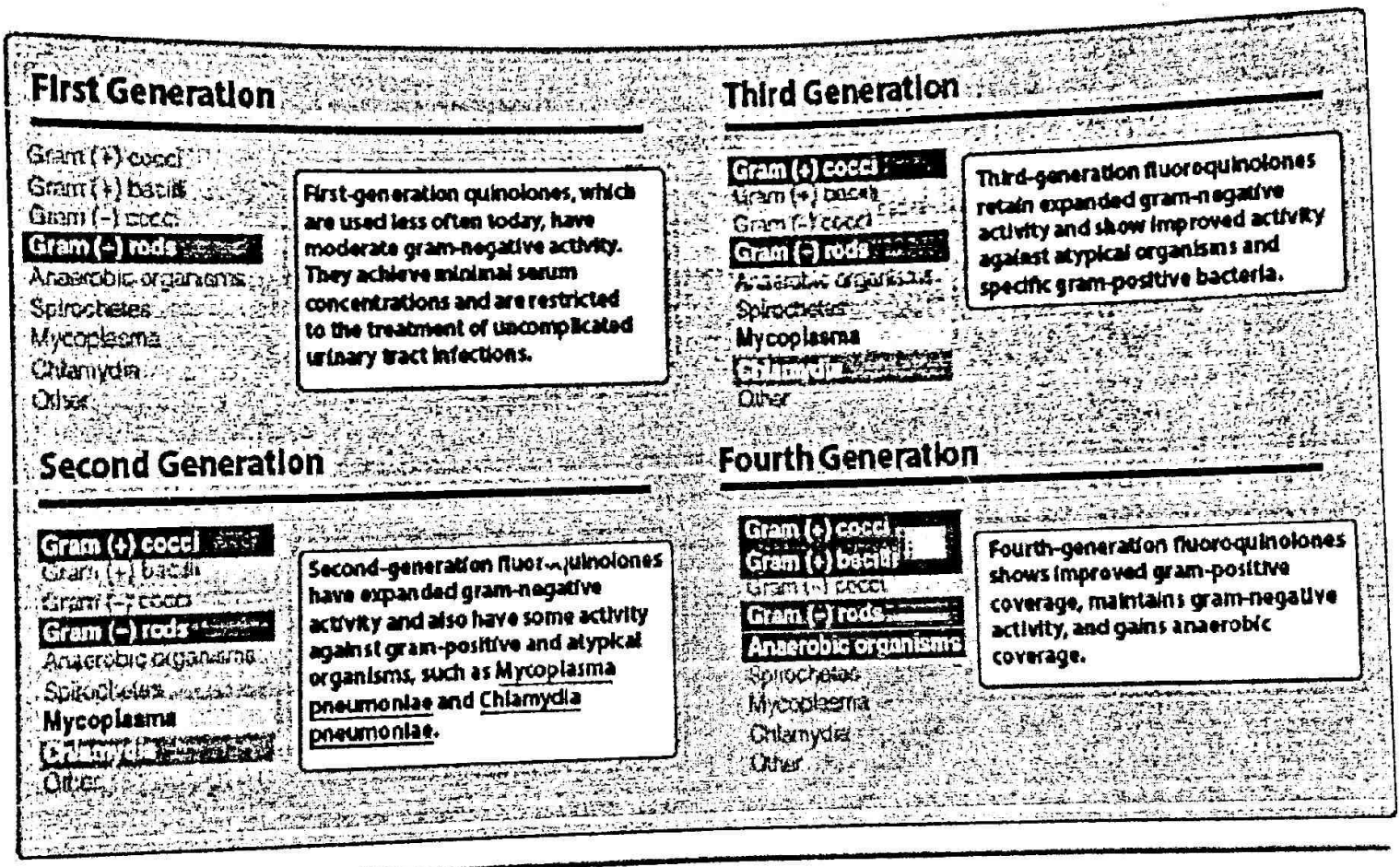


Figure 33.3
Summary of antimicrobial spectrum of quinolones. [Note: The antimicrobial spectrum of specific agents may

Contraindications: *Moxifloxacin* and other fluoroquinolones, may prolong the QTc inte
thus, should not be used in patients who are predisposed to arrhythmias or are
antiarrhythmic medications. Fluoroquinolones should be avoided in pregnancy, in nu
mothers, and in children less than 18 years of age (risk of arthropathy)

Drug interactions: Antacids and cations interfere with the absorption of these agents. *Ciprofloxacin* and *ofloxacin* can increase the serum levels of *theophylline* (inhibiting its metabolism). The third- and fourth-generation fluoroquinolones may raise the serum levels of *warfarin* and *cyclosporine*.

Folate antagonists

FOLATE ANTAGONISTS

Enzymes requiring folate cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) necessary for celiuiar growth and replication. Therefore, in the absence of folate, cells cannot grow or divide.

(1) To synthesize tetrahydrofolic acid (active form), humans must first obtain preformed folate in the form of folic acid from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must synthesize folate de novo.

(2) The sulfonamides (sulfa drugs) inhibit this de novo synthesis of folate. A second type of folate antagonist, *trimethoprim*, prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell's ability to make this conversion. Combining the sulfonamide, *sulfamethoxazole*, with *trimethoprim* provides a synergistic combination.

SULFONAMIDES

Mechanism of action

Dihydrofolic acid is synthesized from *p*-aminobenzoic acid (PABA), pteridine, and glutamate. All the sulfonamides are synthetic analogs of PABA.

Because of their structural similarity to PABA, the sulfonamides compete with PABA for the bacterial enzyme, dihydropteroate synthetase. They inhibit the synthesis of bacterial dihydrofolic acid and. The sulfa drugs, including *cotrimoxazole*, are bacteriostatic.

Antibacterial spectrum

Sulfa drugs are active against selected Enterobacteria in the urinary tract and Nocardia. In addition, *sulfadiazine*, in combination with the dihydrofolate reductase inhibitor *pyrimethamine*, is the preferred form of treatment for toxoplasmosis.

PABA → Dihydrofolic acid → THF

Decreased accumulation: Reduced intracellular concentration of the drugs is due to 1. decreased number of porin proteins in the outer membrane, thereby impairing access of the drugs to the intracellular topoisomerases. 2. An energy-dependent efflux system in the cell membrane.

Pharmacokinetics

1. Absorption: Only 35 to 70 percent of orally administered *norfloxacin* is absorbed, compared with 85 to 95 percent of the other fluoroquinolones. Ingestion of the fluoroquinolones with *sucralfate*, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc , calcium and other divalent cations interfere with their absorption .

2. Elimination:

Plasma levels of free *norfloxacin* are insufficient for treatment of systemic infections. Levels are high in bone, urine (except *moxifloxacin*), kidney, and prostatic tissue, and lung.

Penetration into cerebrospinal fluid is relatively low except for *ofloxacin*. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus effective against intracellular organisms such as Legionella pneumophila.

Most fluoroquinolones are excreted renally (dose needs to be adjusted in renal impairment). *Moxifloxacin* is excreted by the liver.

Adverse reactions

In general, these agents are very well tolerated.

1. Gastrointestinal: The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea.

2. Central nervous system problems: headache and dizziness or light-headedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs.

3. Phototoxicity: Patients taking fluoroquinolones are advised to avoid excessive sunlight, the drug should be discontinued at the first sign of phototoxicity.

4. Connective tissue problems:

a) High risk of articular cartilage erosion (arthropathy) (children or fetus).

b) There is increased risk of tendinitis or tendon rupture (adults). The risk is increased in patients over 60 years of age, those receiving concomitant corticosteroid therapy.

Levofloxacin is classified as **third generation**, having increased activity against gram-positive bacteria and atypical organisms (e.g. mycoplasma ,chlamydia), it retains expanded gram-negative activity.

The **fourth generation** includes only *moxifloxacin* because of its activity against anaerobic, as well as, improved gram-positive activity and it retains gram-negative activity.

Examples of clinically useful fluoroquinolones

1. Ciprofloxacin:

-effective against many systemic infections except MRSA, the enterococci, and pneumococci.

- treating infections caused by many Enterobacteriaceae and other gram-negative bacilli. For example, traveler's diarrhea caused by E. coli.

- The most potent fluoroquinolone for Pseudomonas aeruginosa infections (e.g. pseudomonal infections associated with cystic fibrosis).

- treating resistant tuberculosis and typhoid fever.

2. Norfloxacin: *Norfloxacin* is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in UTIs, prostatitis. It is not effective in systemic infections.

3. Levofloxacin: It can be used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases, .e.g gonorrhea (but not syphilis). *Levofloxacin* is utilized in skin infections, acute sinusitis and has excellent activity against S. pneumoniae respiratory infections.

4. Moxifloxacin: enhanced activity against gram-positive organisms (for example, S. pneumoniae) , excellent activity against many anaerobes. It has very poor activity against P. aeruginosa. *Moxifloxacin* does not concentrate in urine and is not indicated for the treatment of UTIs.

Resistance

The mechanisms responsible for this resistance include

1. Altered target: Mutations in the bacterial DNA gyrase and Topoisomerase IV cause a decreased affinity for fluoroquinolones.

FLUOROQUINOLONES

Naladixic acid is the predecessor to all fluoroquinolones. Introduction of the first fluorinated quinolone, *norfloxacin*, was rapidly followed by development of other members of this group, such as *ciprofloxacin*.

Mechanism of action

The fluoroquinolones enter the bacterium by passive diffusion through water-filled protein channels (porins) in the outer membrane. Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction.

Topoisomerases are enzymes that change configuration of DNA by a nicking, pass-through, and resealing mechanism.

Binding of the quinolone to both the enzyme and the DNA forms a ternary complex that inhibits the resealing step, and can cause cell death by inducing cleavage of the DNA.

Topoisomerase IV is required by bacteria for cell division, for the process of segregating newly replicated DNA.

In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas in gram-positive organisms (for example, the streptococci), the opposite is true.

Antimicrobial spectrum

Fluoroquinolones are **bactericidal**. In general, they are effective against gram negative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia, mycoplasma and some mycobacteria. They are effective in the treatment of gonorrhea but not syphilis. *Levofloxacin* and *moxifloxacin* also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae.

The nonfluorinated quinolone *nalidixic acid* is considered to be first generation, with a narrow spectrum with moderate gram-negative activity (for uncomplicated UTI).

ciprofloxacin and *norfloxacin* are second generation, having expanded activity against aerobic gram-negative and atypical bacteria, also some gram-positive activity. These fluoroquinolones exhibit significant intracellular penetration, allowing therapy for intracellular bacteria (for example, chlamydia, mycoplasma, and Legionella).