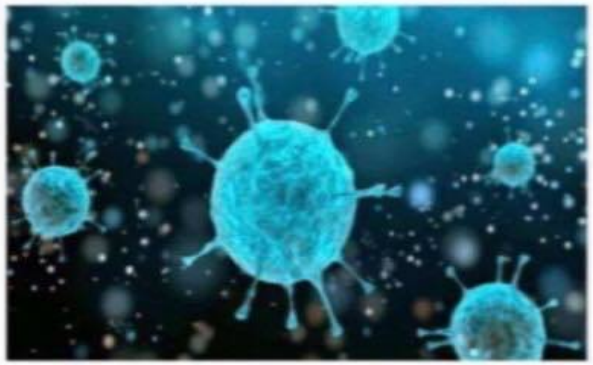
Lecture 13

Second Year

Passion Batch



MICROBIOLOGY

Abdullah abdulmonem

Rama mahdi

Antimicrobial Agents
&
Mechanisms of Resistance
)Two Lectures(

BY

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Learning Objectives

- Identify the characteristics of an ideal antimicrobial agent
- Compare and contrast chemotherapeutic agents, antimicrobial agents, and antibiotics as to their intended purpose
- State the five most common mechanisms of action of antimicrobial agents
- Differentiate between bactericidal and bacteriostatic agents
- State the difference between narrow-spectrum and broad-spectrum antimicrobial agents
- Identify the four most common mechanisms by which bacteria become resistant to antimicrobial agents
- State what the initials "MRSA" and "MRSE" stand for
- Define the following terms: β-lactam ring, β-lactam antibiotics, and β-lactamase
- Name two major groups of bacterial enzymes that destroy the β-lactam ring
- State six actions that clinicians and/or patients can take to help in the war against drug resistance
- Explain what is meant by empiric therapy
- List six factors that a clinician would take into consideration before prescribing an antimicrobial agent for a particular patient
- State three undesirable effects of antimicrobial agents
- Explain what is meant by a "superinfection," and cite three diseases that can result from superinfections
- Explain the difference between synergism and antagonism with regard to antimicrobial agents

Chemotherapeutic agents

Any drug used to treat any condition or disease

Antimicrobial agents

antimicrobials are chemotherapeutics

Chemotherapeutic agents used to treat infectious diseases:

Anti-Bacterial

Anti-Viral

Anti-Fungal

Anti-Protozoal

anti-bacterial is the main kind of antimicrobial and is the most important medically

Antibiotic (AB)

A substance produced by a microorganism that is-effective in killing or inhibiting the growth of other organisms

Anti-Bacterial-

what is the difference between antibiotic and antimicrobial ?
a.biotic must be produced by an organism to kill or inhibit another organism
((but))A.microbial might be synthetic or semisynthetic
(A.microbial=semiS,S,produced by mo)(A.biotic=only by mo)
antimicrobials are wider than antibiotics

:**Examples**

Mould-produced: Penicillin, Cephalosporin

Bacteria-produced: Erythromycin, Chloramphenicol

)mainly soil bacteria

Types of Antibiotics/Antimicrobials

Natural AB. 1

e.g. Peniciilin G

, Semisynthetic AB. 2 semisynthetic produced naturally but differences in radicals occur ()

e.g. Modified AB (Ampicillin, Carbenicillin)

aminopenicillin carboxypenicillin

Synthetic Antimicrobials. 3

e.g. Monobactam (Aztreonam)

Alexander flemming discovery(1945 nobel prize for discovery of ABiotic)
-he left the plate open for 2-3 days(in the weekend) microbes in regionA had grown while in region b no microbial growth occurred (why?)due to the presence of organism C which is penicilium (mould that produces penicillin)
fungi came from the surface of the lab

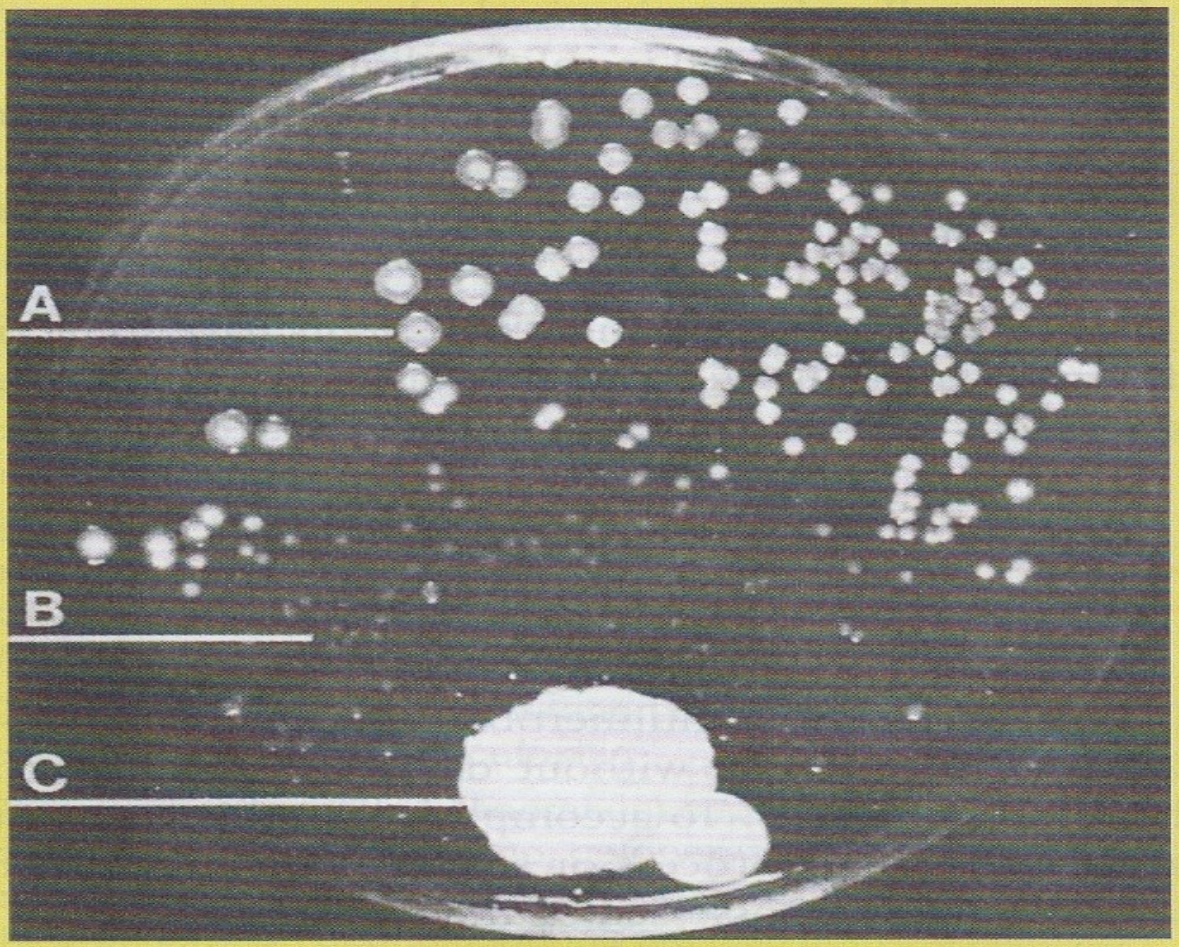


Figure 9-2. The discovery of penicillin by Alexander Fleming. A. Colonies of *S. aureus* (a bacterium) are growing well in this area of the plate. **B.** Colonies are poorly developed in this area of the plate because of an antibiotic (penicillin) being produced by the colony of *P. notatum* (a mould) shown at **(C)**. (This photograph originally appeared in the *British Journal of Experimental Pathology* in 1929.) (From Winn WC Jr, et al. *Koneman's*

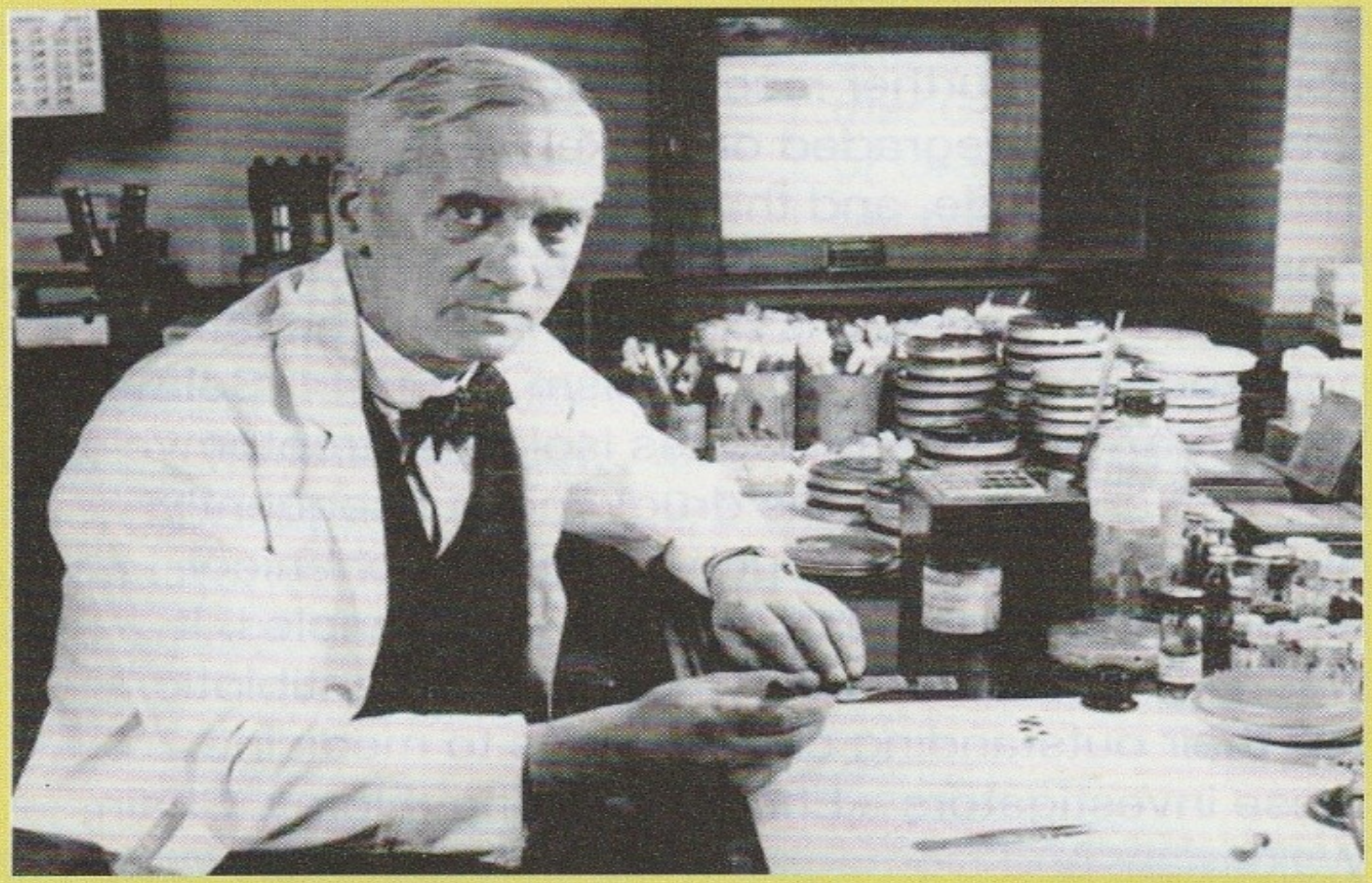


Figure 9-1. Alexander Fleming. (Courtesy of Calibuon at the English Wikibooks project.)

Characteristics of an Ideal Antimicrobial Agent

The ideal antimicrobial agent should:

harmful for the microbial cell but not for the host cell

- Kill or inhibit the growth of pathogens
- Cause no damage to the host (selective toxicity)
- Cause no allergic reaction in the host
- Be stable when stored in solid or liquid form
- Remain in specific tissues in the body long enough to be effective → if the drug was removed in few minutes it wouldn't be effective
- Kill the pathogens before they mutate and become resistant to it

How Antimicrobial Agents Work

To be acceptable, an antimicrobial agent must inhibit or destroy the pathogen without damaging the host (i.e., the infected person). To accomplish this, the agent must target a metabolic process or structure possessed by the pathogen but not possessed by the host.

The five most common mechanisms of action of antimicrobial agents are as follows:

- Inhibition of cell wall synthesis
- Damage to cell membranes
- Inhibition of nucleic acid synthesis (either DNA or RNA synthesis)
- Inhibition of protein synthesis
- Inhibition of enzyme activity

Antibacterial Agents

Bacteriostatic: Inhibit growth of bacteria

-Should NOT be used in immuno -
compromised or leukopenic
patients

Bactericidal: Kill bacteria

Selective toxicity: The drug affects microorganisms but .NOT human cells

Cont./… Antibacterial Agents

classification in this page is with regard to the activity of antimicrobial

Narrow-spectrum antibiotic: Destroy (affect) either gram positive or gram negative bacteria

+Examples: Vancomycin: G+

-Colistin : G-

Broad spectrum antibiotic: Destroy (affect) both gram positive and gram negative bacteria

Examples: Ampicillin -

Chloramphenicol

Tetracycline

Extended spectrum Antibiotics

Broad spectrum antibiotics with extended activity- against certain microbes such as cetain gram negative .bacteria, *Pseudomonas*, or others

pseudomonas the most resistant gram negative bacteria>have the R factor (superbug)

Competitive inhibitors

Example: Sulfonamide

broad spectrum ABiotics doesn't cover all microbes but extended spectrum does

See the Figure

Inhibition of Nucleic Acid synthesis

dihydrpteroate synthetase is an enzyme which works normally on PABA(para amino benzoic acid) to produce folic acid
in the presence of sulfonamides(competitive inhibitor drug)the enzyme is cheated so it will work on sulfonamide instead of PABA and thus no folic acid would be produced >instead nonmetabolite will be produced so the microbe will be killed
^folic acid is necessary for DNAand RNA^

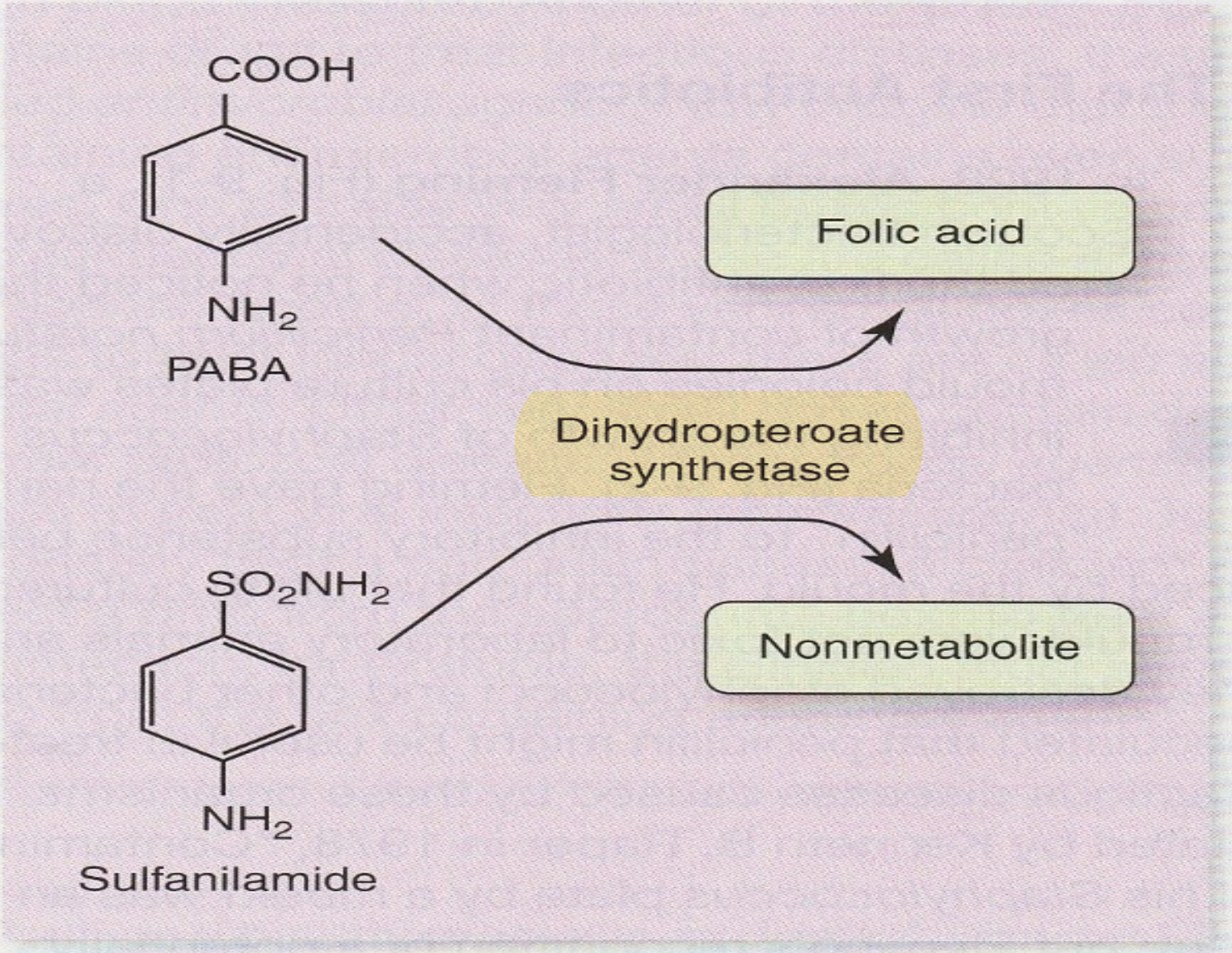


Figure 9-3. The effect of sulfonamide drugs. See text for details.

Inhibition of cell wall synthesis

Interfere with synthesis and cross-linking of peptidoglycan

the most used antibiotic

-affects gram positive mostly

-cross linking means the binding of proteins together in the cell wall

? Human cells are NOT affected; **WHY** *bec they don't have cell walls*

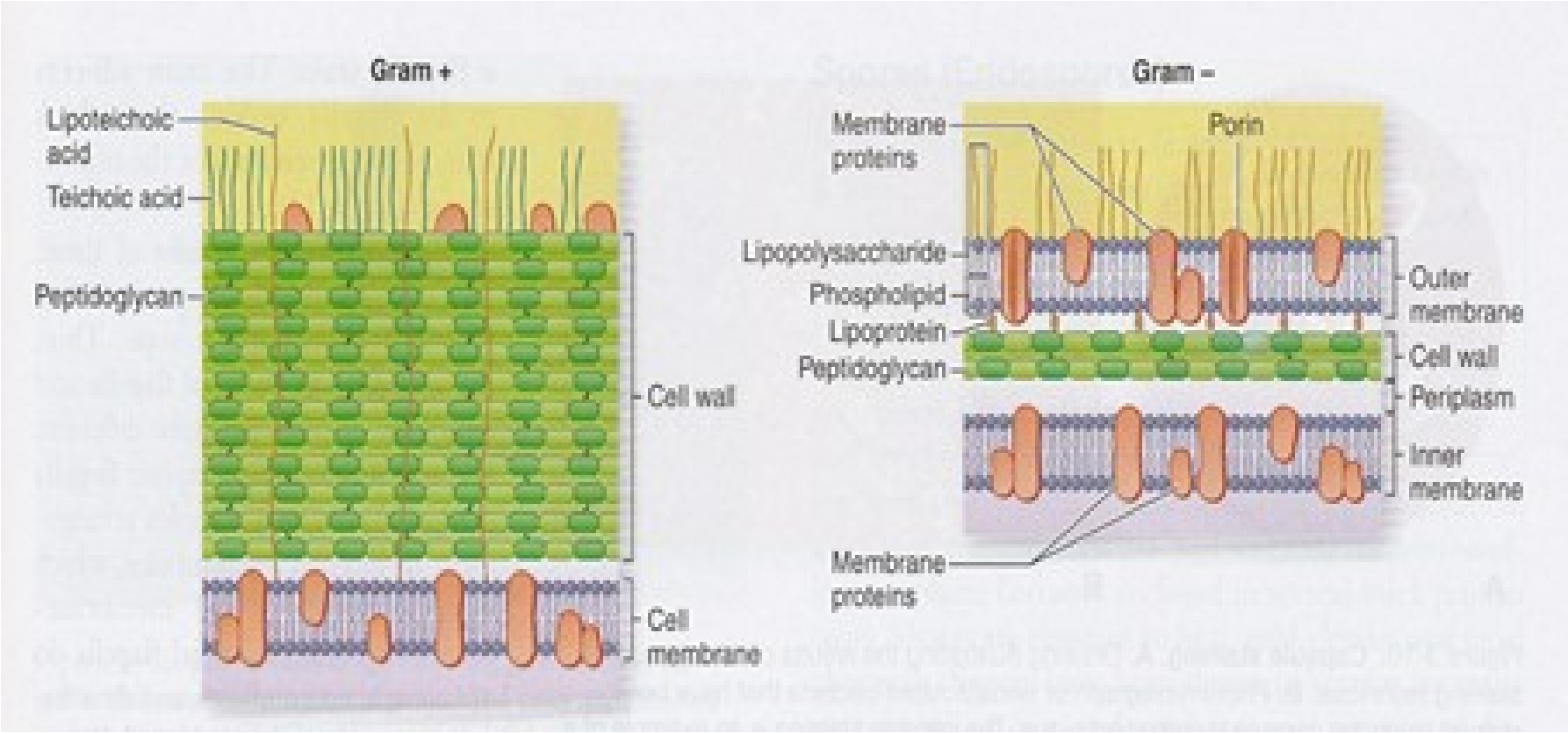


Table 9-2 Antibacterial Agents Listed by Mechanism of Action

Mode of Action	Agent	Spectrum of Activity	Bactericidal or Bacteriostatic
Inhibition of cell wall synthesis	Aztreonam	Gram-negative bacteria	Bactericidal
	Bacitracin (also disrupts cell membranes)	Broad spectrum[a]	Bactericidal
	Carbapenem	Broad spectrum	Bactericidal
	Cephalosporins	Broad spectrum	Bactericidal
	Daptomycin	Broad spectrum	Bactericidal
	Fosfomycin	Broad spectrum	Bactericidal
	Penicillins and semisynthetic penicillins	Broad spectrum	Bactericidal
	Vancomycin	Gram-positive bacteria	Bactericidal

all of cell wall inhibitors are bactericidal
most of them are broad spectrum except aztreonam (G-ve) and vancomycin(G+ve)

-cephalosporins are the most important after penicillins
-daptomycin is used for resistant bacteria
-vancomycin(خط الدفاع الاخير/اخر خيار للطبيب)
when vanomycin is used?when a patient ha take a broad AB that killed normal flora causing super infection by clostridium defficialis that forms pseudomonas colitis in the colon
also we use vancomycin against staphylococcus aureus

Class/Category	Description/Source	Examples of Antibacterial Agents within the Class or Category
Penicillins[a]	Naturally occurring penicillins; produced by moulds in the genus *Penicillium*	Benzylpenicillin (penicillin G), phenoxymethyl penicillin (penicillin V)
	Semisynthetic penicillins: broad-spectrum aminopenicillins	Amoxicillin, ampicillin, bacampicillin, pivampicillin
	Semisynthetic penicillins: broad-spectrum carboxypenicillins	Carbenicillin, ticarcillin
	Semisynthetic penicillins: broad-spectrum ureidopenicillins	Azlocillin, mezlocillin, piperacillin
	Semisynthetic penicillins: penicillinase-resistant penicillins	Cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin
	Penicillin plus β-lactamase inhibitor	Amoxicillin–clavulanic acid (Augmentin), ampicillin–sulbactam (Unasyn), piperacillin–tazobactam (Zosyn), ticarcillin–clavulanic acid (Timentin)

-that table is required for memarizing -only two for each

from the previous page doctor mentioned
-penicillin are the main kind of cell wall inhibotr antibiotics
penicillin V(phenoxymethylpenicillin) is the weakest antibiotic
penicillin G is given IV and IM(very painful)
penicillase resistant AB they make resistant to the cleavage of beta lactam by penicillase(also known as beta lactamase)
penicillin plus Beta lactamase inhibitor :the mechanics is that the inhibitor is like a shield against Blactamase produced by bacteria

الالية تبعت الانهيبيتور عبارة عن درع ضد الانزيم المفرز من البكتيريا ضد هاي المضادات كوسيلة مقاومة

Penicillins *which have got beta lactam ring*

Beta-lactam drugs-

Act on actively dividing bacteria-

Are bactericidal-

: **Natural penicillin**-

Penicillin-G, Penicillin-V •

,Against: G+ such as Strep., some anaerobes •

Spirochetes

G-: *N. meningitidis*, *H. influenzae*

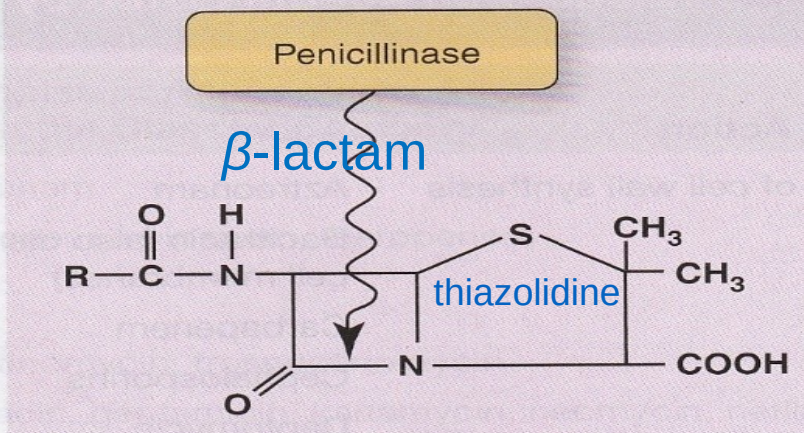
: **Aminopenicillin and Extended penicillin** -

Against G- and G+ bacteria •

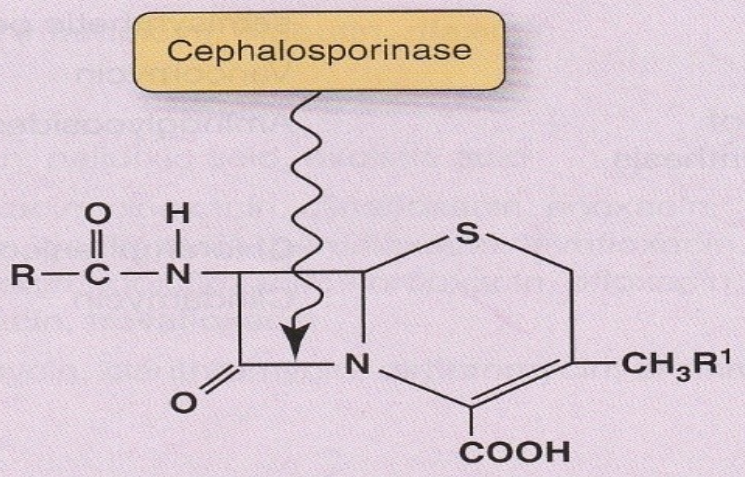
if we use a drug that inhibits the growth of microbes(bacteriostatic)then used with it penicillin>>penicillin wouldn't work as it works on actively dividing bacteria

penicillin is made of two rings:thiazolidine and beta lactam Blactam can be broken by penicillase or cephalosporinase

it mainly works on G+ve and a little bit on G-ve



Penicillin



Cephalosporin

Figure 9-4. Sites of β-lactamase attack on penicillin and cephalosporin molecules. See text for details.

Cephalosporins[a]

Derivatives of fermentation products of the mould, *Cephalosporium acremonium (now called Acremonium strictum)*

ist gen:work mainly on G+ve and some G-ve(narrow)
2nd gen:G+ve mainly but extended againstG-ve
3rd gen:G+ve mainly and more G-ve(those that were not in 1st and 2nd like pneumonas)
4th gen:G+ve mainly ,more extended on G-ve
5th gen:G+ve which are highly resistant to other drugs and weaker activity on G-ve

Narrow-spectrum (first-generation) cephalosporins: cephadroxil, cefazolin, cephalexin, cephalothin, cephaloridine, cephapirin, cephradine; first-generation cephalosporins have good activity against Gram-positive bacteria and relatively modest activity against Gram-negative bacteria

Expanded-spectrum (second-generation) cephalosporins: cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef; second-generation cephalosporins have increased activity against Gram-negative bacteria

Cephamycins (second-generation cephalosporins): cefmetazole, cefotetan, cefoxitin

Broad-spectrum (third-generation) cephalosporins: cefdinir, cefditoren, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftibuten, ceftizoxime, ceftriaxone; third-generation cephalosporins are less active against Gram-positive bacteria than first- and second-generation cephalosporins but are more active against members of the Enterobacteriaceae family and *P. aeruginosa*

Extended-spectrum (fourth-generation) cephalosporins: cefepime, cefpirome; fourth-generation cephalosporins have increased activity against Gram-negative bacteria

- **Fifth generation (e.g. Ceftaroline):**

G+ including methicillin-resistant *Staph*. (MRSA), VISA, VRSA, and weaker activity against **G-** bacteria

Cephalosporins

+First generation: G. 1

-Second generation: Increased activity G. 2

+)besides G (

Third generation: Greater G- & *Pseudomonas*. 3

)besides G+, but less (

+ Fourth generation: Greater G-/*Pseudo* & G. 4

Fifth generation (e.g. Ceftaroline): **G+** as methicillin-. 5
-resistant *Staph*. & weaker on **G**

Cont./... Beta-lactam drugs

Class/Category	Description/Source	Examples of Antibacterial Agents within the Class or Category
Monobactam[a]	Synthetic drug	Aztreonam
Carbapenems[a]	Imipenem is a semisynthetic derivative of thienamycin, produced by *Streptomyces* spp.	Ertapenem, imipenem, meropenem
Glycopeptide	Produced by *Streptomyces orientales*	Vancomycin
Fosfomycin	Originally produced by *Streptomyces* spp.	

Monobactams

Beta-lactam drug-

synthetic drug

Active against gram negative rods-

Not against gram positive bacteria

Not against anaerobes

Example: Aztreonam

Carbapenems

Beta lactam drug-

Active against most **G+, G-**, and **anaerobes-**

DHL:dihydropeptidase is an enzyme produced by renal tubules
impinem is protected from this enzyme by a coat called cilastatin

Examples-

Imipenem: Inactivated by **dihydropeptidase** •

protected by Cilastatin); DHP; renal tubules (

Meropenem: Not inactivated by DHP enzyme •

Ertapenem: Not *P. aeruginosa*, is long acting •

Damage to cell membrane

Polypeptides	Originally derived from *Bacillus polymyxa*	Polymyxins: polymyxin B, polymyxin E (colistin)
	Originally isolated from *Bacillus licheniformis* (formerly named *Bacillus subtilis*)	Bacitracin

polymoxins are rarely used

Disruption of cell membranes	Polymyxin B and polymyxin E (colistin)	Gram-negative bacteria	Bactericidal

Inhibition of Protein synthesis

Inhibition of protein synthesis	Aminoglycosides	Primarily Gram-negative bacteria and *S. aureus*; not effective against anaerobes	Bactericidal
	Chloramphenicol	Broad spectrum	Bacteriostatic
	Clindamycin	Most Gram-positive bacteria and some Gram-negative bacteria; highly active against anaerobes	Bacteriostatic or bactericidal, depending upon drug concentration and bacterial species
	Erythromycin and other macrolides	Most Gram-positive bacteria and some Gram-negative bacteria	Bacteriostatic (usually); bactericidal at higher concentrations
	Ketolides	Broad spectrum	Bacteriostatic
	Linezolid	Gram-positive bacteria	Bacteriostatic
	Mupirocin	Broad spectrum	Bacteriostatic
	Streptogramins	Primarily Gram-positive bacteria	Bactericidal
	Tetracyclines	Broad-spectrum and some intracellular bacterial pathogens	Bacteriostatic

clindamycin in low doses is bacteriostatic while in high doses is bactericidal

no bacteria is resistant to it

very expensive(new drug)

US$154 in the United States per 600 mg pill

Aminocyclitol	Produced by *Streptomyces spectabilis*	Spectinomycin, trospectinomycin
Aminoglycosides	Naturally occurring antibiotics or semisynthetic derivatives from *Micromonospora* spp. or *Streptomyces* spp.	Amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromycin, sisomicin, streptomycin, tobramycin
Macrolides	Erythromycin is produced by *Streptomyces erythraeus*; the others are natural analogs of erythromycin or semisynthetic antibiotics	Azithromycin, clarithromycin, dirithromycin, erythromycin
Ketolides	Semisynthetic derivative of erythromycin	Telithromycin
Tetracyclines	Tetracycline is produced by *Streptomyces rimosus*; the others are semisynthetic antibiotics	Chlortetracycline, oxytetracycline, demeclocycline, methacycline, doxycycline, minocycline, tetracycline
Lincosamides	Lincomycin was initially isolated from *Streptomyces lincolnnensis*; clindamycin is a semisynthetic antibiotic	Clindamycin, lincomycin
Streptogramin	Produced by *Streptomyces* spp.	Quinupristin–dalfopristin
Oxazolidinone	Synthetic drug	Linezolid
Chloramphenicol	Originally produced by *Streptomyces venezuelae*	

(for information)

Tetracyclines

Broad-spectrum (e.g. Tetracycline, Doxycycline)-

Action on ribosome (inhibit protein synthesis)-

Bacteriostatic-

:Effective against-

if a patient took tetracycline with penicillin what happens?not favored at all tetracyclines are bacteriostatic while penicillins work on actively dividing bacteria

G+ and G- bacteria

Chlamydia

Mycoplasma

Rickettsias

Vibrio cholerae

Spirochete (*Borrelia*, *Treponema pallidum*)

Macrolides

Inhibit protein synthesis -

- Bacteriostatic (low doses) -
- Bactericidal (Higher doses)

:Effective against -

Many G+, some G- bacteria .

Chlamydia .

Mycoplasma .

T. pallidum .

Legionella *comes from air conditioning system(from its water)it makes pneumonia* .

Erythromycin, Clarithromycin-

Aminoglycosides

+,Broad-spectrum (against many G-, some G-

):**?**NOT anaerobes, **WHY**

Enterobacteriaceae •

V. cholera •

P. aeruginosa •

Bactericidal-

Inhibit protein synthesis-

Ototoxic, Nephrotoxic-

Example: Gentamicin, Amikacin-

Inhibition of Nucleic Acid Synthesis

Inhibition of nucleic acid synthesis	Rifampin	Gram-positive and some Gram-negative bacteria (e.g., *Neisseria meningitidis*)	Bactericidal
	Quinolones and fluoroquinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin)	Broad spectrum	Bactericidal
Destruction of DNA	Metronidazole	Effective against anaerobes	Bactericidal

Rifamycins	Semisynthetic antibiotics derived from compounds produced by *Streptomyces mediterranei*	Rifampin (rifampicin), rifabutin, rifaximin
Quinolones	Synthetic drugs	Cinoxacin, nalidixic acid, oxolinic acid
Fluoroquinolones	Synthetic drugs	Ciprofloxacin, cinoxacin, clinafloxacin, enoxacin, fleroxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin
Nitroimidazoles	Synthetic drug	Metronidazole, tinidazole
Nitrofurantoin	Synthetic drug	

(for information)

Fluoroquinolones

- Bactericidal

- Inhibit DNA synthesis

- Example: Ciprofloxacin; effective against:
  Enterobacteriaceae.
  P. aeruginosa.

Inhibition of enzyme activity	Sulfonamides	Primarily Gram-positive bacteria and some Gram-negative bacteria	Bacteriostatic
	Trimethoprim	Gram-positive and many Gram-negative bacteria	Bacteriostatic

Trimethoprim/sulfamethoxazole (**TMP 1/SMX 5; e.g. 40/200 or 80/400**), is also known as:

Co-trimoxazole

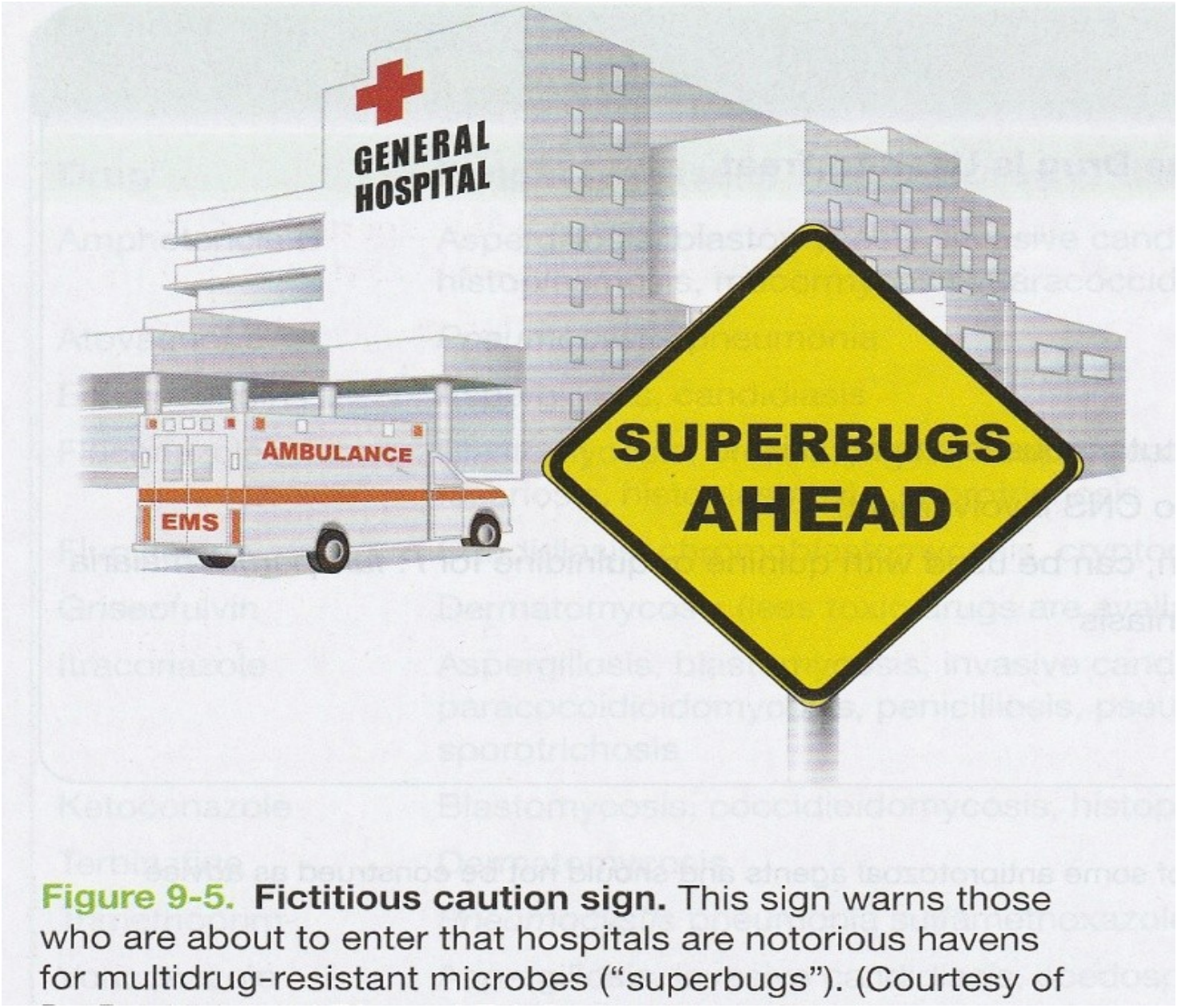


Figure 9-5. Fictitious caution sign. This sign warns those who are about to enter that hospitals are notorious havens for multidrug-resistant microbes ("superbugs"). (Courtesy of