Pharmacology I

Principles of Antimicrobial Therapy

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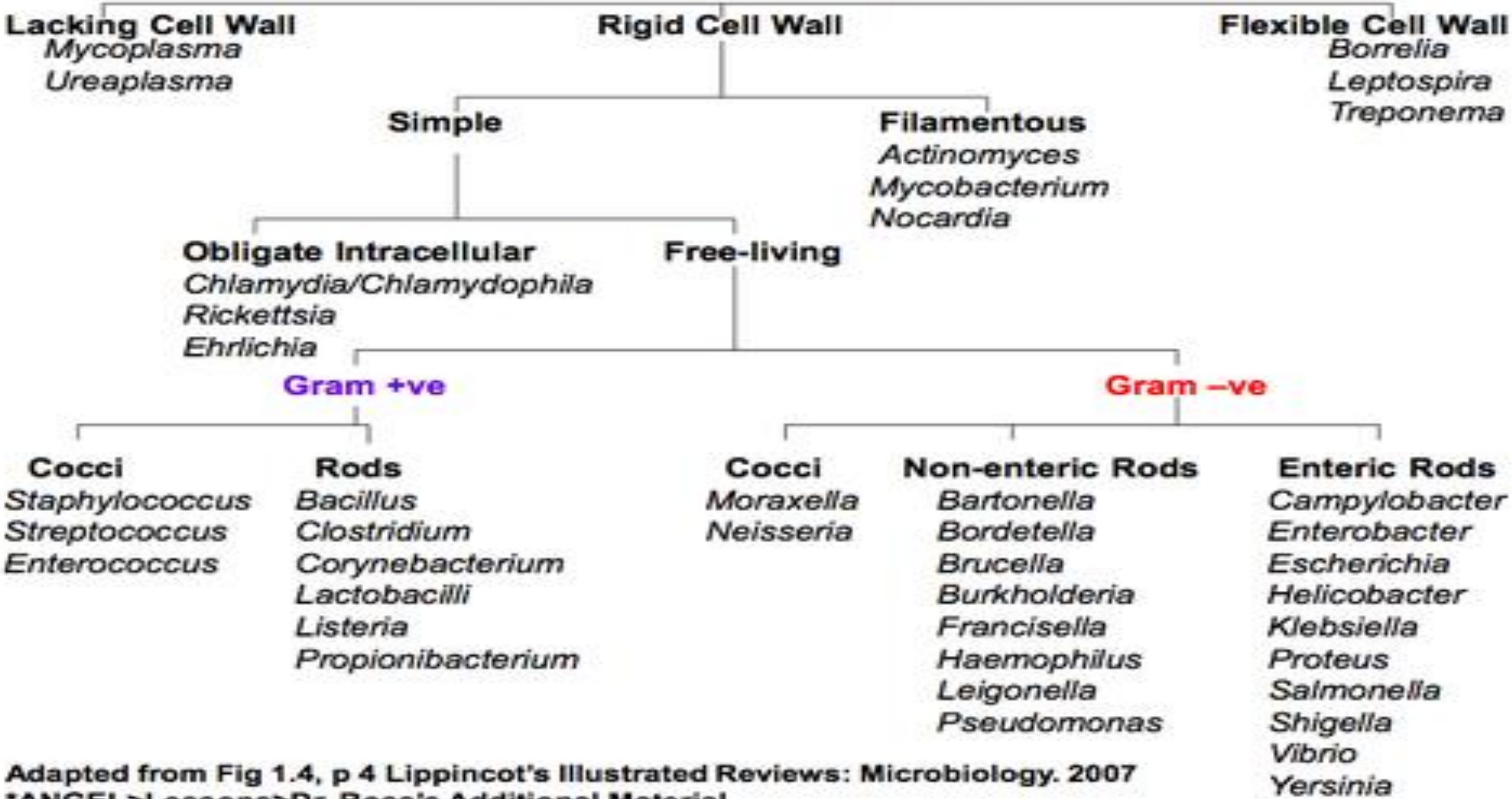
Lecture No. : 7

MEDICALLY IMPORTANT BACTERIA



Adapted from Fig 1.4, p 4 Lippincot's Illustrated Reviews: Microbiology. 2007

*ANGEL>Lessons>Dr. Ross's Additional Material

Principles of Antimicrobial Therapy

- Antimicrobial therapy takes **advantage** of the **biochemical differences** that exist between microorganisms and human beings.
- Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, *they have the ability to injure or kill an invading microorganism without harming the cells of the host*.
- In most instances, the ***selective toxicity is relative*** rather than absolute, requiring that the **concentration of the drug be carefully controlled** to attack the microorganism, while still being tolerated by the host.

Selection of antimicrobial agents

❑ Selection of the most appropriate antimicrobial agent requires knowing:

1) The organism's identity

2) The organism's susceptibility to a particular agent

3) The site of the infection

4) Patient factors

5) The safety of the agent and

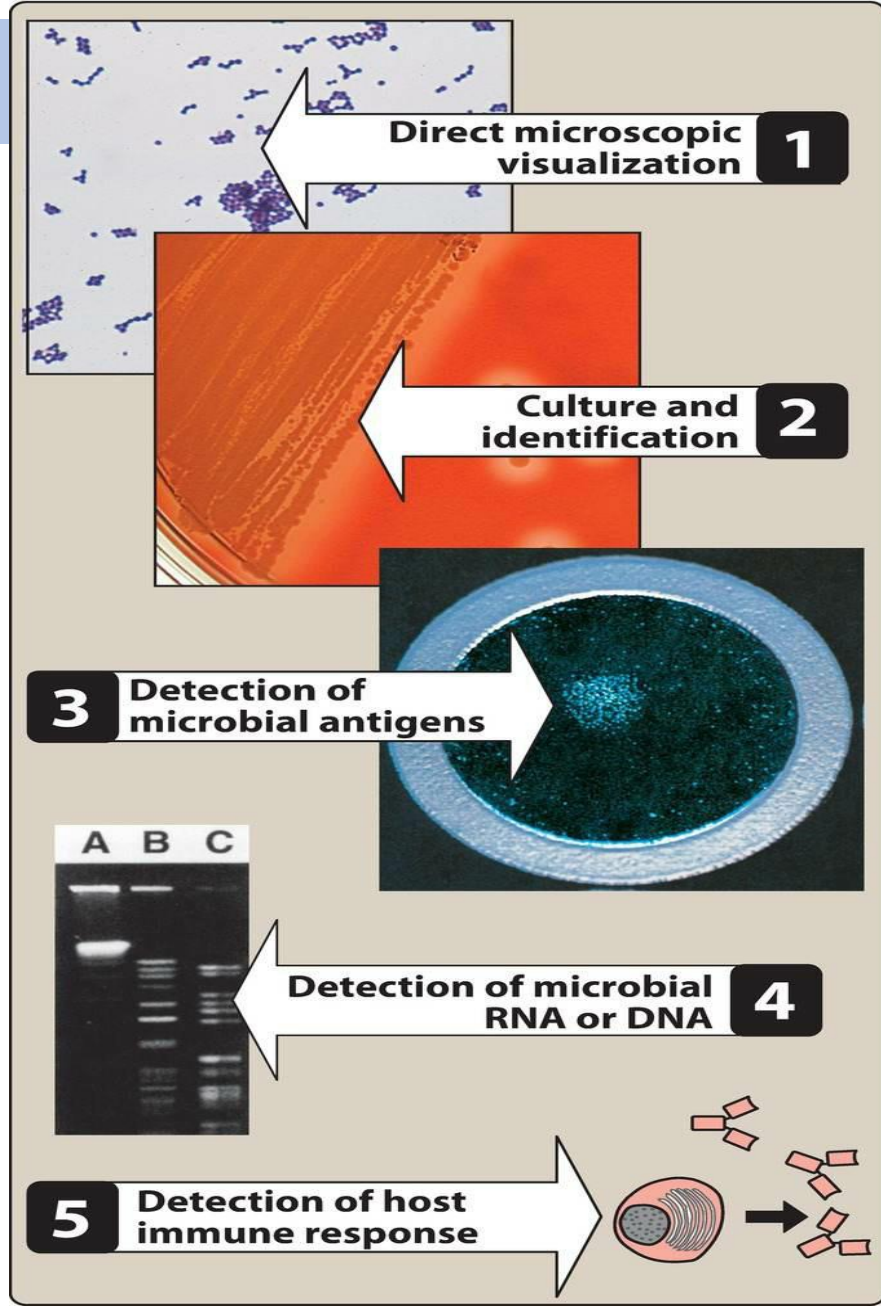
6) The cost of therapy.

- However, some patients require **empiric therapy** (immediate administration of drug(s) prior to bacterial identification and susceptibility testing)

A. Identification of the infecting organism

- A rapid assessment of the nature of the pathogen can sometimes be made ***on the basis of the Gram stain,*** which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine).

Note :it is essential to obtain a sample culture of the organism prior to initiating treatment. Otherwise, it is impossible to differentiate whether a negative culture is due to the absence of organisms or is a result of antimicrobial effects of administered antibiotic



Some laboratory techniques that are useful in the diagnosis of microbial diseases.

B. Empiric therapy prior to identification of the organism

- **Ideally**, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established.

1- Timing:

- **Acutely ill patients** with infections of unknown origin
- For example:
- **A neutropenic patient** (a reduction in neutrophils) or
- **Sepsis**
- **Meningitis** (acute inflammation of the membranes covering the brain and spinal cord) ***require immediate treatment***.

- If possible, **therapy** *should be initiated* ***after specimens for laboratory*** *analysis have been obtained but before the results of the culture and sensitivity are available.*

2. Selecting a drug:

- **Broad-spectrum therapy** may be indicated initially when the organism is unknown or polymicrobial infections are likely.
- For example, **gram-positive cocci** in the spinal fluid of a newborn infant is most likely to be ***Streptococcus agalactiae*** which is sensitive to **penicillin G**.
- By contrast, **gram-positive cocci** in the spinal fluid of a 40-year-old patient are most likely to be ***S. pneumoniae***. This organism is *frequently* ***resistant*** to penicillin G and often requires treatment with a **high-dose third generation cephalosporin (such as ceftriaxone) or vancomycin**.

C. Determining antimicrobial susceptibility of infective organisms:

- Some pathogens, such as ***Streptococcus pyogenes*** and ***Neisseria meningitidis***, usually have predictable susceptibility patterns to certain antibiotics.
- In contrast, ***most gram-negative bacilli, enterococci,*** **and** ***staphylococcal species*** often show ***unpredictable*** *susceptibility patterns and require susceptibility testing* to determine appropriate antimicrobial therapy.
- The minimum inhibitory (MIC) and bactericidal concentrations (MBC) of a drug can be experimentally determined.

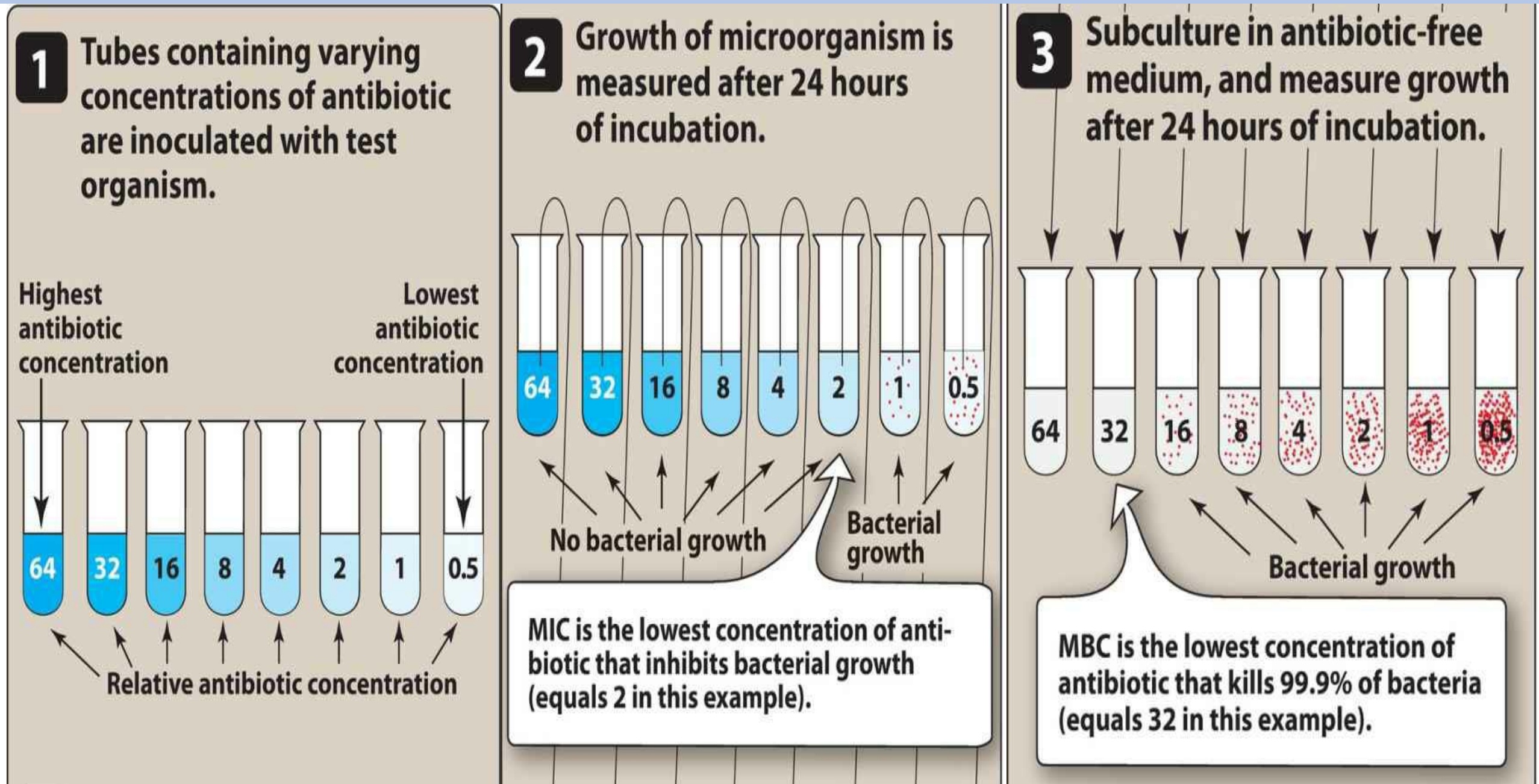
2. Minimum inhibitory concentration:

- The minimum inhibitory concentration (MIC) is the lowest antimicrobial concentration that **prevents visible growth** of an organism after 24 hours of incubation.

3. Minimum bactericidal concentration:

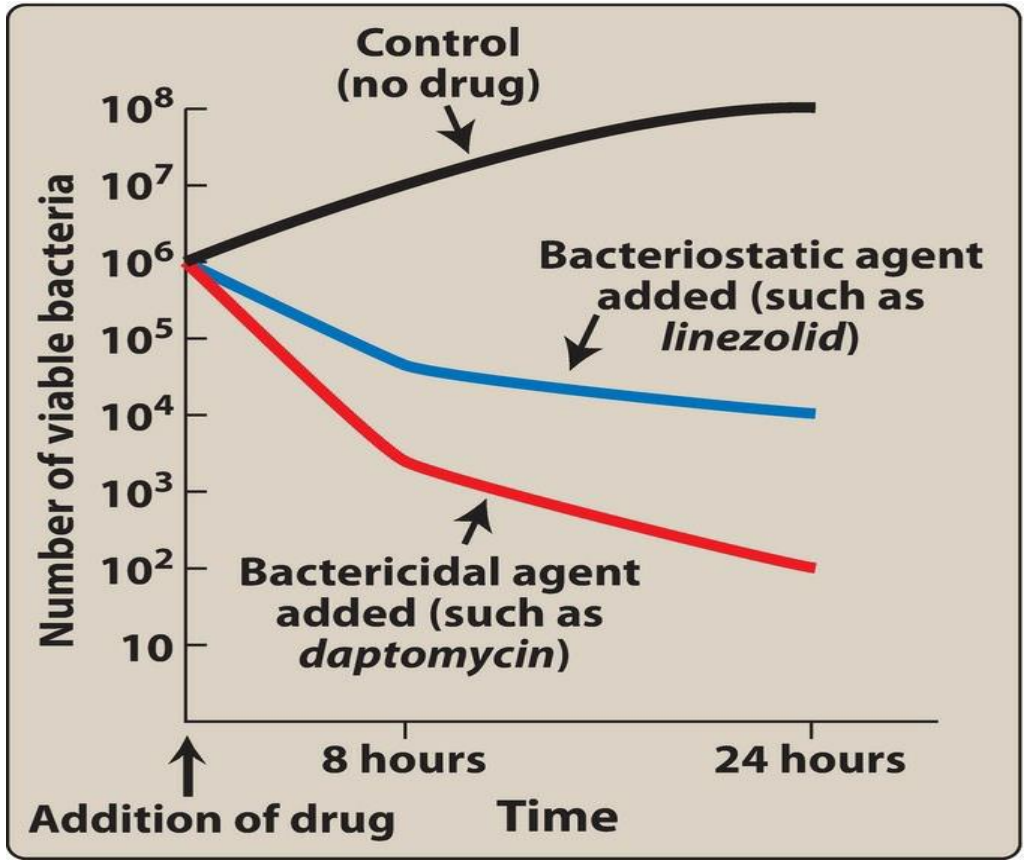
- The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a **99.9% decline in colony count** after overnight broth dilution incubations.

C. Determining antimicrobial susceptibility of infective organisms:



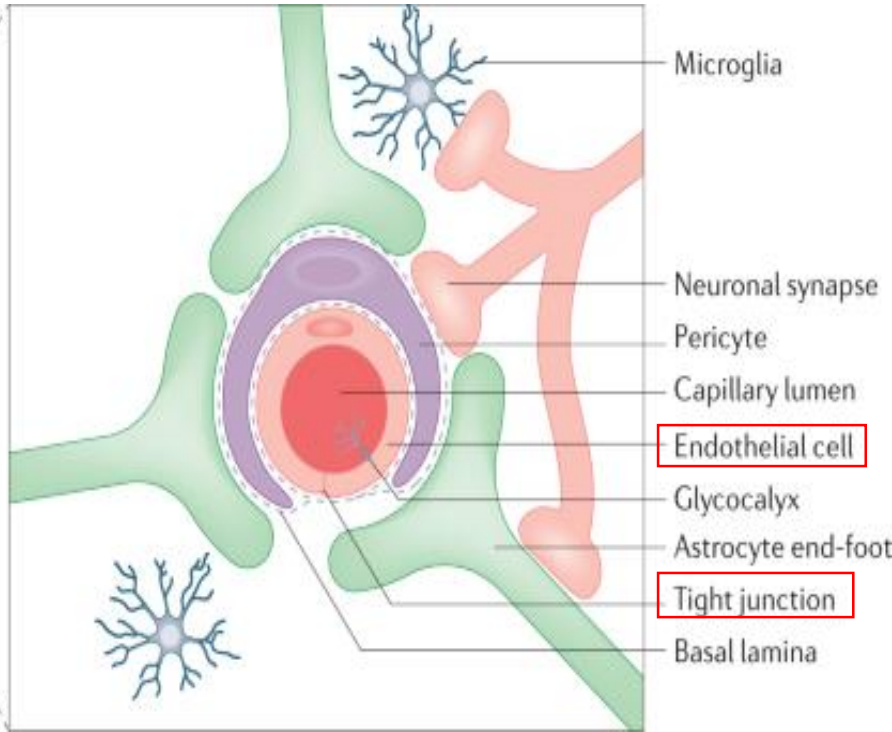
1. Bacteriostatic versus bactericidal drugs:

- Antimicrobial drugs are classified as either **bacteriostatic or bactericidal.**
- **Bacteriostatic drugs** arrest the growth and replication of bacteria at serum(or urine) levels
- **Bactericidal drugs** kill bacteria at drug serum levels achievable in the patient.
- Because of their ***more aggressive antimicrobial action***, **bactericidal** agents are often the drugs of choice in **seriously ill and immunocompromised patients**.



D. Effect of the site of infection on therapy:

- **The blood–brain barrier BBB**: This barrier is formed by the single layer of endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are ***small and lipophilic***.



D. Effect of the site of infection on therapy:

- **The penetration and concentration of an antibacterial agent in the CSF are particularly influenced by the following:**

1. Lipid solubility of the drug.

2. Molecular weight of the drug.

3. Protein binding of the drug.

Factors influence drug penetration into CSF through BBB

1-Lipid solubility of the drug:

- **Lipid soluble drugs**, such **as chloramphenicol and metronidazole**, have significant penetration into the CNS,
- whereas **β-lactam antibiotics**, such as **penicillin**, are *ionized at physiologic pH and have* ***low solubility in lipids***.
- In infections such as meningitis, the barrier does not function as effectively, and local permeability is increased.
- *Some β-lactam antibiotics can enter the CSF in therapeutic amounts when the meninges are inflamed*.

Factors influence drug penetration into CSF through BBB

2. Molecular weight of the drug:

- A compounds with a high molecular weight (for example,vancomycin) penetrate poorly, even in the presence of meningeal inflammation.

3. Protein binding of the drug:

- A high degree of protein binding of a drug restricts its entry into the CSF.

E. Patient factors affect selection of Antimicrobial

- **The condition of the patient also affects selection of the antimicrobial agent.**

1. Immune system

2. Renal dysfunction

3. Hepatic dysfunction

4. Poor perfusion

5. Age

6. Pregnancy and lactation

7. Risk factors for multidrug-resistant organisms

E. Patient factors affect selection of Antimicrobial

- **The condition of the patient also affects selection of the antimicrobial agent.**

1. Immune system:

- Alcoholism, diabetes, HIV infection, malnutrition, autoimmune diseases, pregnancy, or advanced age can affect A patient's immunocompetence.
- High ***doses of bactericidal agents*** *or* ***longer courses*** of treatment may be required.

E. Patient factors affect selection of Antimicrobial

2. Renal dysfunction:

- Poor kidney function may cause accumulation of certain antibiotics. (For eg, vancomycin, aminoglycosides)

3. Hepatic dysfunction:

- Antibiotics that are concentrated or eliminated by the liver (for example, erythromycin and doxycycline) must be used with caution when treating patients with liver dysfunction.

E. Patient factors

4. Poor perfusion:

- Decreased circulation to an anatomic area, such as the lower limbs of a diabetic patient, reduces the amount of antibiotic that reaches that area, making these infections difficult to treat.

E. Patient factors

5. Age:

- Renal or hepatic elimination processes are often **poorly developed in newborns**, making neonates particularly vulnerable to the toxic effects of *chloramphenicol and sulfonamides*.
- **Young children** should not be treated with **tetracyclines or quinolones**, which affect bone growth and joints, respectively.
- **Elderly patients** may have decreased renal or liver function, which may alter the pharmacokinetics of certain antibiotics.

E. Patient factors

6. Pregnancy and lactation:

- Many antibiotics cross the placental barrier or enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

E. Patient factors

7. Risk factors for multidrug-resistant organisms

- Infections with **multidrug-resistant pathogens** need broader antibiotic coverage when initiating empiric therapy. Common risk factors for infection with these pathogens include:

1. Prior antimicrobial therapy in the preceding 90 days,
2. Hospitalization for greater than 2 days within the preceding 90 days,
3. Current hospitalization exceeding 5 days,
4. Admission from a nursing home,
5. high frequency of resistance in the community or local hospital unit (assessed using hospital antibiograms), and
6. immunosuppressive diseases and/or therapies.

CATE-GORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfamethoxazole*
D	Human fetal risk present, but benefits may outweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy	

Figure 37.4
FDA categories of antimicrobials and fetal risk.

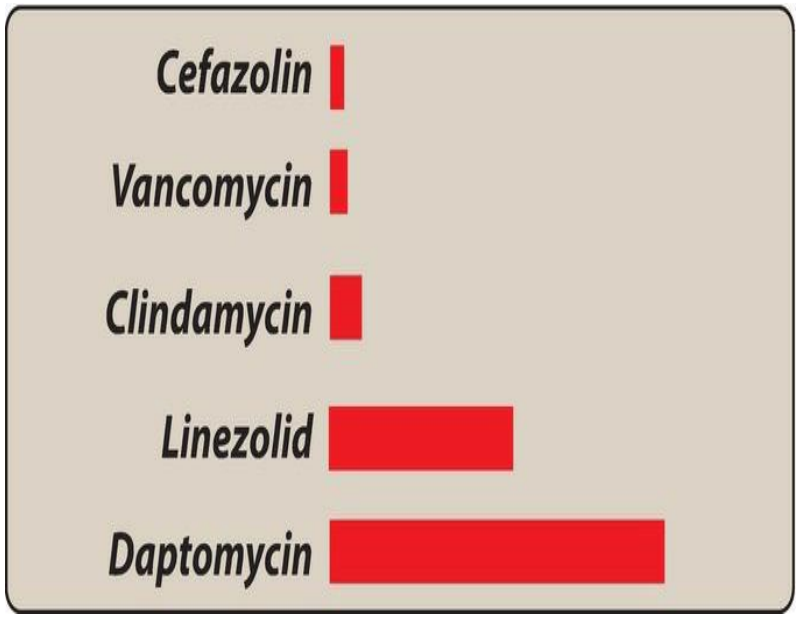
F. Safety of the agent

- Antibiotics such as the penicillins are among the least toxic of all drugs because they interfere with a site or function unique to the growth of microorganisms.
- Other antimicrobial agents (for example, chloramphenicol) have **less specificity** and are **reserved *for life-threatening infections*** because of the potential for serious toxicity to the patient.

G. Cost of therapy

- Often several drugs may show similar efficacy in treating an infection but vary widely in cost.
- For example, treatment of **methicillin-resistant Staphylococcus aureus** (MRSA) generally includes one of the following:

1. **Vancomycin,**
2. **Clindamycin,**
3. **Daptomycin,**
4. **Linezolid.**



Relative cost of some drugs used for the treatment of Staphylococcus aureus.

Route of Administration

- The **oral route** of administration is appropriate for **mild infections** that can be treated **on an outpatient basis**.
- **In hospitalized patients** requiring **intravenous therapy initially**, the **switch to oral agents** should occur as soon as possible.
- However, some antibiotics, *such as vancomycin, the aminoglycosides, and amphotericin B* are so poorly absorbed from the gastrointestinal (GI) tract that adequate serum levels cannot be obtained by oral administration.
- **Parenteral administration** is used for drugs **that are poorly absorbed from the GI tract** and for **treatment of patients with serious infections**.

Determinants of Rational Dosing

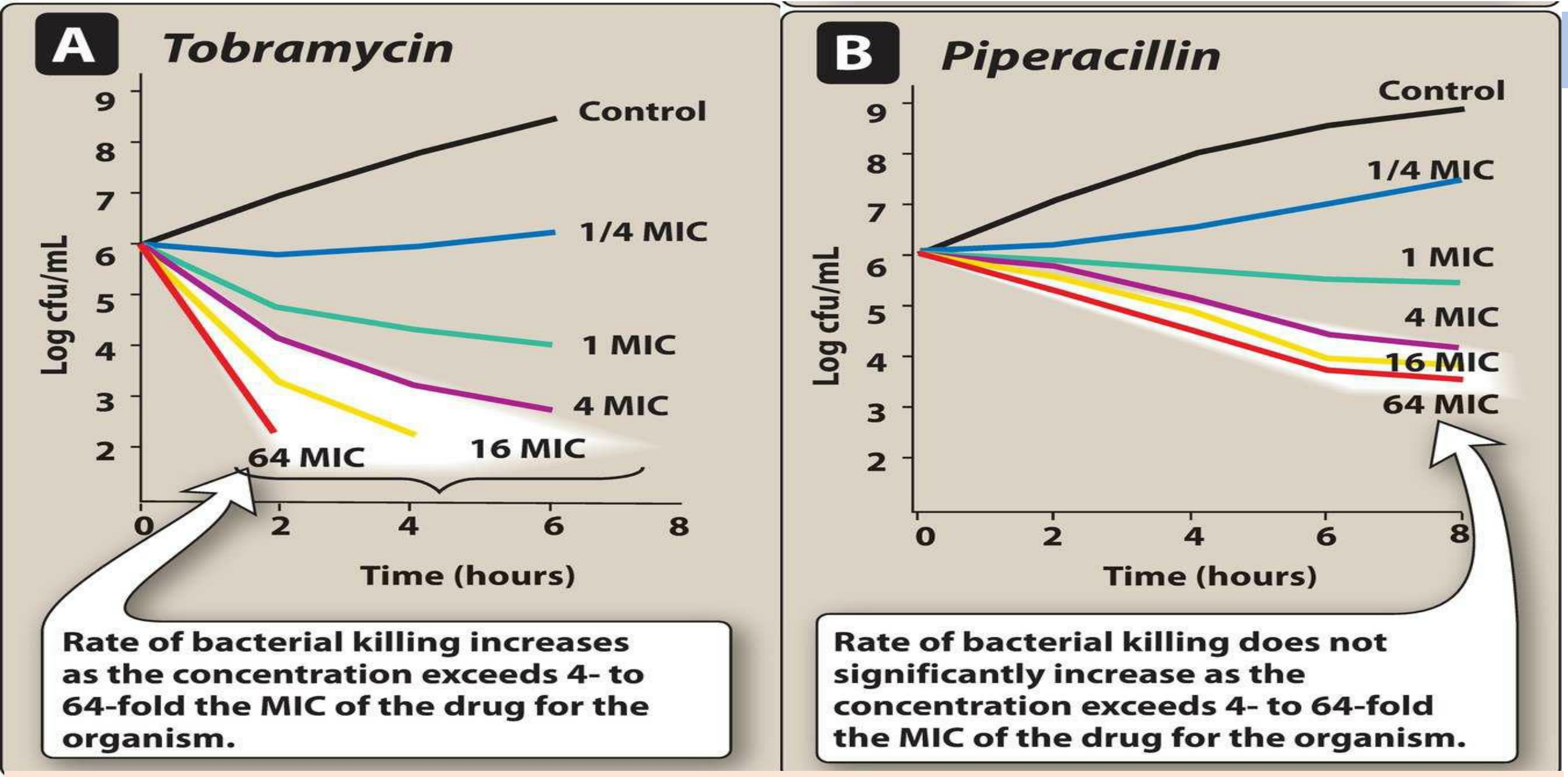
A. Concentration-dependent killing

- Certain antimicrobial agents, including ***aminoglycosides and daptomycin***, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism.
- Giving drugs **once-a-day bolus infusion** achieves high peak levels, favoring rapid killing of the infecting pathogen.

Determinants of Rational Dosing

B. Time-dependent (concentration-independent) killing

- In contrast, ***β-lactams, glycopeptides, macrolides, clindamycin, and linezolid*** do not exhibit concentration-dependent killing.
- The clinical efficacy of these antimicrobials is best predicted by the **percentage of time that blood concentrations of a drug remain above the MIC**.
- This effect is sometimes called **concentration-independent or time-dependent killing**.



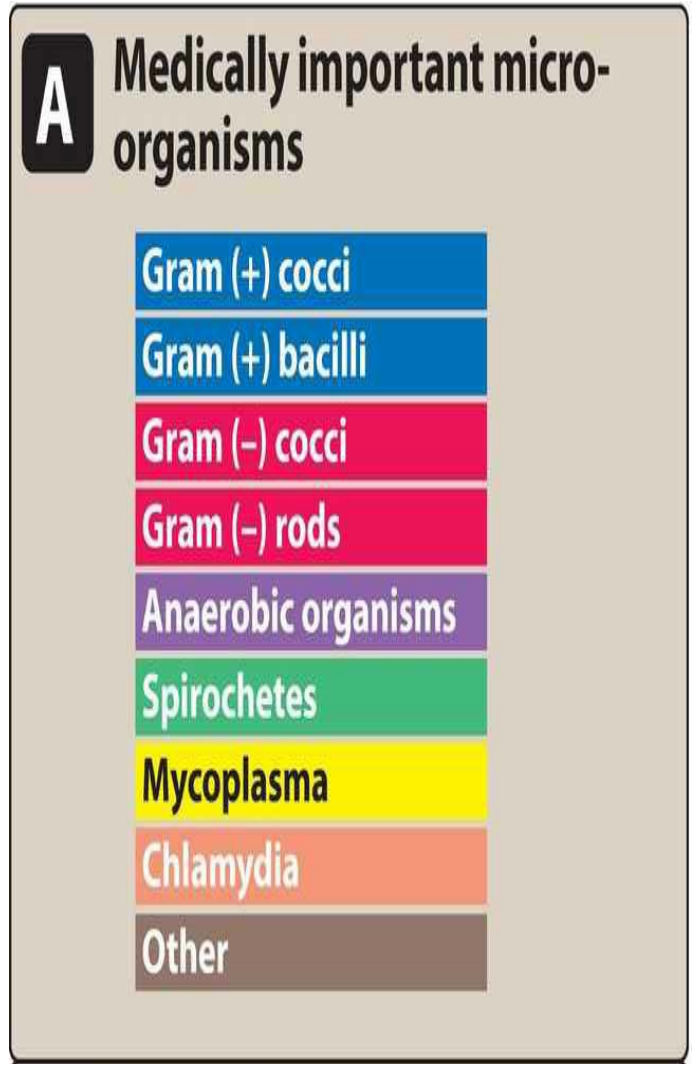
A. Significant dose-dependent killing effect shown by tobramycin. B. Non-significant dose-dependent killing effect shown by piperacillin **cfu** = colony-forming units;

C. Postantibiotic effect: PAE

- The PAE is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.
- Antimicrobial drugs exhibiting a long PAE (for example, **aminoglycosides** and **fluoroquinolones**) **often require only one dose per day, particularly against gram negative bacteria**.

Chemotherapeutic Spectra

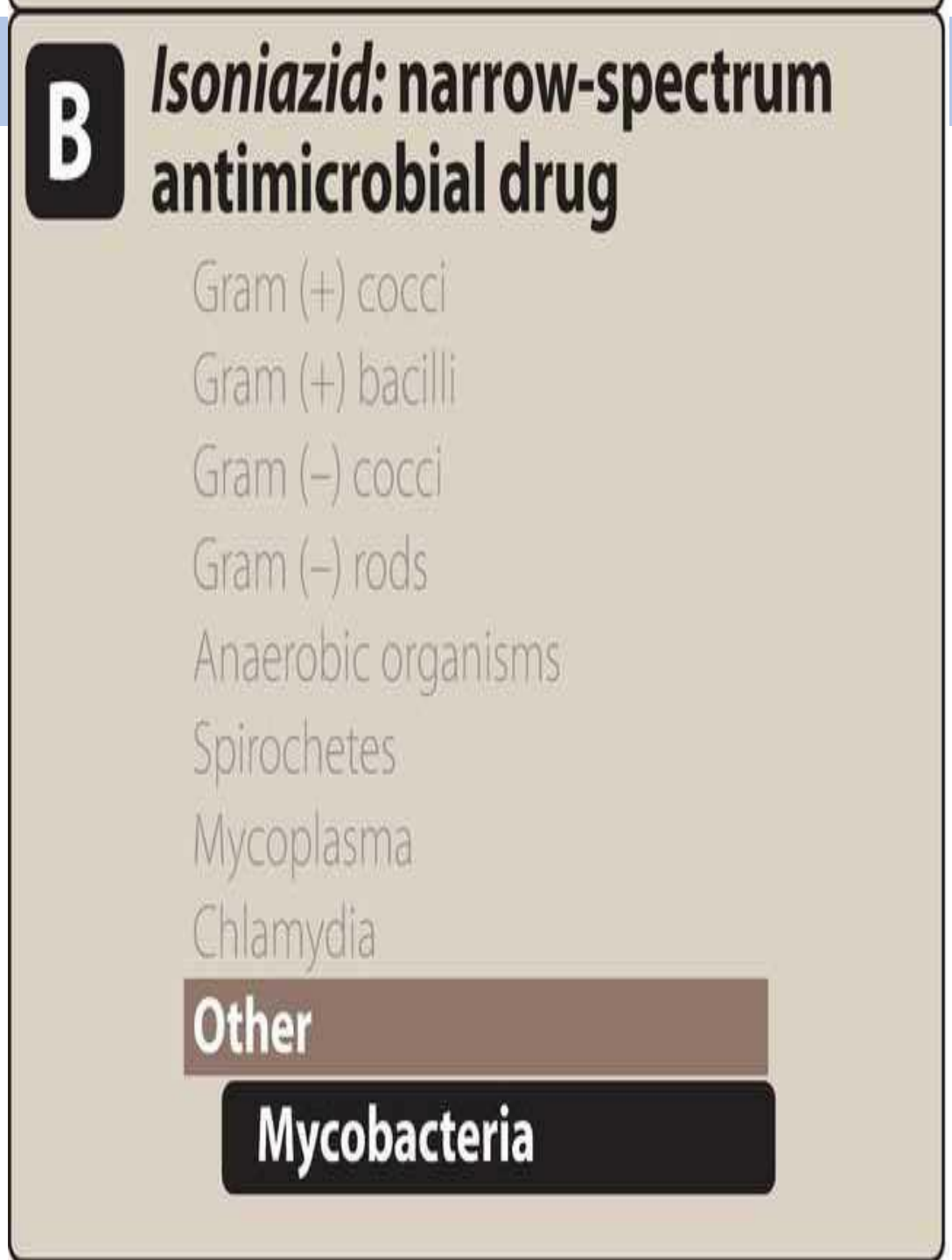
- The clinically important bacteria have been organized into eight groups *based on* ***Gram stain, morphology, and biochemical or other characteristics***.
- They are represented as a color-coded list (A).
- The ninth section of the list is labeled “Other,” and it is used to represent any organism not included in one of the other eight categories.
- In (B–D), the list is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.



Chemotherapeutic Spectra

A. Narrow-spectrum antibiotics

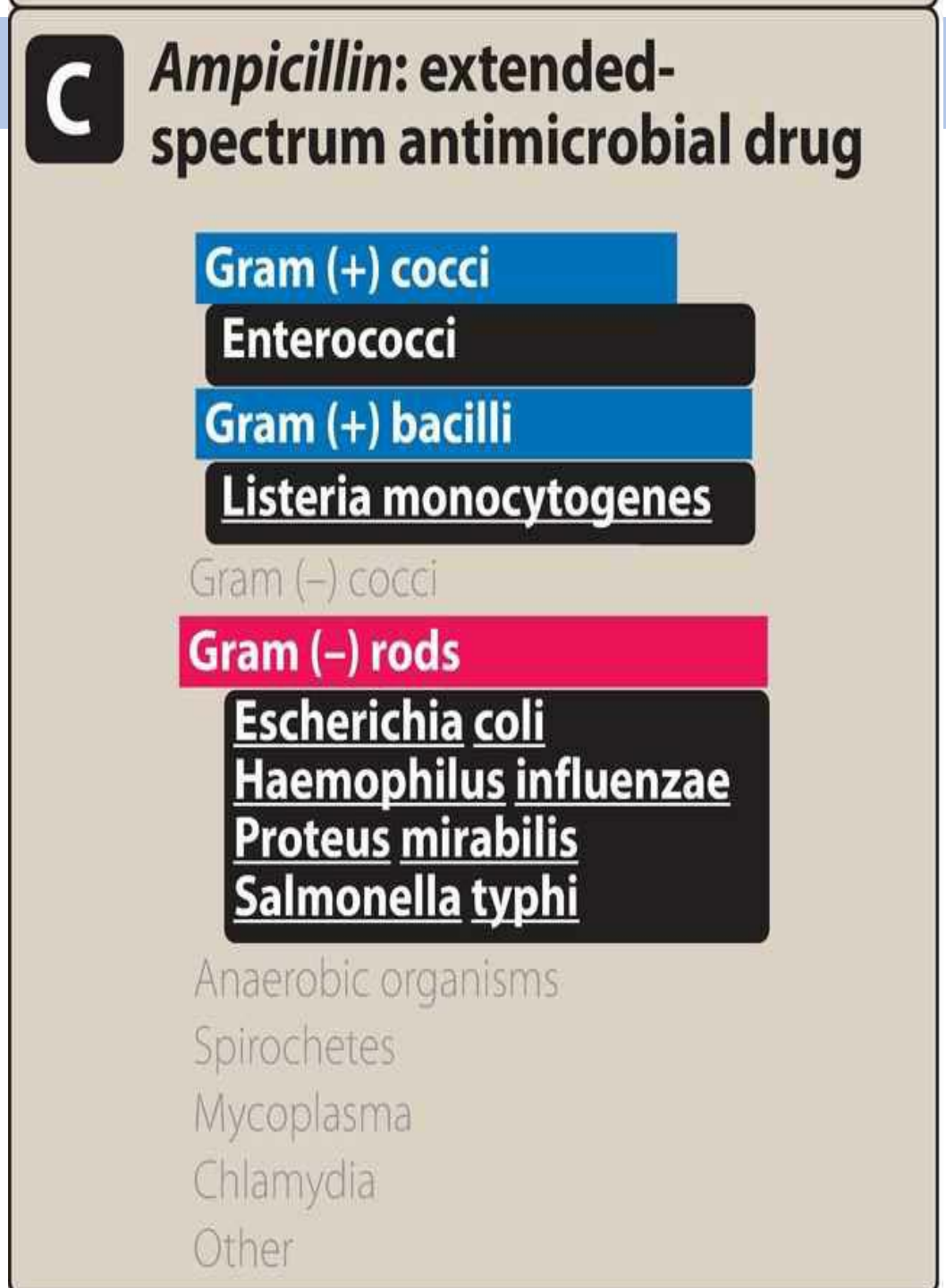
- Agents acting only on a single or a limited group of microorganisms are said to have a **narrow spectrum**. For example, **isoniazid** is active only against Mycobacterium tuberculosis.



Chemotherapeutic Spectra

B. Extended-spectrum antibiotics

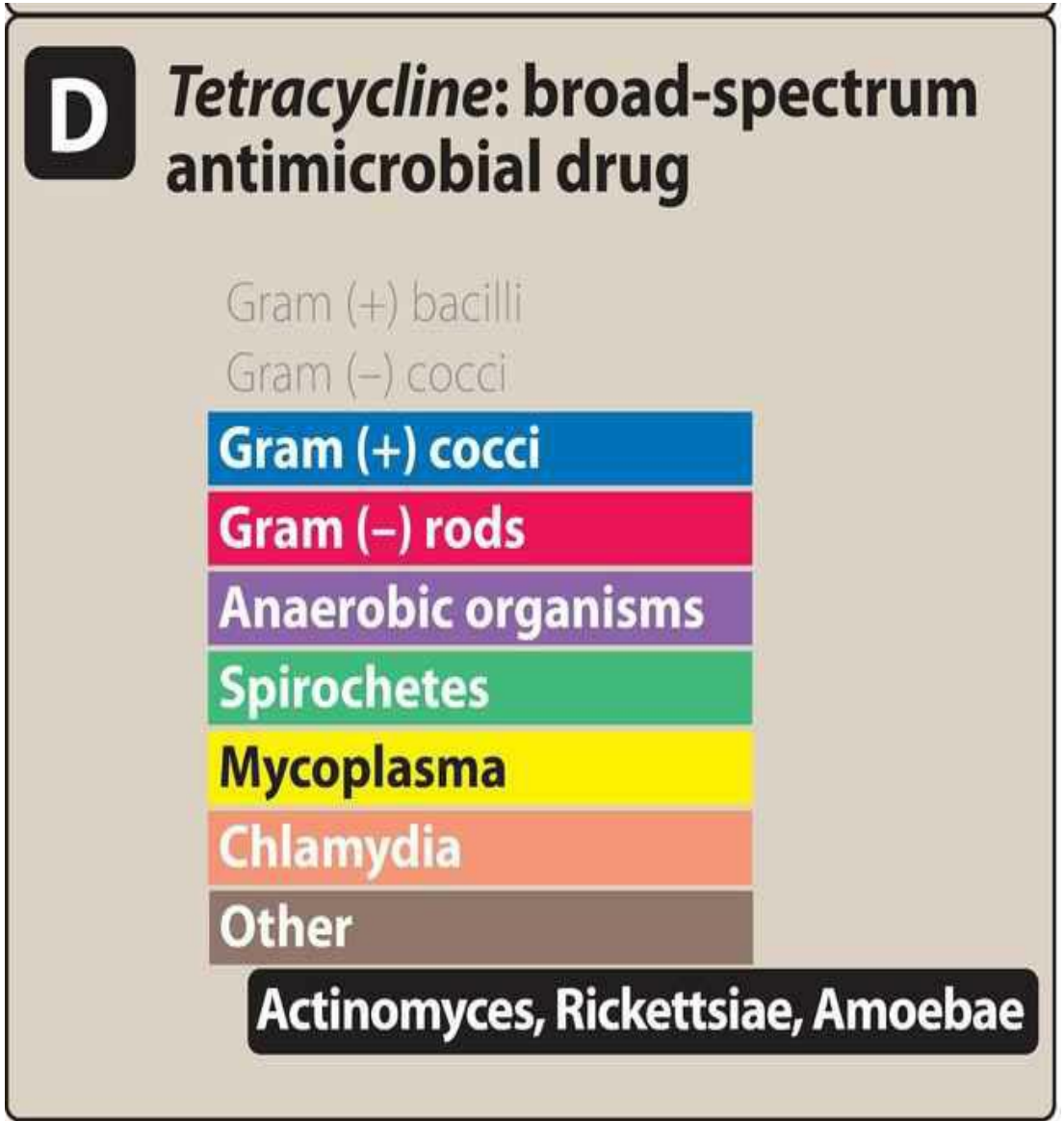
- Extended spectrum is the term applied to antibiotics that are modified to be effective against **gram-positive organisms** and also **against a significant number of gram-negative bacteria**. For example, **ampicillin**



Chemotherapeutic Spectra

C. Broad-spectrum antibiotics

- Drugs such as **tetracycline, fluoroquinolones and carbapenems** affect a wide variety of microbial species and are referred to as **broad- spectrum antibiotics.**



Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection due to organisms such as Clostridium difficile, the growth of which is normally kept in check by the presence of other colonizing microorganisms.

Combinations of Antimicrobial Drugs

A. Advantages of drug combinations

- Certain combinations of antibiotics, such as **β-lactams** and **aminoglycosides**, **show synergism**; that is, the combination is more effective than either of the drugs used separately.
- Multiple drugs used in combination are only indicated in special situations (for example, when an **infection is of unknown origin** or in the **treatment of enterococcal endocarditis**) and when there are organisms with variable sensitivity, such as when treating **tuberculosis.**

Combinations of Antimicrobial Drugs

B. Disadvantages of drug combinations

- A number of antibiotics act only when organisms are multiplying.
- Thus, coadministration of an agent that causes **bacteriostasis** plus a second agent that is **bactericidal** may result in the ***first drug interfering with the action of the second***.
- **For example**, ***bacteriostatic tetracycline drugs*** *may interfere with the bactericidal effects of* ***penicillins and cephalosporins***.
- *Another concern is the development of antibiotic resistance by giving unnecessary combination therapy.*

Drug Resistance:

Drug resistance is mediated by:

1. Modification of target sites:

- For example, *S.pneumoniae* resistance to β-lactam antimicrobials involves alterations in one or more of the major bacterial penicillin binding proteins.

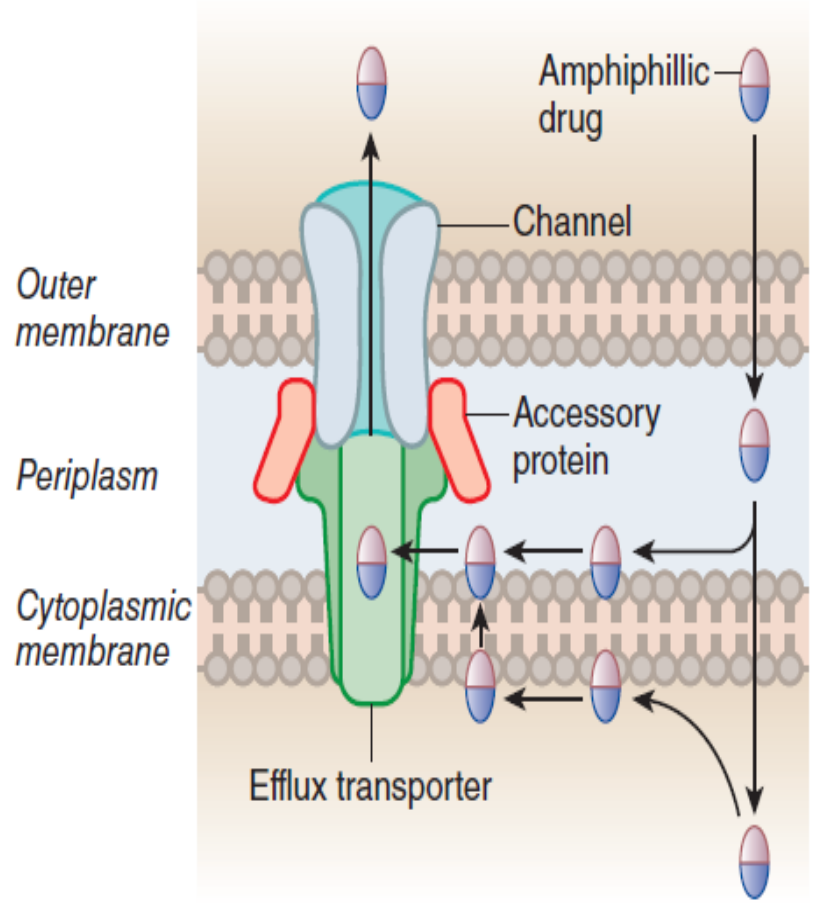
2. Enzymatic inactivation:

- The **ability to destroy or inactivate** the antimicrobial agent can also confer resistance on microorganisms.

Drug Resistance:

3. Decreased accumulation:

- *Decreased uptake or increased efflux* of an antibiotic.
- For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an **alteration in the number and structure of porins** (channels) in the outer membrane.
- Also, the presence of an **efflux pump can limit levels** of a drug in an organism, as seen with tetracyclines.



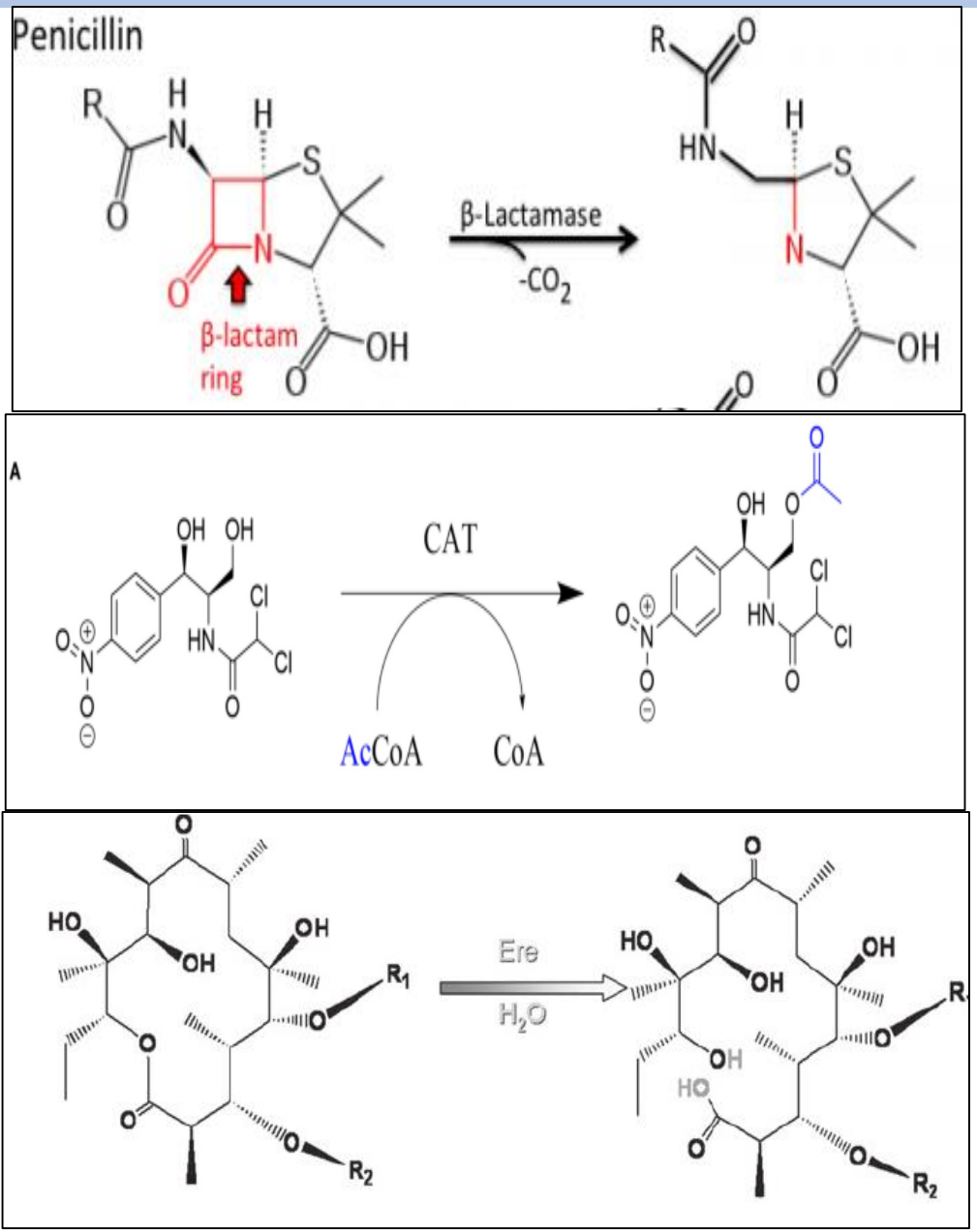
Drug Resistance:

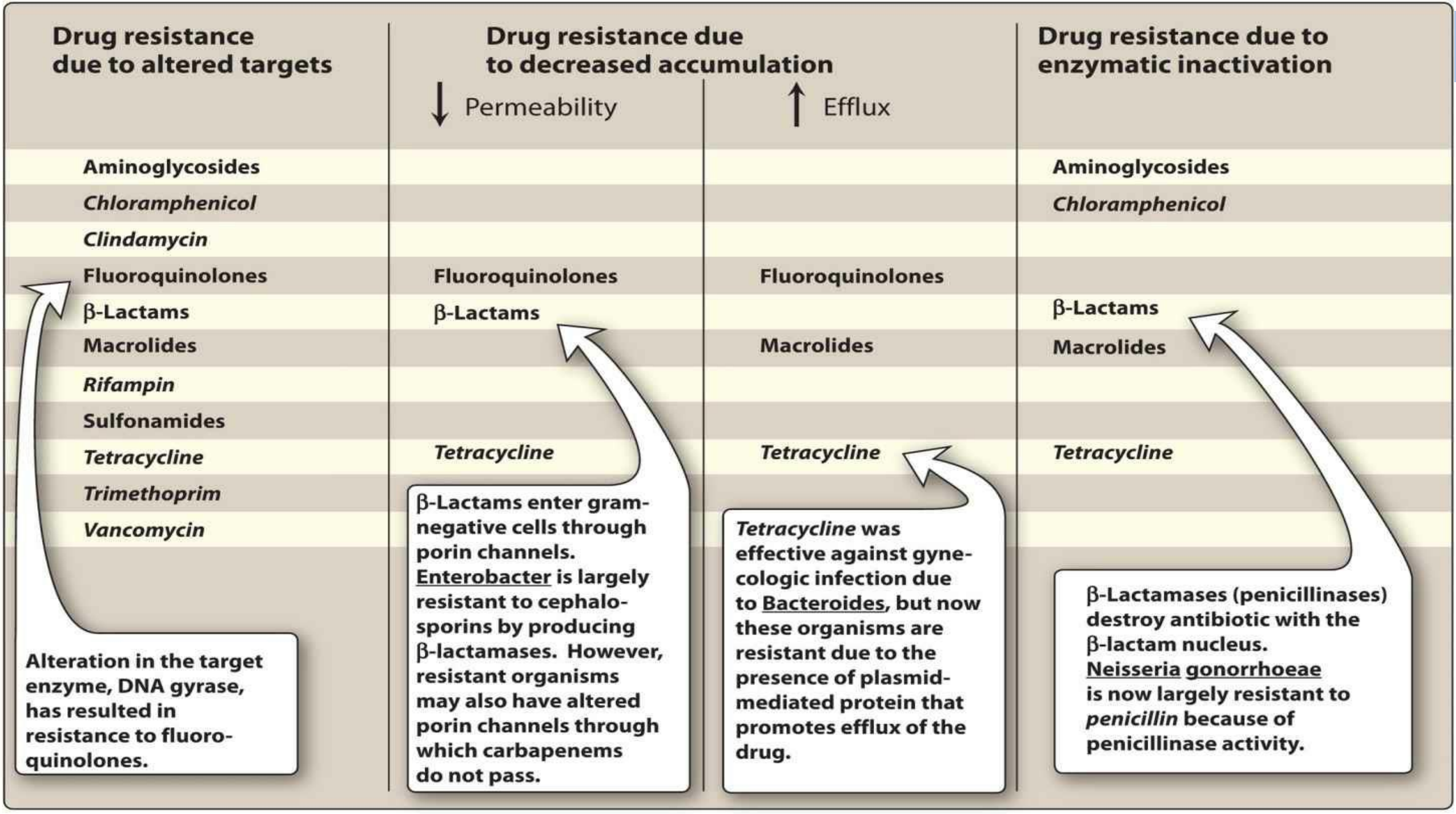
Examples of antibiotic-inactivating enzymes include

1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs.

2) Acetyltransferases that transfer an acetyl group to the antibiotic, inactivating **chloramphenicol** or **aminoglycosides**; and

3) Esterases that hydrolyze the **lactone** ring of **macrolides**.



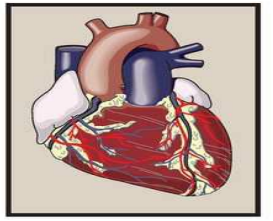

Drug resistance due to altered targets
Drug resistance due to decreased accumulation
Permeability
Efflux
Drug resistance due to enzymatic inactivation
Aminoglycosides
Chloramphenicol
Clindamycin
Fluoroquinolones
β-Lactams
Macrolides
Rifampin
Sulfonamides
Tetracycline
Trimethoprim
Vancomycin
Fluoroquinolones
β-Lactams
Tetracycline
Fluoroquinolones
Macrolides
Tetracycline
Aminoglycosides
Chloramphenicol
β-Lactams
Macrolides
Tetracycline
Alteration in the target enzyme, DNA gyrase, has resulted in resistance to fluoro-quinolones.
β-Lactams enter gram-negative cells through porin channels. Enterobacter is largely resistant to cephalo-sporins by producing β-lactamases. However, resistant organisms may also have altered porin channels through which carbapenems do not pass.
Tetracycline was effective against gyne-cologic infection due to Bacteroides, but now these organisms are resistant due to the presence of plasmid-mediated protein that promotes efflux of the drug.
β-Lactamases (penicillinases) destroy antibiotic with the β-lactam nucleus. Neisseria gonorrhoeae is now largely resistant to penicillin because of penicillinase activity.

Prophylactic Use Of Antibiotics

- **Clinical situations**, such as ***dental procedures*** *and* ***surgeries***, **require the use of antibiotics for the prevention rather than for the treatment of infections**.
- Because the unselective use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the **benefits outweigh the potential risks**.
- The **duration of prophylaxis should be closely observed** to prevent the unnecessary development of antibiotic resistance.

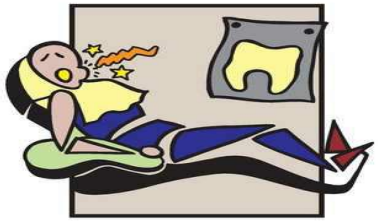
1

Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.



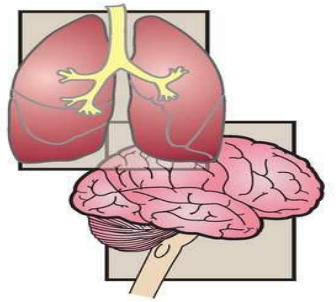
2

Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.



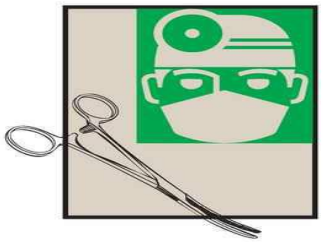
3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



4

Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



Complications of Antibiotic Therapy

A. Hypersensitivity:

- Penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, rang from urticaria (hives) to anaphylactic shock.

Complications of Antibiotic Therapy

B. Direct toxicity:

- For example,

✓**aminoglycosides** can cause **ototoxicity** by interfering with membrane function in the auditory hair cells.

✓**Chloramphenicol** can have a direct toxic effect on mitochondria, leading to bone marrow suppression.

✓**Fluoroquinolones** can have effects on cartilage and tendons, and tetracyclines have direct effects on bones.

Complications of Antibiotic Therapy

C. Superinfections Drug therapy,

- Particularly with broad-spectrum antimicrobials or combinations of agents, can ***lead to alterations of the normal microbial flora of the upper respiratory, oral, intestinal, and genitourinary tracts***, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.
- These infections usually require secondary treatments using specific anti-infective agents.

X. Sites of Antimicrobial Action

- **Antimicrobial drugs can be classified in a number of ways:**

1) By their chemical structure

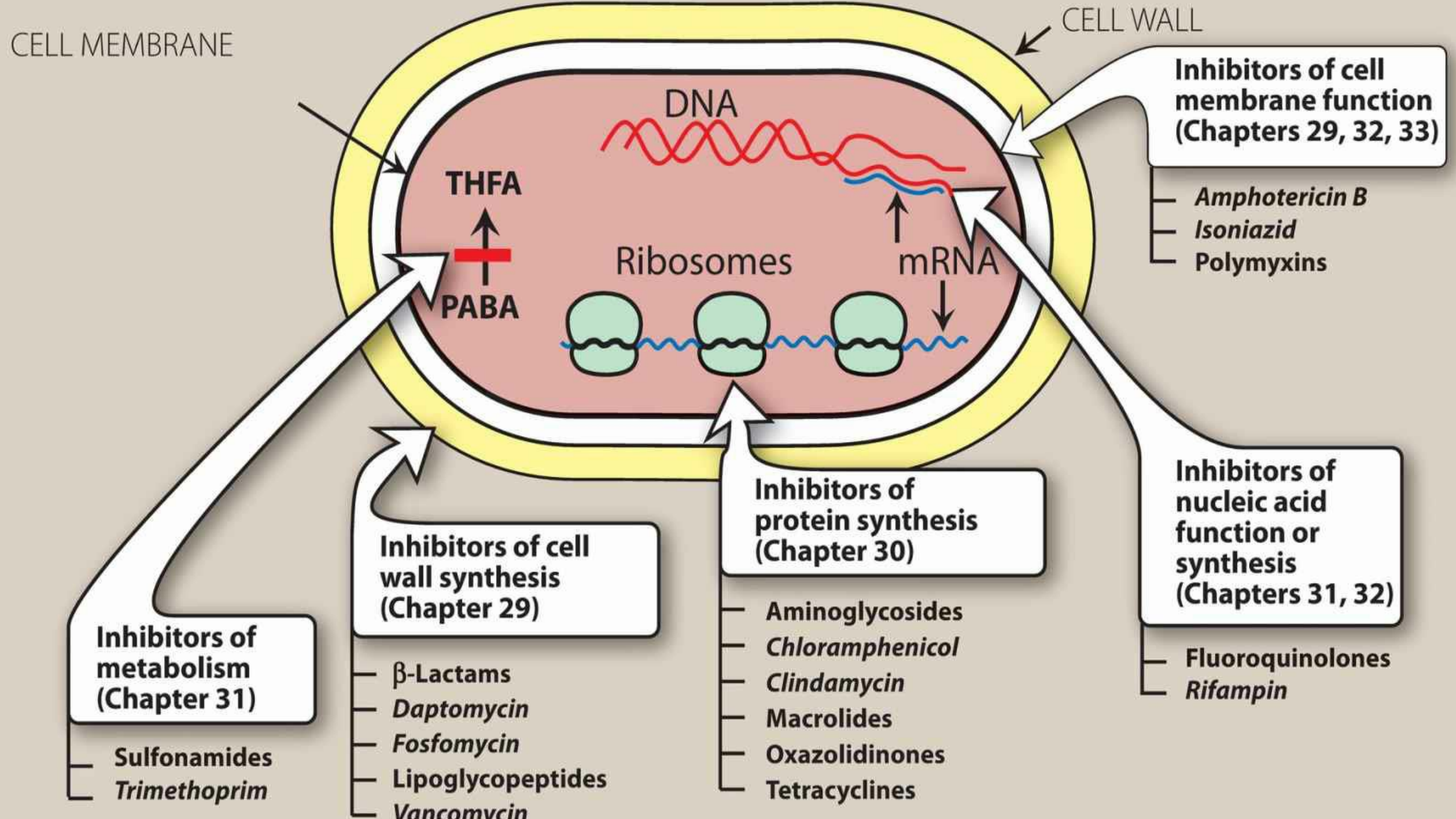
(for example, β-lactams or aminoglycosides),

2) By their mechanism of action

(for example, cell wall synthesis inhibitors),

3) By their activity against particular types of organisms

(for example, bacteria, fungi, or viruses).


CELL MEMBRANE
CELL WALL
DNA
THFA
PABA
Ribosomes
mRNA
Inhibitors of cell membrane function (Chapters 29, 32, 33)
Amphotericin B
Isoniazid
Polymyxins
Inhibitors of metabolism (Chapter 31)
Sulfonamides
Trimethoprim
Inhibitors of cell wall synthesis (Chapter 29)
β-Lactams
Daptomycin
Fosfomycin
Lipoglycopeptides
Vancomycin
Inhibitors of protein synthesis (Chapter 30)
Aminoglycosides
Chloramphenicol
Clindamycin
Macrolides
Oxazolidinones
Tetracyclines
Inhibitors of nucleic acid function or synthesis (Chapters 31, 32)
Fluoroquinolones
Rifampin