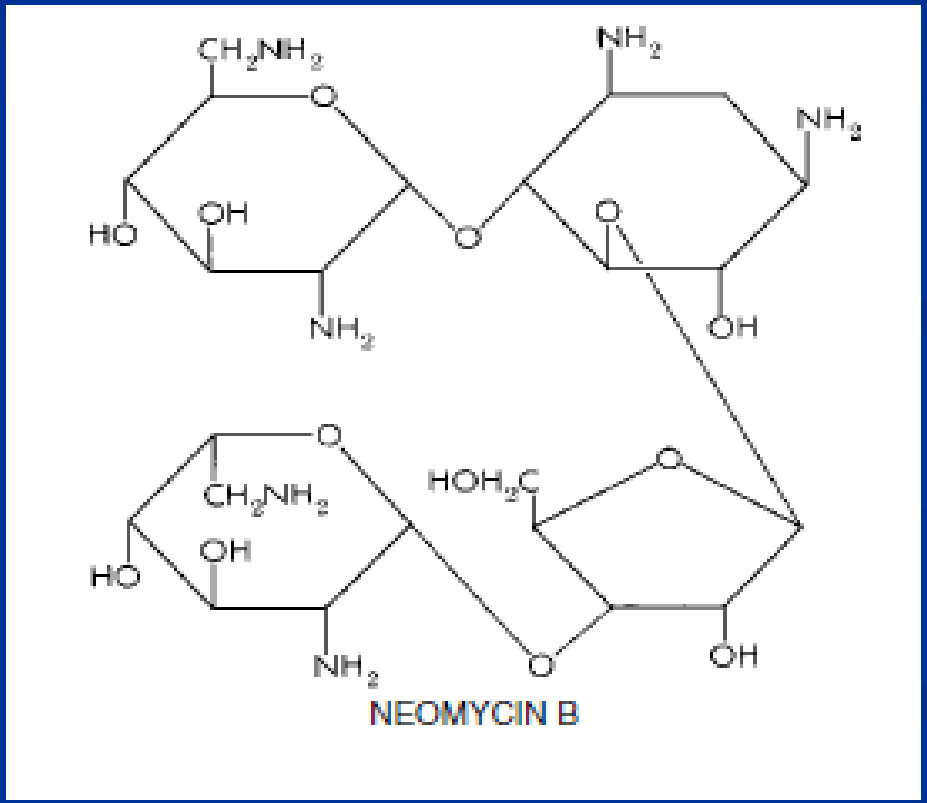
The Aminoglycosides

- Active against gram negative bacteria.
- Hydrophilic compounds, do not cross membranes, do not distribute well.
- All given by injection, or locally applied.
- Not metabolized.
- Excreted by the kidneys.
- Ototoxic and nephrotoxic.

The aminoglycosides consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus, which usually is in a central position



NEOMYCIN B

glycosidic linkage is a type of covalent bond that joins a carbohydrate (sugar) molecule to another group

a **hexose** is a monosaccharide with six carbon atoms

- The polycationic aminoglycoside chemical structure results in a binding both to the anionic outer bacterial membrane and to anionic phospholipids in the cell membranes of mammalian renal proximal tubular cells.
- The former contributes to the bactericidal effects of these compounds, while the latter binding accounts for their toxicity. Because of their hydrophilicity, the transport of aminoglycosides across the hydrophobic lipid bilayer of eukaryotic cell membranes is impeded

MECHANISM OF ANTIBACTERIAL ACTION

- The antibacterial actions of the aminoglycosides involve two possibly synergistic effects.

- First, the positively charged aminoglycoside binds to negatively charged sites on the outer bacterial membrane, thereby disrupting membrane integrity.

- It is likely that the aminoglycoside-induced bacterial outer membrane degradation accounts for the rapid concentration dependent bactericidal effect of these compounds.

MECHANISM OF ANTIBACTERIAL ACTION

- Second, aminoglycosides bind to various sites on bacterial 30S ribosomal subunits, disrupting the initiation of protein synthesis and inducing errors in the translation of messenger RNA to peptides.
- They also bind to sites on bacterial 50S ribosomal subunits, although the significance of this binding is uncertain.
- In addition, they have a post antibiotic effect; that is, they continue to suppress bacterial regrowth even after removal of the antibiotic from the bacterial microenvironment.
- It is likely that ribosome disruption accounts for this postantibiotic activity.

- The postantibiotic effect is characterized by prolonged suppression of bacterial regrowth after the initially high aminoglycoside concentration has fallen to a subinhibitory level.
- Perhaps resumption of bacterial ribosomal function requires the time-consuming synthesis of new ribosomes after their disruption by aminoglycosides.
- The postantibiotic effect explains why aminoglycosides can be given in single daily doses despite their short half-life

- Penetration of aminoglycosides through the outer bacterial membrane occurs both by outer membrane disruption and by diffusion through outer membrane porins.

- Penetration through the inner bacterial membrane occurs in two phases.

- The first requires that the cytosol have a negative electron potential and therefore be inhibited by the presence of a low pH.

- The second phase depends on aerobic bacterial metabolism and therefore will be inhibited by low oxygen tension

- The latter two observations are of considerable clinical relevance, since
- both a low pH and a low oxygen tension

frequently occur in bacterial abscesses.

- Administration of B-lactam antibiotics will reverse the negative effects of both low pH and low oxygen tension on the ability of

aminoglycosides to penetrate into bacteria;

- this ability accounts in part for the synergism that occurs between

aminoglycoside and B-lactam antibiotic drugs.

The Aminoglycosides

- Used to treat infections caused by aerobic gram-negative bacteria and rapidly bactericidal.
- They inhibit protein synthesis by binding to the 30S ribosomal subunit

and alter protein synthesis.

- **Streptomycin: 1947.**
  - **Used only in TB.**

The Aminoglycosides

- Gentamicin.
- Tobramycin.
- Amikacin.
- Netilmicin
- Neomycin:

The Aminoglycosides

- **Gentamicin:**
  - Widely used in hospitals.
  - Good for Staphylococcus and Gram-negative organisms.
  - Short $T_{1/2.}$
  - Toxic, blood level monitoring is required.
  - Incompatible with other drugs, so given separately.

The Aminoglycosides

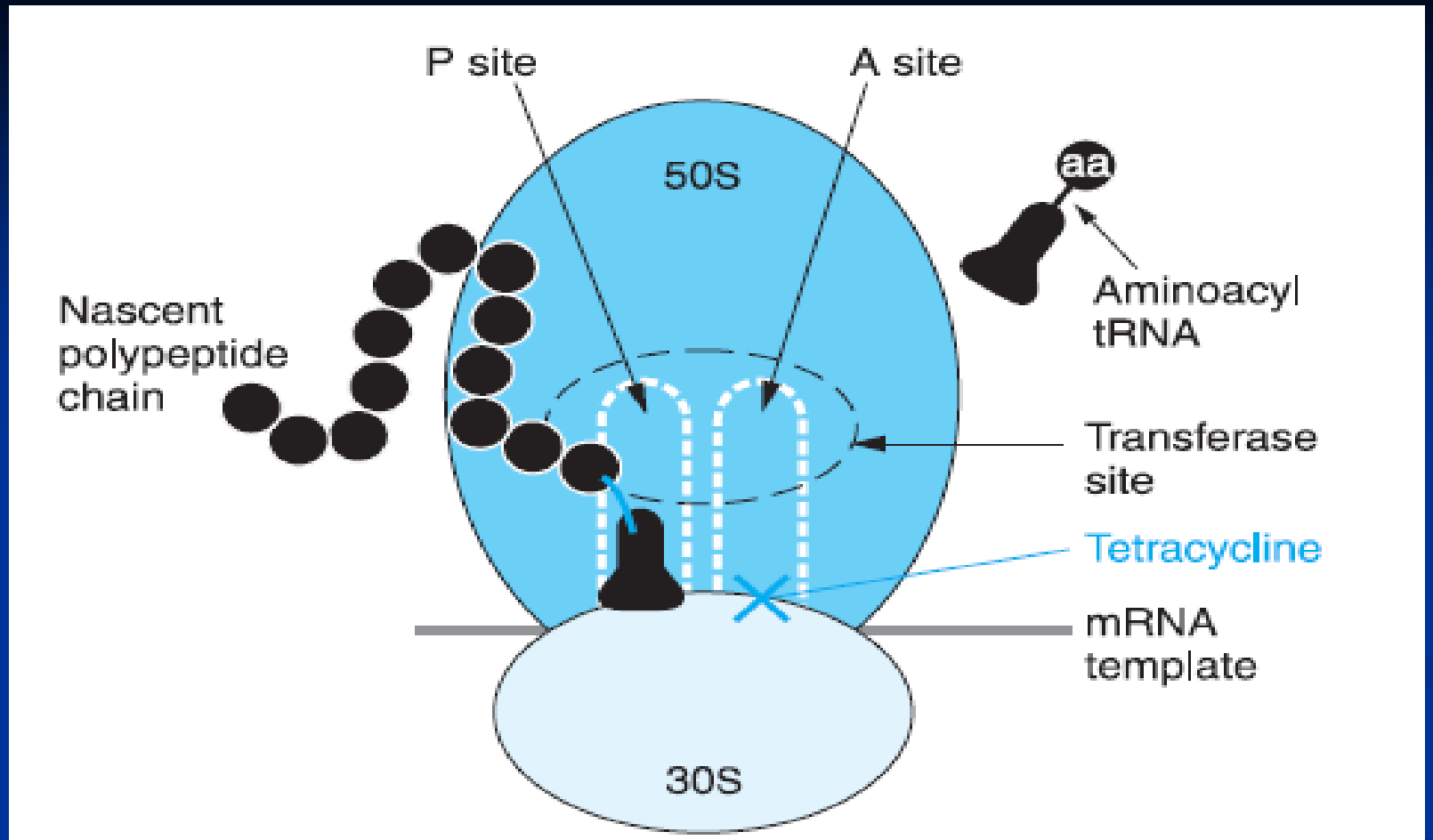
- **Neomycin:**
  - Very toxic, not given systemically.
  - Given to sterilize the bowel before surgery.
  - Also locally as drops or ointment in ear, nose, eye, or skin infections.

Tetracyclines

- Wide spectrum of activity (Gram positive and negative bacteria), but resistance develops very rapidly.
- Bacteriostatic, only stop bacterial growth, do not kill bacteria. So, we depend on the presence of a good patient's immune system.

Tetracyclines

- Disrupt function of 30S or 50S ribosomal subunits to reversibly inhibit protein synthesis.
- Orally absorbed, but absorption affected by food, and dairy products.
- Widely distributed in the body.



Tetracyclines inhibit bacterial protein synthesis by binding to the 30S subunit and blocking tRNA binding to the A site.

A transfer RNA is an adaptor molecule composed of RNA, typically 76 to 90 nucleotides in length that serves as the physical link between the mRNA and the amino acid sequence of proteins

Tetracyclines

- Rarely used nowadays, EXCEPT:
  - **Doxycycline:** given once daily for acne.
- Adverse Effects:
  - Nausea, vomiting, diarrhea.
  - Changes in normal flora leading to diarrhea and candida infection.
  - Bone deposits in children, appears on teeth

Chloramphenicol

- Broad spectrum
- Very widely distributed.
- Very effective, no resistance.
- Very toxic. (the gray-baby syndrome)
- Disrupt function of 50S ribosomal subunits to reversibly inhibit protein synthesis.

Gray baby syndrome is a rare but serious side effect that occurs in newborn infants (especially premature babies) following the accumulation of antibiotic chloramphenicol.

Chloramphenicol

- Was the drug of choice for Salmonella(Typhoid Fever), but replaced by safer drugs.
- Still used for meningitis caused by *H. influenzea.*
- Aplastic anemia:
  - Incidence is common 1/40,000.
  - Delayed for a few months after intake.
  - Fatal.

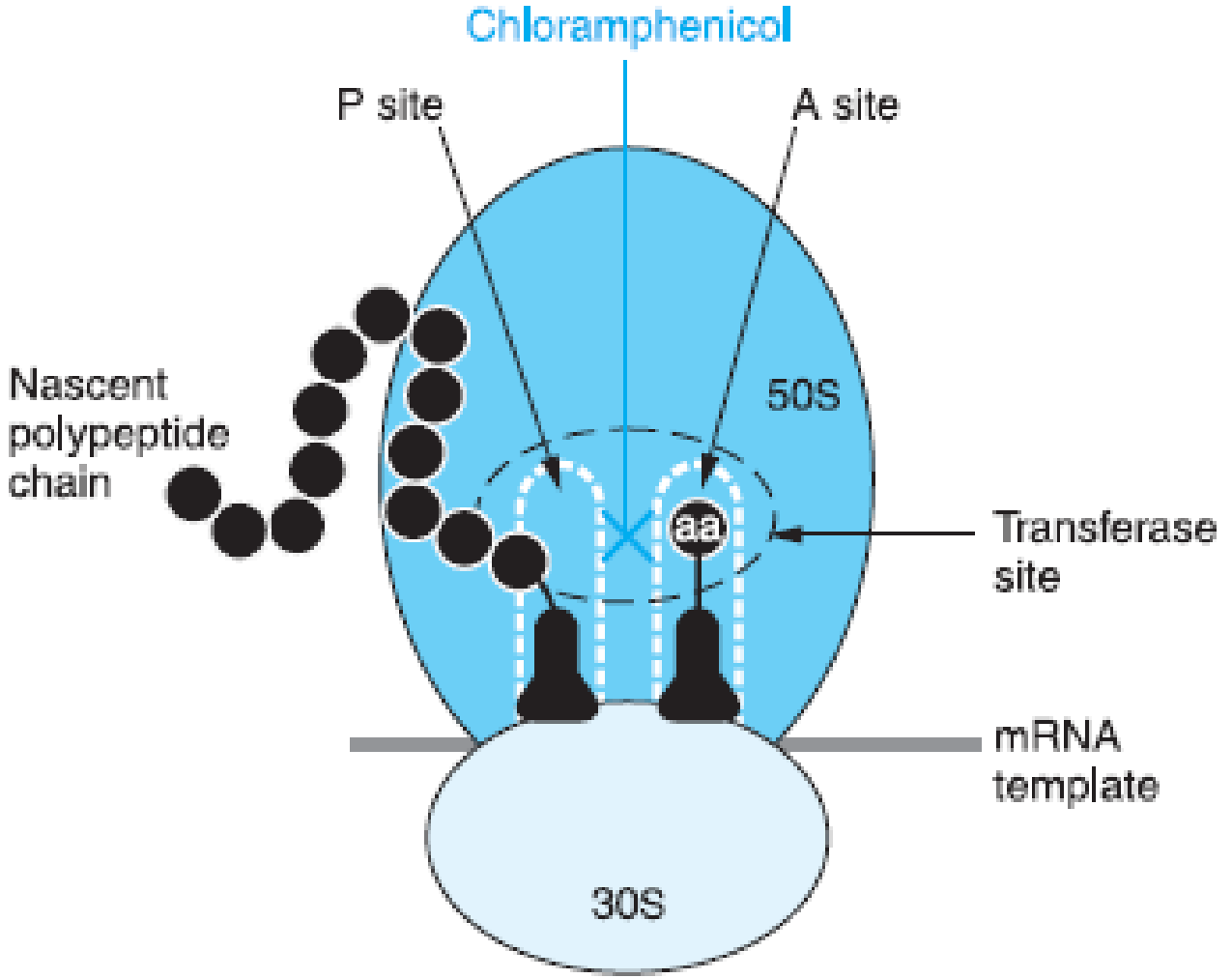


Figure 46–2. Inhibition of bacterial protein synthesis by chloramphenicol. Chloramphenicol binds to the 50S ribosomal subunit at the peptidyltransferase site and inhibits the transpeptidation reaction.

transpeptidation reaction
A reaction involving the transfer of one or more amino acids from one peptide chain to another,

Mechanism of Action

- Chloramphenicol (Chloromycetin) is a nitrobenzene derivative that affects protein synthesis by binding to the 50S ribosomal subunit preventing peptide bond formation.

- It prevents the attachment of the amino acid end of aminoacyl-tRNA to the A site, hence the association of peptidyltransferase with the amino acid substrate.

Mechanism of Action

- Resistance due to changes in the ribosome binding site results in
  - ❖ a decreased affinity for the drug,
  - ❖ decreased permeability,
  - ❖ and plasmids that code for enzymes
- that degrade the antibiotic.
- The drug-induced inhibition of mitochondrial protein synthesis is probably responsible for the associated toxicity.

Antibacterial Spectrum

- Chloramphenicol is a broad-spectrum antibiotic that is effective against gram-positive and gram-negative bacteria, including Rickettsia, Mycoplasma, and Chlamydia spp.

- Chloramphenicol is also effective against most anaerobic bacteria, including Bacteroides fragilis.

Absorption, Distribution, Metabolism, and Excretion

- Chloramphenicol is rapidly and completely absorbed from the gastrointestinal tract and is not affected by food ingestion or metal ions.
- Parenteral administration

is generally reserved for situations in which oral therapy is contraindicated, as in the treatment of meningitis and septicemia or when vomiting prohibits oral administration

Absorption, Distribution, Metabolism, and Excretion

- The biological half-life of chloramphenicol is 1.5 to 3.5 hours. Although up to 60% of the drug is bound to serum albumin, it penetrates the brain and CSF and crosses the placental barrier.
- Chloramphenicol is inactivated in the liver by glucuronosyltransferase and is rapidly excreted (80–90% of dose) in the urine.

Clinical Uses

The potentially fatal nature of chloramphenicolinduced bone marrow suppression restricts its use to a few life-threatening infections in which the benefits outweigh the risks. There is no justification for its use in treating minor infections.

Chloramphenicol is no longer recognized as the treatment of choice for any bacterial infection. In almost all instances, other effective antimicrobial agents are available.

Since effective CSF levels are obtained, it used to be a choice for treatment of specific bacterial causes of meningitis:

- Haemophilus influenzae,
- Neisseria meningitidis,
- and S. pneumoniae

Additionally, it was effective against H. influenzae–related arthritis, osteomyelitis, and epiglottitis.

- The development of B-lactamase-producing strains of H. influenzae increased the use of chloramphenicol.

- However, with the advent of third-generation cephalosporins such as ceftriaxone and cefotaxime, chloramphenicol use has significantly decreased.
- If the patient is hypersensitive to B-lactams, chloramphenicol administration is appropriate therapy for meningitis caused by N. meningitidis and S. pneumoniae.

- Chloramphenicol remains a major treatment of typhoid and paratyphoid fever in developing countries.

- However, with increasing resistance to ampicillin, trimethoprim-sulfamethoxazole and, to some extent, chloramphenicol, fluoroquinolones and some third-generation cephalosporins (e.g., ceftriaxone) have become the drugs of choice

- Chloramphenicol also is widely used for the topical treatment of eye infections.
- It is a very effective agent

because of its extremely broad spectrum of activity and its ability to penetrate ocular tissue.

- The availability of

safer, less irritating instilled ophthalmic antibiotics and the increase in fatal aplastic anemia associated with the use of this dosage form suggest that this agent might best be withdrawn.

- Chloramphenicol is an alternative to tetracycline for rickettsial diseases, especially in children younger than 8 years,
- alone or in combination with other antibiotics,

it has been used to treat vancomycin-resistant enterococci.

- Another indication for chloramphenicol is in

the treatment of serious anaerobic infections caused by penicillin-resistant bacteria, such as B. fragilis