# Protein Synthesis Inhibitors

***Aminoglycosides***

- By the end of this long group discussion the students should be able to

a. Enumerate the aminoglycosides

b. Explain the mechanism of action of aminoglycosides

c. Describe the antibacterial spectrum of aminoglycosides

d. Describe the mechanism of action of resistance of aminoglycosides

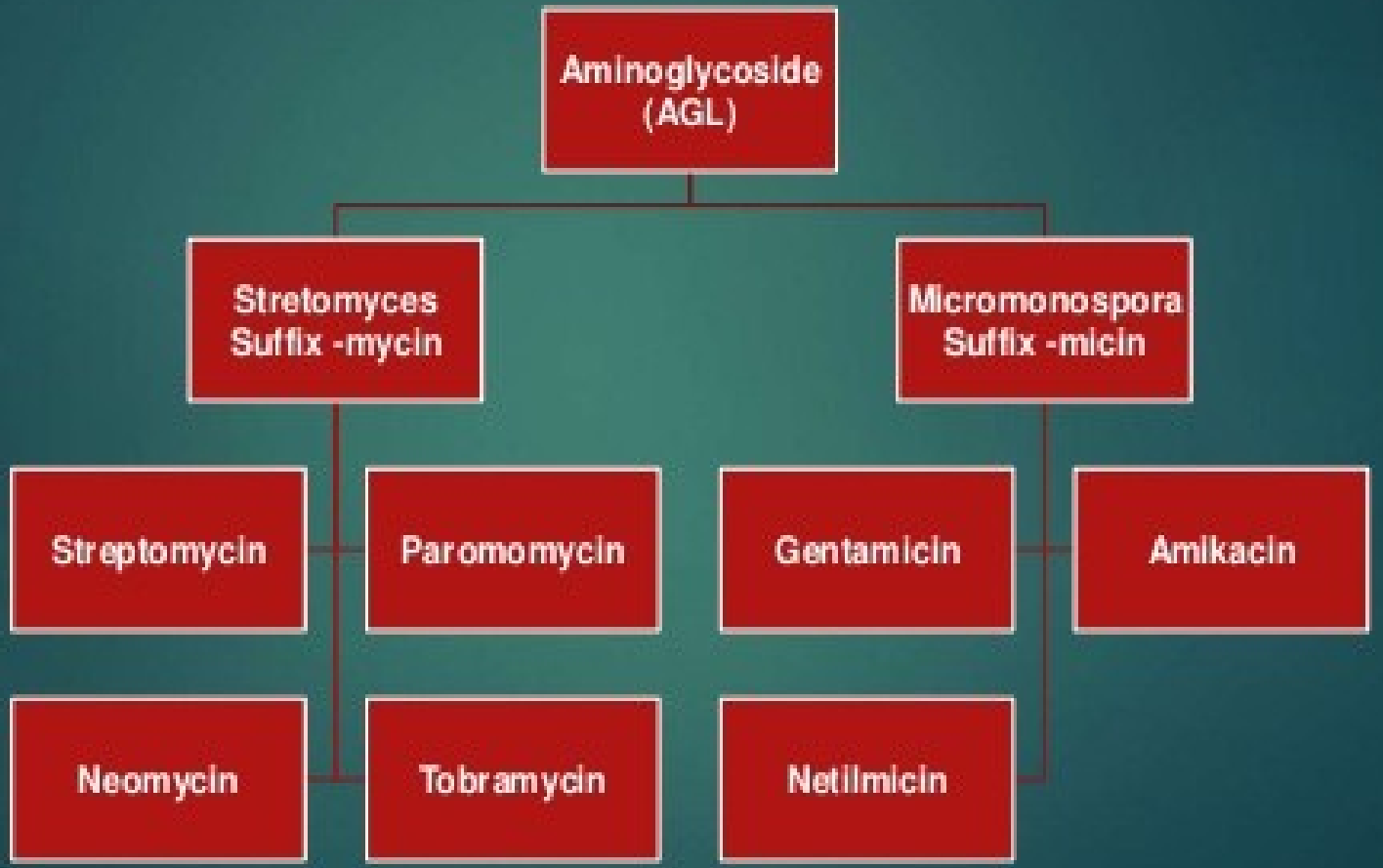
e. Briefly describe the pharmacokinetics of aminoglycosides

f. Explain the adverse effects of aminoglycosides

# *Aminoglycosides*

- **Aminoglycoside** antibiotics had been the mainstay for treatment of serious infections due to aerobic gram negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones and the carbapenems.

# Common Members of Aminoglycosides



# CLASSIFICATION

## Systemic Aminoglycosides

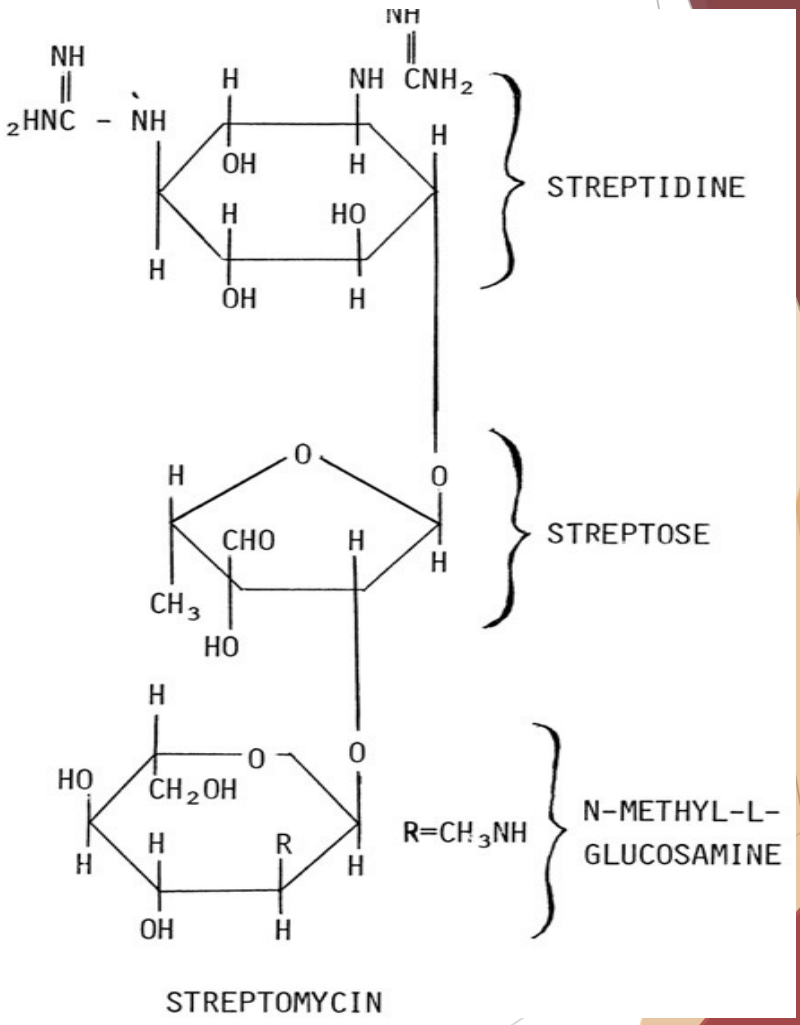
- Streptomycin
- Gentamicin
- Kanamycin
- Tobramycin
- Amikacin
- Sisomicin
- Netilmicin
- Paromomycin

## Topical Aminoglycosides

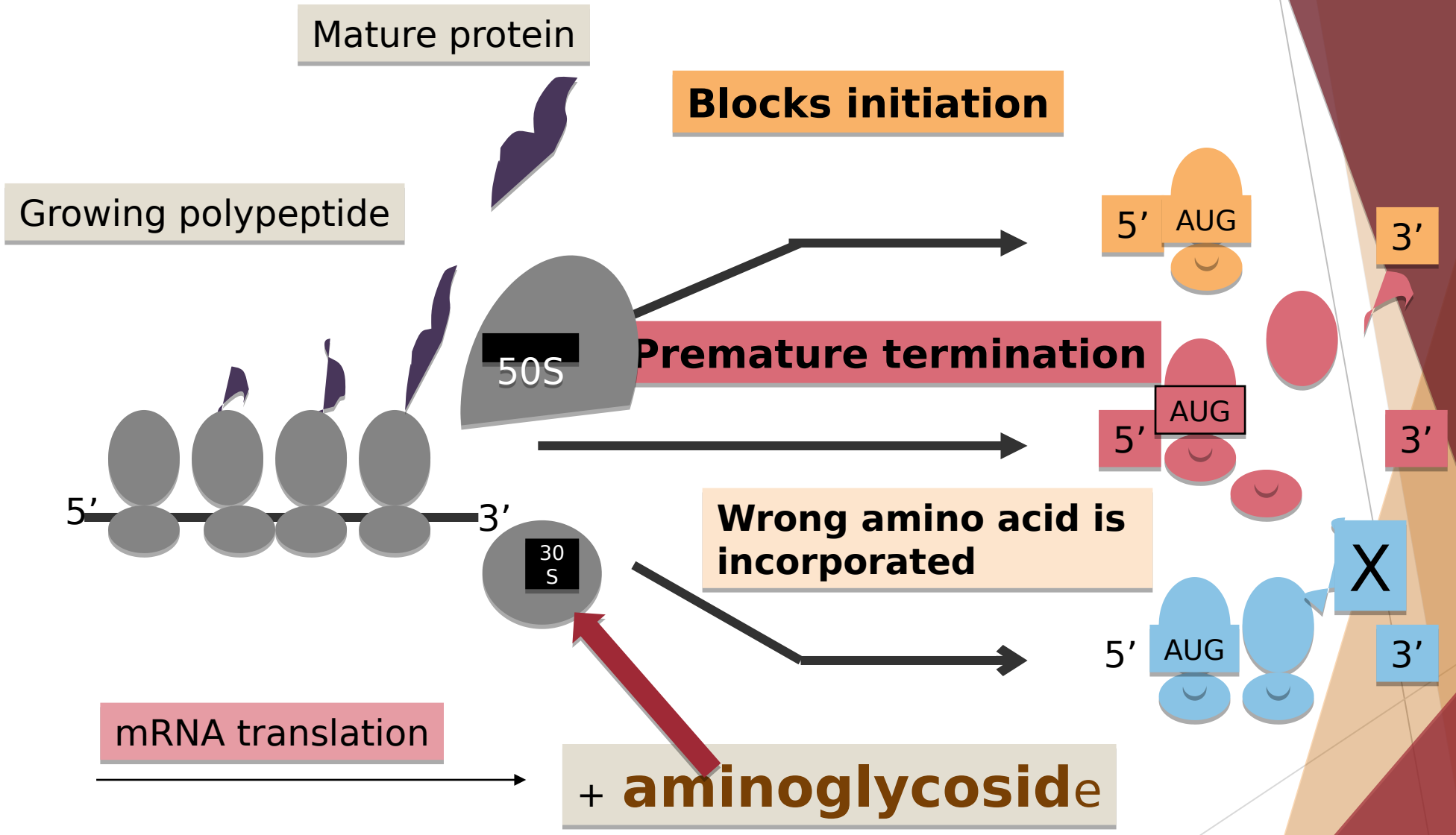
- Neomycin
- Framycetin

# AMINOGLYCOSIDES

- Amino sugars linked through glycosidic bonds.
- Polycations: This is in part responsible for many of their shared pharmacokinetic properties as well as precludes their entry via cell membrane




STREPTOMYCIN




# Effects of Aminoglycosides

# Post antibiotic effect

- Aminoglycosides exhibit concentration dependent killing.
- They also possess significant Post-antibiotic effect.
- Single daily dosing at least as effective as and no more toxic than multiple dosing.

## THERAPEUTIC USES OF THE AMINOGLYCOSIDES

| | |
|---|---|
| **Streptomycin** | **T.B., Endocarditis** |
| **Gentamicin** | **Endocarditis, gram negative infections, Pseudomonas** |
| **Tobramycin** | **Gram negative infections, Pseudomonas** |
| **Amikacin** | **Reserve drug for gram negative-infections** |

# Resistance

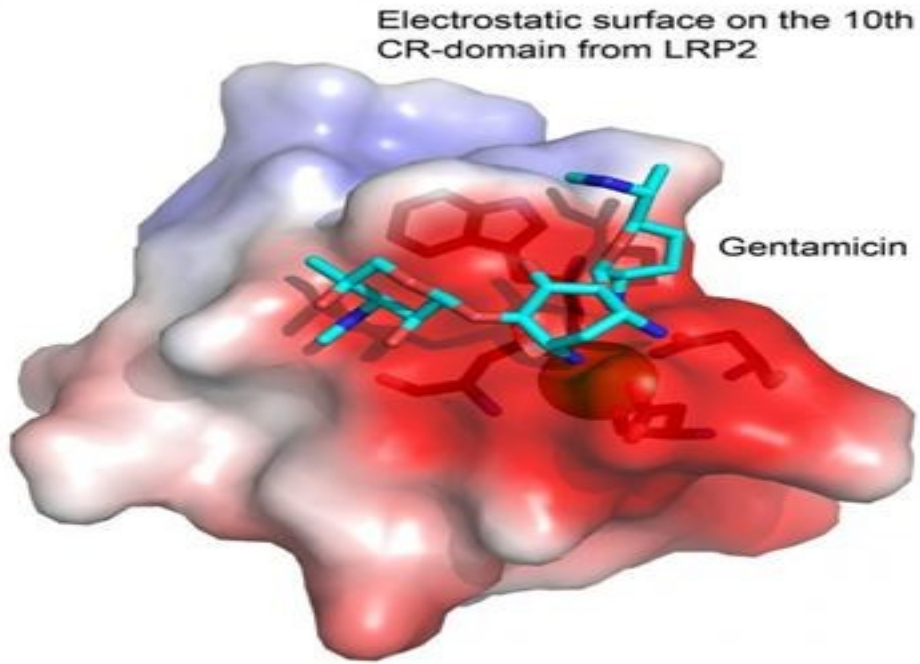
- Resistance can be caused by
- 1) **decreased uptake** of drug when the oxygen-dependent transport system for aminoglycosides or porin channels are absent and
- 2) plasmid-associated synthesis of enzymes (for example**,acetyltransferases,nucleotidyltransferases,** and **phosphotransferases)** that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity;
- 3)**. deletion /alteration** of receptor molecule on the 30S ribosomal unit resulting in failure of binding of aminoglycoside to it.

# Pharmacokinetics

- **Absorption** : they being highly polar & polycationic have inadequate absorption via GIT. It for this reason that they are given parentally. Except neomycin that due to severe nephrotoxicity it used topically or orally prior to sterilize bowel prior to surgery.
- They are bactericidal which is concentration and time dependent and also has post antibiotic effect. Given as a single dose ---reducing the side effects and less strain on the pocket.
- In case pregnancy, neonatal infections and endocarditis it is given in divided doses.
- **Distribution** : Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for *neomycin , the aminoglycosides may*be administered intrathecally. They accumulate in the renal cortex and endolymph of ears. Can cross the placental and reach amniotic fluid.
- Rapidly excreted renally.

# Clinical uses of AMINOGLYCOSIDES

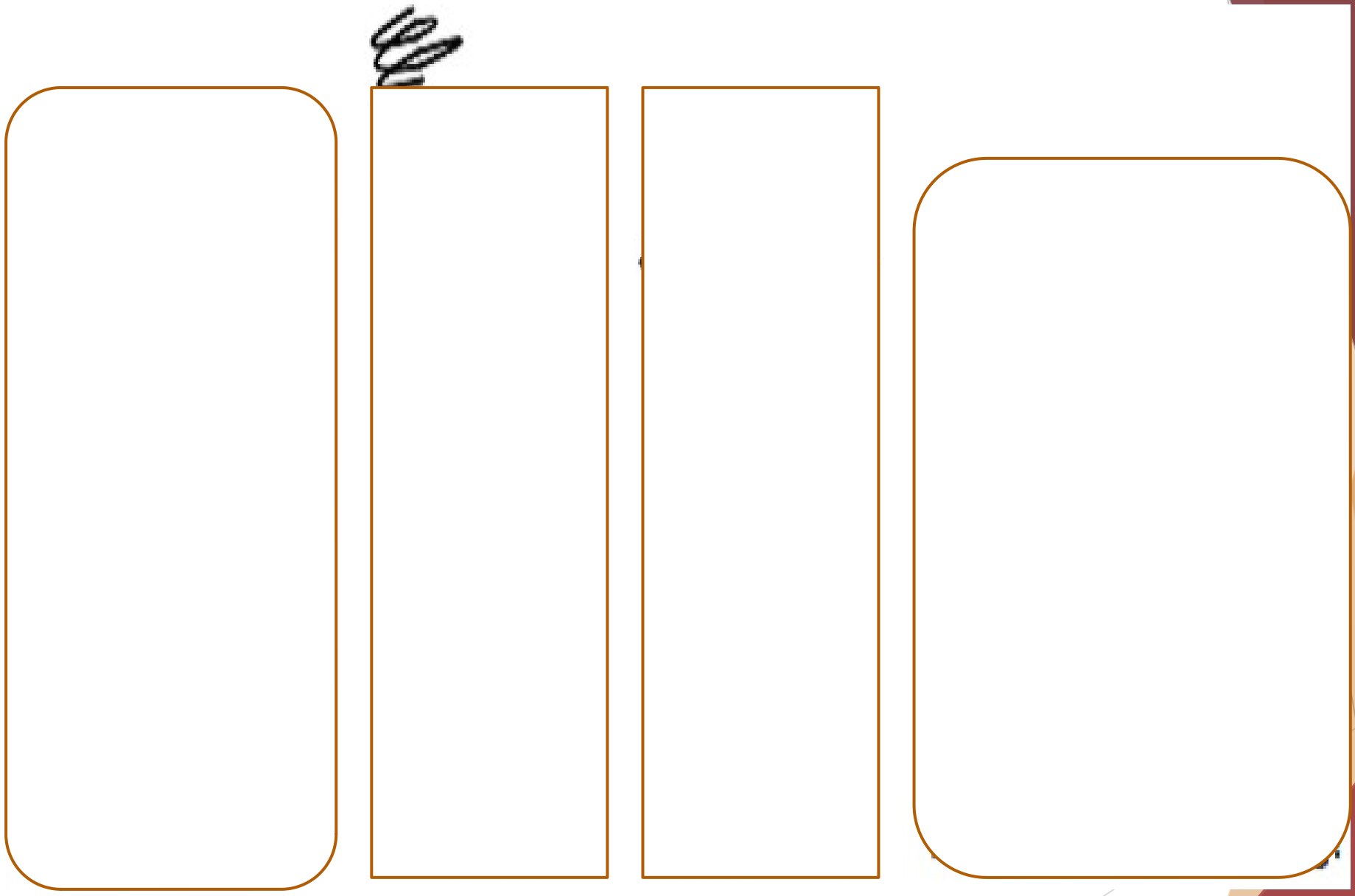
- Respiratory infections,
- Subacute bacterial endocarditis,
- Plague
- Tularemia
- Meningitis (*Gentamycin*)
- Urinary tract infections
- Osteomyelitis
- Lung abcesses
- Septic processes caused by *Pseudomonas aeruginosa*
- Tuberculosis (*Streptomycin, Kanamycin, and Amikacin*).



# Therapeutic uses

- **Tuleremia** is a serious infectious disease caused by the intracellular bacterium *Francisell tularensis*. Vector in between is usually tics. Gentamicin is effective against it.
- **Infections due to enterococci**. Enterococci are usually resistant to many antibiotics and so require two drugs to induce synergistic effect for therapeutic effect. Recommended therapy is gentamicin or streptomycin in combination with vancomycin or other β-lactum anti-biotic.
- **Brucellosis(gm-ive)** ---gentamycin + doxycycline
- **Klebsiella infections(gm-ive)----** gentamycin+ anti-pseudomonal penicillin
- **Pseudomonas(gm-ive)** ----tobramycin +anti-pseudomonal
- **Yersenia(gm-ive)** ---streptomycin +doxycycline

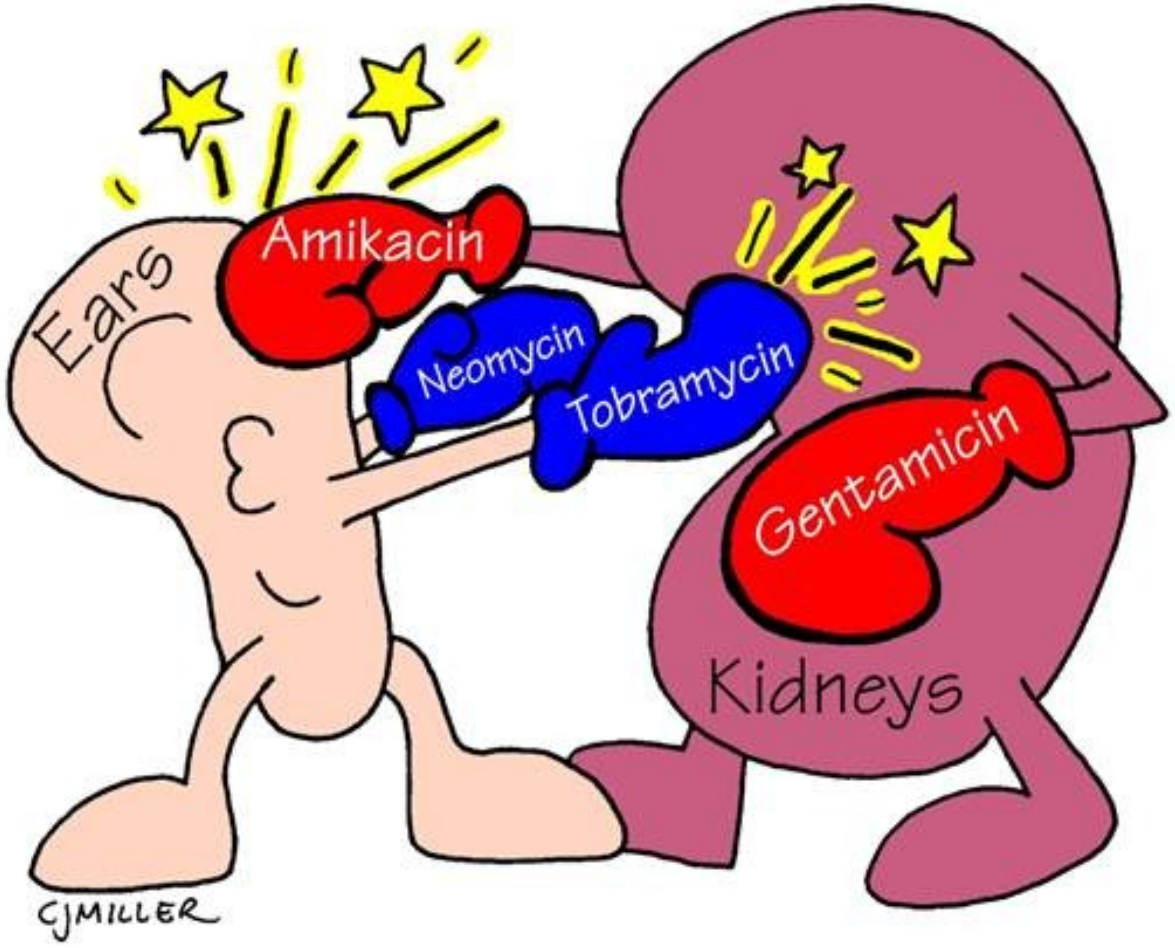
# Adverse Effects



# Adverse Effects

- Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells (renal cortex) disrupts calcium mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

# AMINOGLYCOSIDE TOXICITY

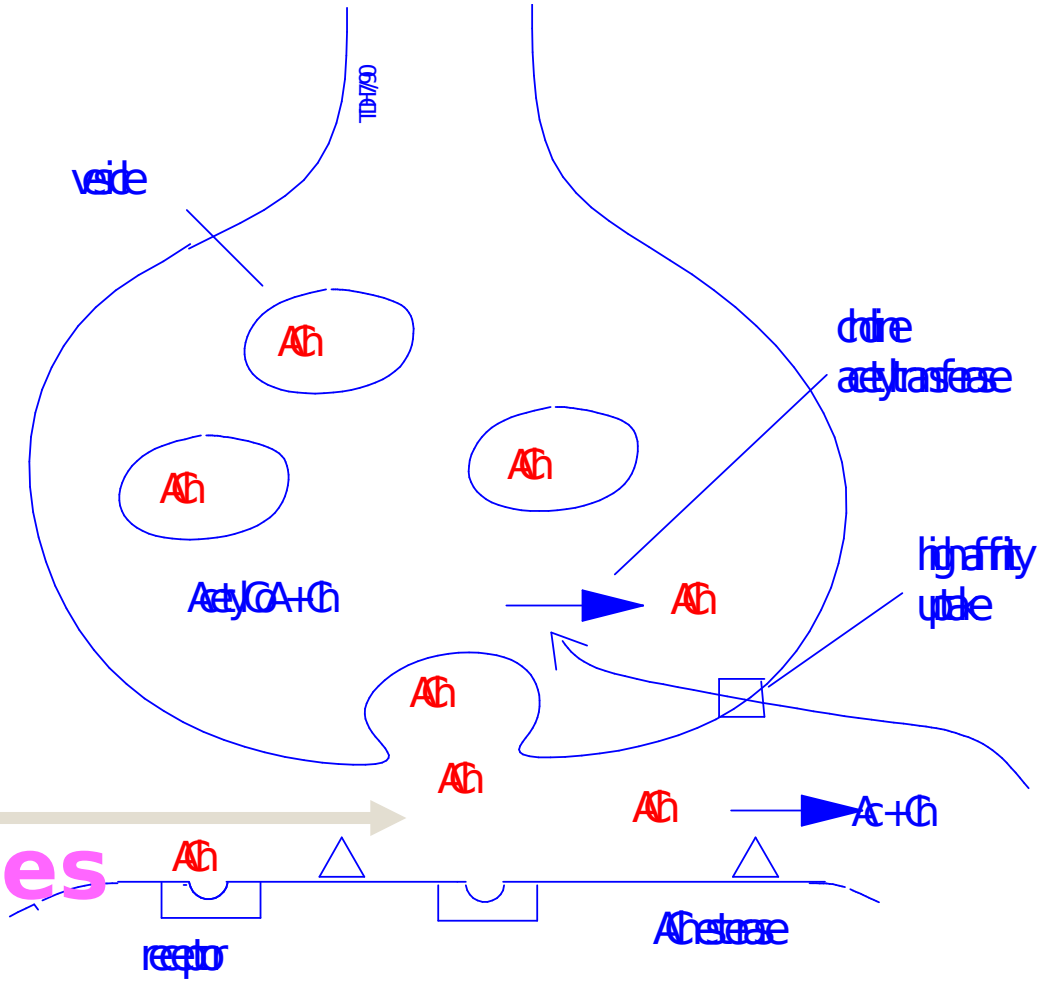



Major toxic effects of Aminoglycosides are Ototoxicity & Nephrotoxicity

# NEUROMUSCULAR BLOCKADE

- Rare but potentially serious.
- Occurs at high concentrations of aminoglycosides  or in patients with an underlying risk factor.
- Acute neuromuscular blockade, respiratory paralysis and death can occur.

# Amino Glycosides



**Aminoglycosides include: TANGS:**

**T**obramycin

**A**mikacin

**N**eomycin

**G**entamicin

**S**treptomycin

**AMINO:**

**A**gainst **A**erobic gram negatives

**M**ainly bactericidal

**I**nhibit protein synthesis at 30s subunit

**N**ephrotoxic

**O**totoxic

**Side effects of Aminoglycosides include: remember of NANO:**

**N**eurotoxicity

**A**llergic reactions

**N**ephrotoxicity

**O**totoxicity

# Aminoglycoside Uses

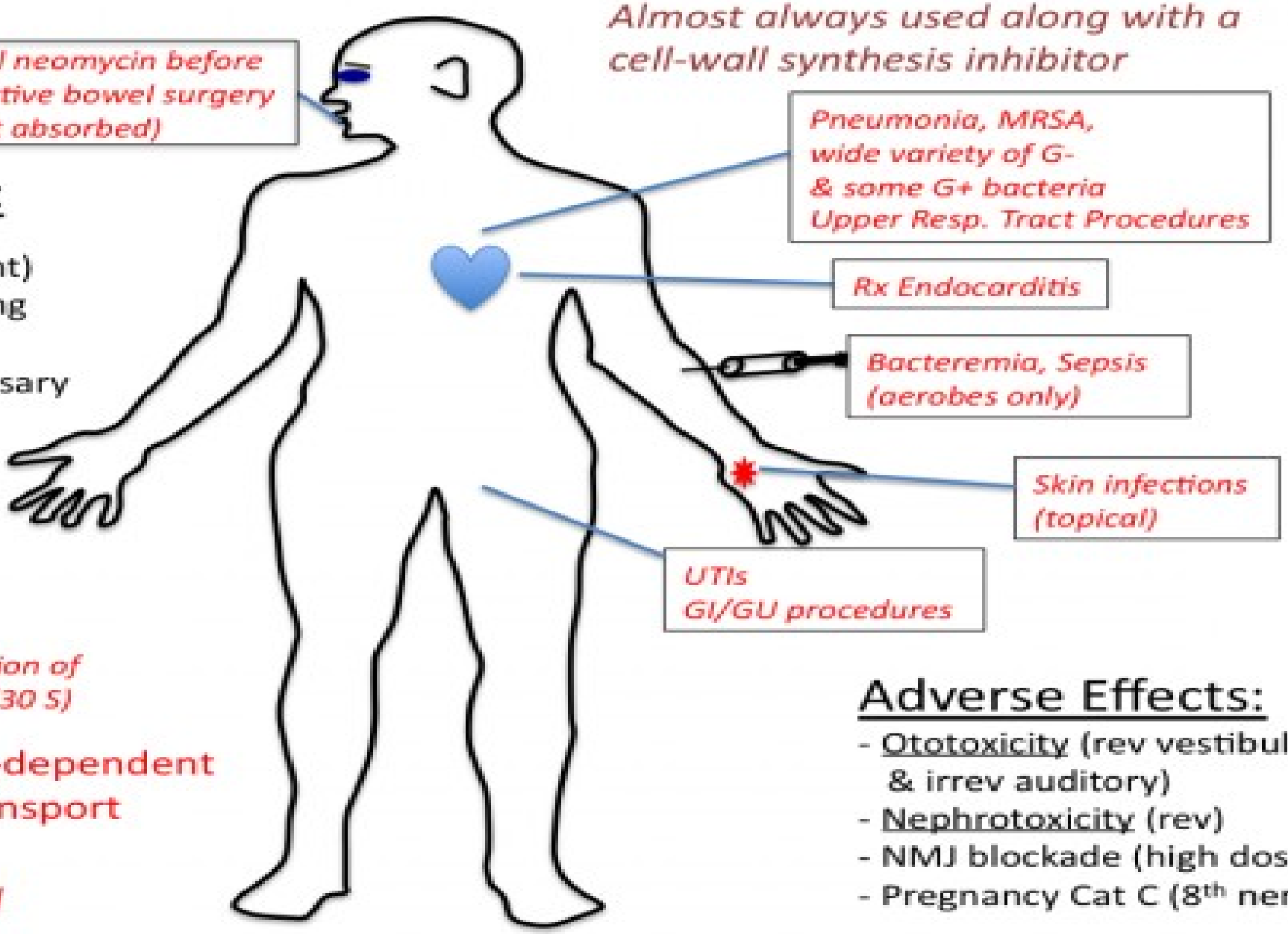
## Routes:

im *or* iv,
topical

## Pharmacokinetics:

-Vd = ECS (25% body weight)
- adjust maintenance dosing based upon [creatinine]
- plasma monitoring necessary

*Almost always used along with a cell-wall synthesis inhibitor*



*Oral neomycin before elective bowel surgery (not absorbed)*

*Pneumonia, MRSA, wide variety of G- & some G+ bacteria Upper Resp. Tract Procedures*

*Rx Endocarditis*

*Bacteremia, Sepsis (aerobes only)*

*Skin infections (topical)*

*UTIs GI/GU procedures*

## Mechanism:

*Irreversible inhibition of Protein Synthesis (30 S)*


$O_2$-dependent transport

*bactericidal*

## Adverse Effects:

- Ototoxicity (rev vestibular & irrev auditory)
- Nephrotoxicity (rev)
- NMJ blockade (high dose)
- Pregnancy Cat C (8th nerve)


Thank
You