Antibiotics

An Basic Pharmacological Overview

Dr. M.A. Strydom

Block 18

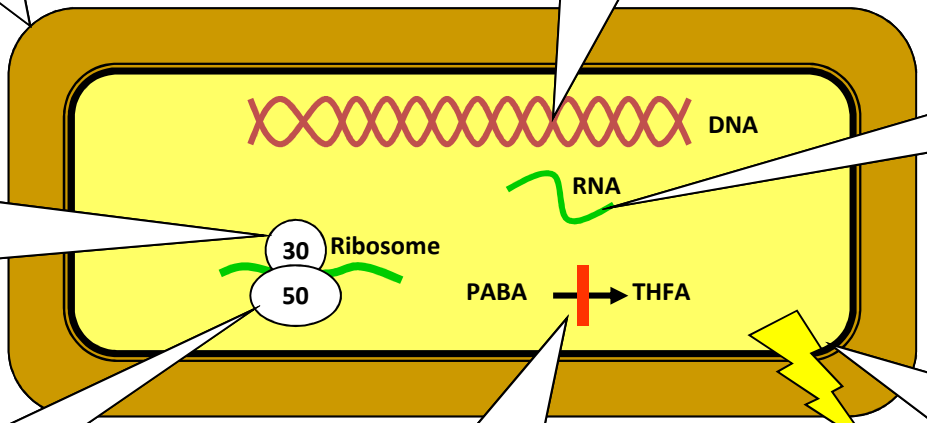
SITES OF ANTIMICROBIAL ACTION

Cell wall synthesis
- Beta-lactams
- Vancomycin
- Isonizide **(Inhibit cell membrane Fx)**
- Ethambutol

DNA replication
- Quinolones (Inhibit DNA gyrase)
- Metronidazole

RNA synth.
- Rifampicin

Protein synth. (Ribosome S30)
- Aminoglycosides
- Tetracyclines



Changes permeability of membrane
- Polymixen

Protein synth. (Ribosome S50)
- Chloramphenicol
- Macrolides
- Clindamycin

Anti-metabolites
- Sulfonamides
- Trimethoprim

(Inhibit folic acid metab)

ß-LACTAMS

PENICILLIN

- **Natural penicillins:**
  - Benzylpenicillin (Pen G)
  - Phenoxymethylpenicillin (Pen V)
- **ß-Lactamase-resistant penicillins:**
  - Oxacillin
  - Cloxacillin
  - Flucloxacillin
  - Dicloxacillin
  - Methicillin
  - Nafcillin
- **Broad-spectrum penicillins:**
  - Amoxicillin
  - Ampicillin
- **Extended-spectrum penicillins:**
  (Antipseudomonal penicillins)
  - Piperacillin
  - Ticarcillin
  - Indanyl carbenicillin

CEPHALOSPORINS

- **1st GENERATION:**
  - Cefadroxil
  - Cefazolin
  - Cephalexin
  - Cephalothin
- **2nd GENERATION:**
  - Cefaclor
  - Cefamandole
  - Cefprozil
  - Cefuroxime
  - Cefotetan*
  - Cefoxitin*

***Cephamycins:**
Anaerobe coverage
e.g. *B. fragilis*

- **3rd GENERATION**
  - Cefdinir
  - Cefixime
  - Cefoperazone
  - Cefotaxime
  - Ceftazidime
  - Ceftibuten
  - Ceftizoxime
  - Ceftriaxone
- **4th GENERATION**
  - Cefepime

CARBAPENEMS

- Imipenem (with Cilastatin)
- Meropenem
- Ertapenem

MONOBACTAMS

- Aztreonam
- Spectrum:

Only aerobic Gr(-) bacteria

ß-LACTAMASE INHIBITORS

- **Clavulanic acid**
- **Sulbactam**
- **Tazobactam**

ß-LACTAM MECHANISM OF ACTION

Interfere with the synthesis of the bacterial cell wall peptidoglycan.

Interfere with last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotic unstable membrane.

CELL LYSIS THEN OCCUR:

- **Osmotic pressure**
- **Activation of autolysis**

PENICILLIN SPECTRA

Natural penicillins:

- Benzylpenicillin (Pen G)
- Phenoxymethylpenicillin (Pen V)

ß-Lactamase-resistant penicillins:

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Broad-spectrum penicillins:

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(Antipseudomonal penicillins)

- Piperacillin
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*** Resistant strains are increasingly seen**

1. **Gram(+) cocci:** ***Strep. pneumoniae****
   Strep. pyogenes
   Strep. viridans group
   Staph. epidermidus*
   Staph. aureus*
2. **Gram(-) cocci:** ***Neisseria gonorrhoeae & N. menegitidis***
3. **Gram(+) bacilli:** ***Bacillus anthracis***
   Corynebacterium diphtheriae
4. **Anaerobes (non-ß-Lactamase producing):**
   Clostridium welchii, tetani & perfringens
5. **Spirochetes:** ***Treponema pallidum (Syphilis)***

Active against streps & staphs, but <u>not</u> enterococci, anaerobes and gram(-) cocci & bacilli

Same spectrum as the natural penicillins, but <u>more</u> activity against <u>gram(-) bacilli</u>: e.g.

- **<u>2 GIT:</u>** ***Salmonella & Shigella***
- **<u>2 UTI:</u>** ***E. coli & Proteus mirabilis***
- **<u>2 Resp:</u>** ***H. influenza & Pertussis***

Same spectrum as the natural penicillins, plus <u>gram(-) bacilli (KEEPS)</u>, plus <u>*pseudomonas.*</u>

K	**E**	**E**	**P**	**S**
Klebsiella	E. coli	Enterobacter	Proteus	Serratia

CEPHALOSPORINS SPECTA

- **1st GENERATION:**
  - Cefadroxil
  - Cefazolin
  - Cephalexin
  - Cephalothin
- **2nd GENERATION:**
  - Cefaclor
  - Cefamandole
  - Cefprozil
  - Cefuroxime
  - Cefotetan §
  - Cefoxitin §

Gram(+) cocci:
- *Staph. aureus** (* Except MRSA)
- *Staph. epidermidis*
- *Strep. pneumoniae*
- *Strep. pyogenes*
- Anaerobic streptococci

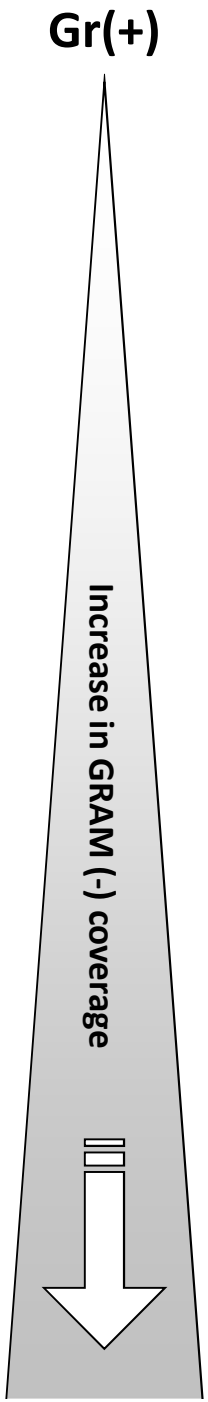
Gram(-) bacilli:
- *E. coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

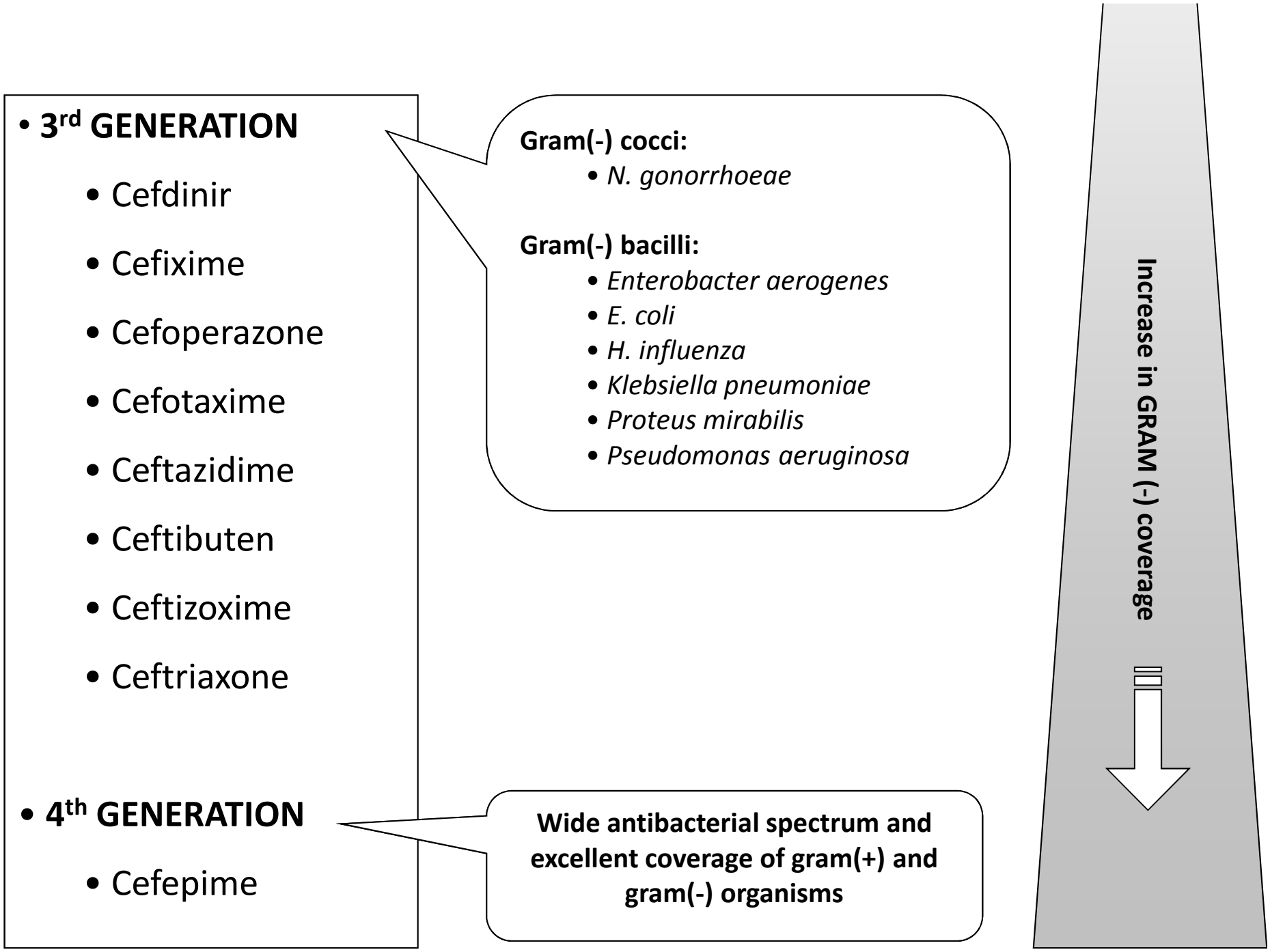
Gram(+) cocci:
- *Strep. pneumoniae*
- *Strep. pyogenes*
- Anaerobic streptococci

Gram(-) cocci:
- *N. gonorrhoeae*

Gram(-) bacilli:
- *Enterobacter aerogenes*
- *E. coli*
- *H. influenza*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

(§) The Cephamycins are active against anaerobes, e.g. *Bacteroides fragilis* of with Cefoxitin is the most potent.

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• 4th GENERATION
• Cefepime
Gram(-) cocci:
• N. gonorrhoeae
Gram(-) bacilli:
• Enterobacter aerogenes
• E. coli
• H. influenza
• Klebsiella pneumoniae
• Proteus mirabilis
• Pseudomonas aeruginosa
Wide antibacterial spectrum and excellent coverage of gram(+) and gram(-) organisms
Increase in GRAM (-) coverage

CARBAPENEMS

- Imipenem (with Cilastatin)
- Meropenem
- Ertapenem

Cilastatin is a dihydropeptidase inhibitor.

Dihydropeptidase is a enzyme present on the renal brush border which is responsible for the inactivation of imipenem.

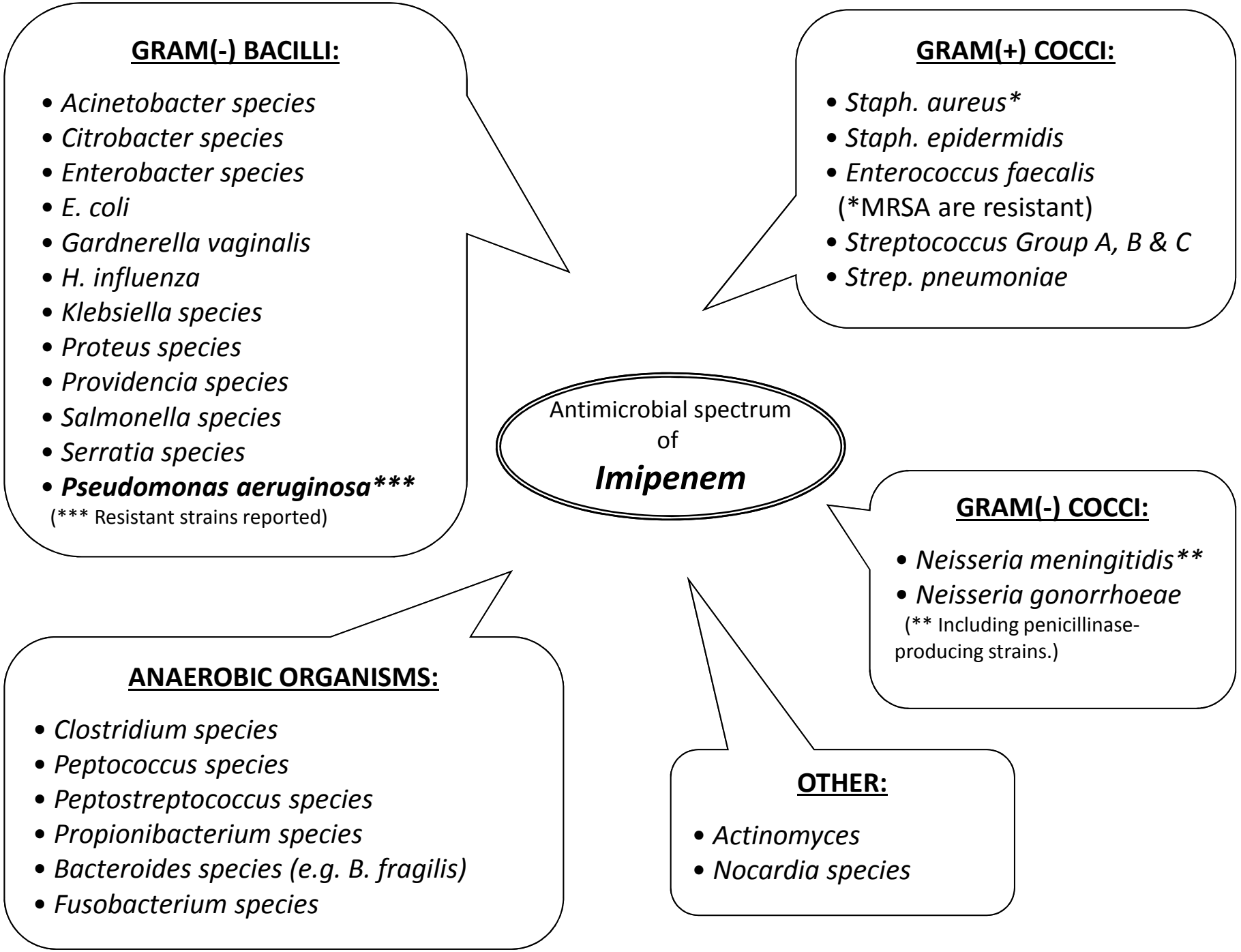
Carbapenems have the broadest bacterial coverage of all the ß-lactams

Spectrum:

Gr(+), Gr(-), Anaerobes

Only the cabapenem class of ß-lactams exhibits **concentration-dependent killing** and have a **postantibiotic** effect.

All the other ß-lactams exhibits time-depending killing with no postantibiotic effect.


GRAM(-) BACILLI:
• Acinetobacter species
• Citrobacter species
• Enterobacter species
• E. coli
• Gardnerella vaginalis
• H. influenza
• Klebsiella species
• Proteus species
• Providencia species
• Salmonella species
• Serratia species
• Pseudomonas aeruginosa***
(*** Resistant strains reported)
GRAM(+) COCCI:
• Staph. aureus*
• Staph. epidermidis
• Enterococcus faecalis
(*MRSA are resistant)
• Streptococcus Group A, B & C
• Strep. pneumoniae
Antimicrobial spectrum
of
Imipenem
GRAM(-) COCCI:
• Neisseria meningitidis**
• Neisseria gonorrhoeae
(** Including penicillinase-producing strains.)
ANAEROBIC ORGANISMS:
• Clostridium species
• Peptococcus species
• Peptostreptococcus species
• Propionibacterium species
• Bacteroides species (e.g. B. fragilis)
• Fusobacterium species
OTHER:
• Actinomyces
• Nocardia species

MACROLIDES

DRUGS:

Erythromycin
- 1st macrolide: Pen substitute
- $t_{1/2}$ = 2 h

Clarithromycin
- methylated form of erythromycin
- $t_{1/2}$ = 3.5 h

Azithromycin
- Larger lactone ring
- $t_{1/2}$ = > 40 h

Telithromycin
- Ketolide, a erythromycin derivative
- $t_{1/2}$ = 10 h

MECHANISM OF ACTION:

Inhibit Protein Synthesis: Bind irreversibly to site on **50S** subunit of bacterial ribosome, thus, inhibiting translocation steps of protein synthesis.

PHARMACOKINETICS:

Route: **1. Orally**
2. IV:
Erythromycin IV is associated with a high-incidence of thrombophebitis.
Azithromycin IV has a better outcome.

Distribution:
- All body fluids, but *NOT* CSF!
- Diffuse in prostatic fluid
- Concentrate in liver
- Accumulates in macrophages

Drug interactions:
Erythromycin, Clarithromycin & Telithromycin inhibit liver microsomal enzyme *cyt*-P-450.

Excretion:

Erythromycin & Azithromycin:
Concentrate in bile (active metabolite), reabsorbed through enterohepatic circulation, converted to inactive metabolite → Urine.

Clarithromycin: Renal & Hepatic → Urine.

SPECTRUM:

1. ERYTHROMYCIN
Same as Pen G

2. CLARITHROMYCIN:
Same as Erythromycin, plus…
- *H. influenza*
- More activity (than Erythromycin) agianst IC pathogens *Chlamydia, Legionella, Moraxella, Ureaplasma spp., +* ***H. pylori***

3. AZITHROMYCIN:
- Less active against *Streps & Staphs*
- More active against Resp. infections:
  - *H. influenza*
  - *Moraxella catarralis*
- Drug of choice: *Chlamydia trachomatis Urethrists*

RESISTANCE:

Most hosp. acquired *Staphs* are resistant.

Mechanisms:
- MO unable to uptake drug / efflux pumps
- ↓ Affinity for 50S site
- Presence of plasmid-associated erythromycin-esterase

SIDE-EFFECTS:

- GIT Disturbances (NB!!!)
- Cholestatic Jaundice
- Ototoxicity: Transient deafness, essp. ↑ dosages

- **CONTRAINDICATED:**
- Pt. with liver dysFx
- Pt. with renal dysFx

TETRACYCLINES

DRUGS:

- Tetracycline
- Doxycycline
- Minocycline
- Demeclocycline

MECHANISM OF ACTION

Inhibit protein synthesis by binding reversibly to the **30S** subunit of bacterial ribosomes.

RESISTANCE:

- Widespread R limits their use
- Active efflux of the drug

Any MO resistant to one tetracycline is resistant to all!

ß-Lactamase-producing *staphs* are resistant to tetracyclines!

KINETICS:

Route:

Orally (adequate, but incomplete abs)
IV, IM (Doxycycline preferred)

Forms unabsorbable chelates with:
- **Ca^{2+}**, Mg^{2+}, Al^{3+}, Fe^{2+}, Fe^{3+}

Adequate penetration to most body fluids. All enter CSF, but only Minocycline provides therapeutic levels in CSF.

All tetracyclins cross the placenta and concentrate in fetal bones & teeth.

Excretion:

Most are reabsorbed from bile, metabolized to glucoronides, and excreted in the urine.

SIDE-EFFECTS:

1. GIT Discomfort.
2. **Deposition of drug in bones & teeth of growing children**.
3. Phototoxicity
4. Vestibular problems (Dizziness, nausea & vomiting)
5. **CONTRA-INDICATIONS:**
   - Pregnancy
   - Breastfeeding mothers
   - Children < 8 yrs

SPECTRUM:

Broad-spectrum AB for Gr(+) , Gr(-), plus non-bacteria MO

< Bacteriostatic >

1. Gr(+) bacilli: *Bacillus anthracis*

2. Gr(-) rods: *Brucella spp (*Tetracycline + Aminoglycoside)*
Vibrio cholerae
Yersinia pestis

3. Anaerobes: *Clostridium perferinges*
Clostridium tetani

4. Chlamydiae spp.

5. Mycoplasma pneumoniae

6. Spirochetes: *Borrelia burgdorferi (Lyme Disease)*
Leptospira interrogans

7. Richettsia richettsii ("Rocky Mountain Spotted fever")

TETRACYCLINES
(cntd)

CO-TRIMOXAZOLE

Sulfamethoxazole + Trimethoprim

Mechanism of Action:

The synergistic antimicrobial activity of Co-trimoxazole results from its inhibition of two sequential steps **(sequential blockage)** in the synthesis of tetrahydrofolic acid.

Sulfamethoxazole inhibits the incorporation of PABA into folic acid by acting as a *PABA antagonist*.

Trimethoprim inhibits the enzyme *dihydrofolate reductase*.

Spectrum: *Rx:* UTI, Resp Infections & PCP

UTI & Prostate:	*E. coli , Proteus mirabilis*	**Gr(-) rods**
GIT Infecions:	*Salmonella typhi, Shigella*	
Resp Infections:	*H. influenza, Legionella pneumophila*	
Listeriosis:	*Listeria monocytogenes*	**Gr(+) bacilli**
PCP:	*Pneumocystis carnii (jeroveci)*	**Fungus: Yeast**

Side-Effects:

- Skin rash
- Nausea & Vomiting
- Hematological disturbances:
  - Megaloblastic anemia
  - Leukopenia
  - Thrombocytopenia

Kinetics:

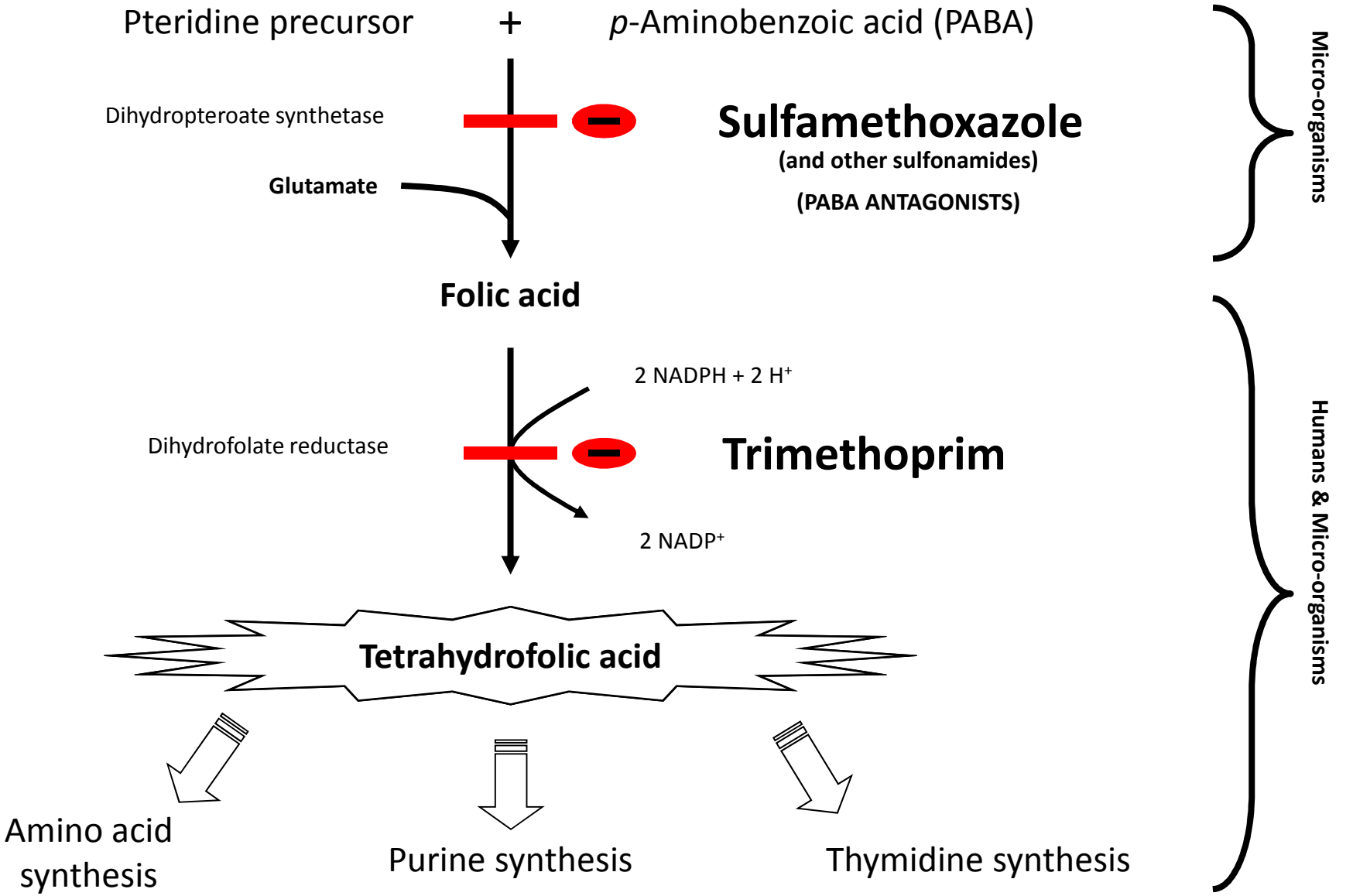
Route: **Orally** / IV (for PCP)

- Trimethoprim is more lipid soluble than Sulfamethoxazole.
- Trimethoprim reaches high [ ] in acidic areas of prostatic and vaginal fluids.

Excretion: Unchanged drug + metabolites appear in urine.

CO - TRIMOXAZOLE

(Mechanism of Action)



CHLORAMPHENICOL

MECHANISM OF ACTION:

Binds to **50S** ribosomal subunit and inhibits protein synthesis at the peptidyltransferase reaction.

_____

↑Levels may also inhibit mammalian mitochondrial protein synthesis, which may cause bone marrow toxicity*.

PHARMACOKINETICS

Route: Orally or IV

DRUG IS LIPOPHILLIC
- Completely absorbed in the GIT
- Widely distributed throughout the body
- Crosses BBB

Excretion: 10%(GF) + 90%(Secreted) (metab)
<----------URINE---------->

SPECTRUM:

- Broad-spectrum antibiotic: active against wide range of Gr(+) & Gr(-)
- Excellent activity against anaerobes, e.g. *B. fragilis*
- *Richettsiae*
- NO ACTIVITY AGAINST: *Pseudomonas aeriginosa & Chlamydiae*

**Mitochondrial Ribosomal Interference within mammalian cells.*

SIDE-EFFECTS

Use is limited to life-threatening infections due to serious S/E:

1. Anemias

2. **GRAY BABY SYNDROME:**

Neonates ↓ Capacity to glucuronylate the drug
Under-developed renal Fx

Thus, ↓ Excretion = Accumulation = Mitochondrail RI*
*Poor feeding, depr. breathing, CV collapse, **cyanosis ("Gray baby")**, death.

3. Drug Interactions: Inhibitions of *cyt*-P-450

CLINDAMYCIN

MECHANISM OF ACTION:

Binds to the **50S** ribosomal subunit, thus, inhibiting the translocation steps of protein synthesis.

RESISTANCE:

Clostridium difficile is **ALWAYS** resistant to clindamycin!

KINETICS

- Well absorbed via the oral route
- Distributes well into all body fluids, EXCEPT CSF!
- Do NOT penetrate the brain
- Good bone penetration

EXCRETION:

- Metabolites in bile & urine (GF)

SPECTRUM:

Primarily for the Rx of **anaerobic** infections, e.g. *B. fragilis*

Active against non-enterococcal, Gr(+) cocci

SIDE-EFFECTS:

1. Skin rashes
2. **Pseudomembranous colits**
   - Overgrowth of *Clostridium defficile*
   - Rx: 1st line → Metronidazole
     2nd line → Vancomycin
     (When metronidazole is not effective)

VANCOMYCIN

Vancomycin is a **Tricyclic Glycoprotein!** NB for Multi-resistant organisms!

Mechanism of Action

Inhibit bacterial cell wall synthesis by binding to D-Ala-D-Ala portions of cell wall precursors and prevents polymerization of peptidoglycans. Thus, weakening of cell wall and damaging of the underlying cell membrane.

Pharmacokinetics:

NOT ABSORBED IN THE GIT!!!

Route:

1. **Slow IV:** For Systemic infection / Prophylaxis
2. **Orally:** For Anti-biotic induced colitis* (*Clostridium defficile*) (*When metronidazole is ineffective)

Excretion: Mostly unchanged in the urine
Normal $t_{1/2}$ of drug = 6-10 h

If in end-stage renal disease the $t_{1/2}$ may increase to over 200 h

Spectrum : ONLY GRAM (+) !!!

Gram(+) cocci:

- *Staph. aureus** (*Inc MRSA)
- *Staph. epidermidis** (*Inc MRSE)
- *Strep. Group A, B, C*
- *Strep. Pneumoniae*
- *Enterococcus faecalis*

Gram(+) bacilli:

- *Listeria monocytogenes*

Anaerobes:

- *Clostridium species*

Other:

- *Actinomyces*

Side-Effects:

- Fever
- Chills
- Phlebitis at infusion site
- **Flushing "Red-man syndrome"***
- **Shock***

***Rapid infusion leads to histamine release**

Restrict Rx for…

- Serious infections (ß-Lactam resistant)
- Gr(+) micro-organisms
- Patient with serious Gr(+) infection with ß-Lactam hypersensitivity.

Resistance:

- Plasmid-mediated changes in permeability to the drug
- Decreased binding to receptor (e.g. D-Ala → in resistant MO → D-Lactate)

If MO is resistant to Vancomycin? Newer protein synthesis inhibitors, nl: quinopristin/dalfopristin & linezolid

AMINOGLYCOSIDES:

- **Amikacin**
- **Gentamicin**
- **Tobramycin**
- **Streptomycin**

Mechanism of Action:

Binds to the **30S** ribosomal subunit and distorts its structure, thus, **interfering with the initiation of protein synthesis.**

They also allow misreading of the mRNA causing mutations or premature chain termination.

Kinetics:

Route: Topical & **Parenteral (IV)**

- **[ ]-Dependent killing, with PAE!**
- **Aminoglycosides = Highly polar!**
- Dosage based on lean body mass, because these drugs don't distribute into fat.
- Don't cross BBB (May be administered Intrathecally)
- Crosses placental barrier!
- High [ ] accumulate in renal cortex, endolymph & perilymph of inner ear… Toxic!

Excretion: No metabolism in host, thus, unchanged drug appears in urine (GF).

SPECTRUM:

Aerobic* Gram (-) bacilli, incl. *Ps. aeruginosa*:

- *Brucella spp.* (Gentamicin + Doxycycline)
- *Francisella tularensis* (Gentamicin)
- *Klebsiella spp* (Gentamicin + Antipseudomonal Penicillin)
- *Pseudomonas aeruginosa* (Tobramycin + Antipseudomonal Penicillin)
- *Yersinia pestis* (Streptomycin + Doxycycline)

Gram (+) cocci:

- *Enterococcus spp.* (Gentamicin + PenG)
- *Streptococcus agalactiae* (Gentamicin + PenG)

***Oxygen-dependent transport system of MO is needed for drug entry. Thus, only aerobic MO will be targeted by aminoglycosides.**

Side-Effects:

- **Ototoxicity** (↑ Peak levels + duration of Rx = ↑ Risk)
- **Nephrotoxicity**
- Neuromuscular paralysis
- Skin rash (with Neomycin)

Fluoroquinolones

1st GEN: Nalidixic acid---------- **Narrow spectrum: MO confined to Urinary Tract**

2nd GEN: Ciprofloxacin, Norfloxacin, Ofloxacin

Systemic aerobic GRAM (-) organisms causing UTIs:

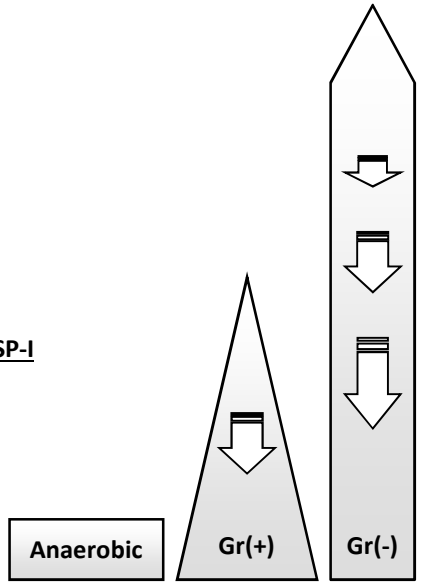
Enterobacteriacea, Pseudomonas spp., H. influenza, Moraxella catarrhalis, Legionella spp., Chlamydia, Neisseria gonorrhea

3rd GEN: Gatifloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin

Same as above, plus:

- **INCREASED ACTIVITY AGAINST GRAM(+) MO causing RESP-I**
  - *Streptococcus pneumoniae*
- **ATYPICAL MO:** *Mycoplasma pneumoniae*

4th GEN: Trovafloxacin---------- **Improved Gr(+) coverage**, Maintains Gr(-) activity, **Gains anaerobic coverage**



Mechanism of Action:

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.

DNA gyrase = Responsible for super-coiling of DNA

Topoisomerase IV = Responsible for cell division

[ ]-Dependent Killing, with PAE! Bacteriocidal

Pharmacokinetics:

Route: Oral or IV

↳ Sucrulfate, antacids (Al^{3+}/Mg^{2+}), dietary supp. (Fe/Zn), Ca^{2+} = ↓ ABSORPTION

- All quinolones distributes well into all body tissues/fluids
- High levels in bone, urine, kidney, prostatic tissue and lungs

Excretion: Renal route → Urine

Resistance may develop due to:

1. Altered targets: DNA site mutations
2. ↓ Accumulation: ↓ Porins
   ↑ Efflux pumps

Side-Effects:

- GIT disturbances
- Headache & dizziness
- Phototoxicity
- Drug interactions: (-) cytP450
- Connective tissue problems: DON'T USE IN: Preg, breast feeding, < 18 yrs (Articular cartilage erosion)
- CI: Spar/Levo/Moxi- , prolong QT…. Arrhythmias!!!!