ANTIMICROBIALS

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Antibiotics are Life Saving drugs..

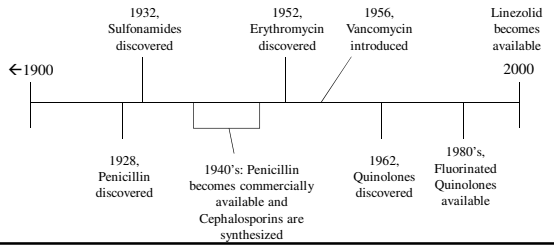
- ***Antimicrobials are considered as the greatest discovery of the twentieth century***.
- In the pre-antibiotic era, infectious diseases accounted for significant morbidity and mortality and invasive medical procedures were fraught with the risk of infection.
- All this changed with the use of antimicrobial agents.

Antibiotics

- An **antibiotic** (from Latin *anti*, "against" and Greek *βιοτικός* - *biotikos*, "fit for life") is a chemotherapeutic agent that inhibits or abolishes the growth of bacteria.
- The term originally referred to any agent with biological activity against living organisms, or more recently against micro-organisms, including bacteria, fungi, or protozoa;
- however modern usage of the term "antibiotic" is specific to agents with antibacterial activity

History of Antibiotics

Time line of events



History of Antibiotics (1800's)

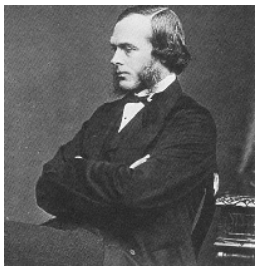
- 1800's Limited ideas on how diseases were generated
- No such thing as antiseptics or sterile surgical conditions existed or were practiced
- Surgical instruments were used from one operation to another without cleansing

History of Antibiotics (1800's)

- Pasteur & Koch had shown a connection between disease & bacteria
- People received smallpox vaccinations
- Not many had high opinions of this work
- One person did however:

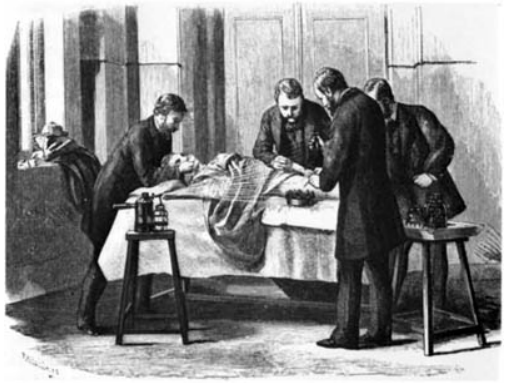
History of Antibiotics (1800's)

Joseph Lister



Joseph Lister

- He is credited for introducing antiseptic surgical procedures
- He introduced the human use of carbolic acid to clean wounds and infected areas
- He also used carbolic spray in theatres to disinfect these areas
- Most of his work was based on studies by Semmelweiss
- Today still he is recognized - '*Listerene*'



Ignatz Semmelweiss (1818-1865)

'Defender of motherhood'

- He was a physician at a maternity hospital in Vienna – '*Allgemeine Krankenhaus*'
- The hospital had 2 sections:
  - (1) staffed by doctors
  - (2) staffed by widwives and nurses
  - Mortality rate in section (1) ~ 18% - 36%
  - Mortality rate in section (2) ~ 1%

Ignatz Semmelweiss (1818-1865)

- He noticed dr's went straight from the post-mortum room (female 'puerperal fever' victims were dissected here) to deliver new babies
- Midwives were not involved in these dissections
- Was there a connection?

Ignatz Semmelweiss (1818-1865)

- In May 1847, he got dr's to wash their hands with chlorinated lime water after dissections and before delivering any babies
- By the end of the year, mortality dropped from 12.2% to 3.4% and to 1.2% the year after
- A few years later some people began to make the connection between disease and 'unseen' things

Ernest Duchesne (1896)

Did he discover penicillin's antibiotic properties

32 years before Alexander Fleming?

Ernest Duchesne (1896)

- He had seen that barracks stablehands were purposely storing saddles in dark humid places
- This was done in order for some kind of fungus to form on the leather
- According to stablehands these fungi were excellent for healing wounds on the backs of horses

Ernest Duchesne (1896)

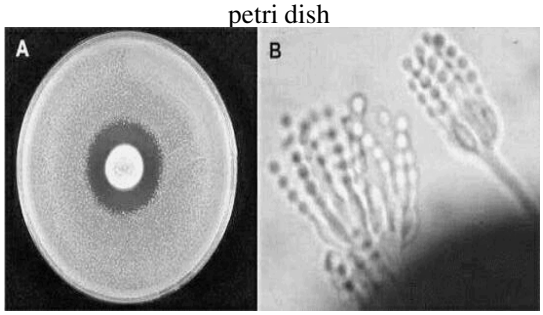
- In 1897 in Lyon he defended his doctoral thesis "*Contribution to the study of vital competition in micro-organisms: antagonism between moulds and microbes*"
- He died early with his work largely ignored and eventually forgotten

The French honouring their "Flemming"

Alexander Fleming - 1928

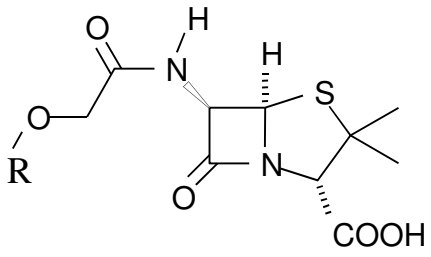
1928 - Alexander Fleming

Bread mold (*Penicillin notatum*) growing on petri dish



1939 - *Florey, Chain, and Associates*

Isolated, purified and synthesized large amounts of Penicillin



BUSHMAN ?

But the miracle seems to be short lived

- Irresponsible and erratic use of these life-saving instruments has resulted in the development of **drug resistance** in many organisms and deaths due to hospital-acquired infections is on the rise.
- It appears that our complacency is leading us into bigger problems in the millennium that has just dawned.

Hospital acquired resistance

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

"Antibiotics have been given for everything from headaches to ingrown toenails; they are swallowed, sucked, injected and smeared; they are painted on cuts, dumped into wounds, fed to the chickens and pigs and spread on the floors of the hospital wards."

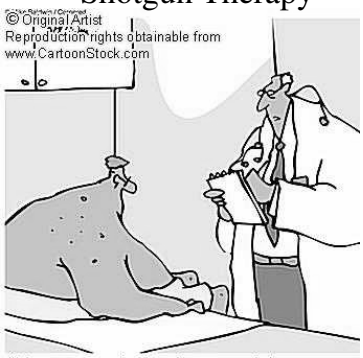
-Dr. Richard Novick

Why do doctors over-prescribe antibiotics?

70-80% of prescriptions for antimicrobials are probably written unnecessarily

- **Lack of confidence:**
  - **Inability to make a fairly accurate clinical diagnosis is one of the most common causes for over-drugging.**
  - **Inability to convince the patient about the nature and simplicity of the illness and about the non-requirement of antibacterials is another reason.**
  - **Some doctors may harbour a notion that it is better to give "*something powerful*" for every patient so as to achieve "dramatic" results (*Shot Gun therapy*).**

'Shotgun Therapy'



"It's a prescription for one of those new super-antibiotics. You won't just get better, you'll get even."

CLASIFICATION OF ANTIMICRIOBIAL AGENTS

- Inhibitors of cell wall synthesis
- Inhibitors of protein synthesis
- Inhibitors of metabolism (folate inhibitors)
- Inhibitors of nucleic acid

The Action of Antimicrobial Drugs

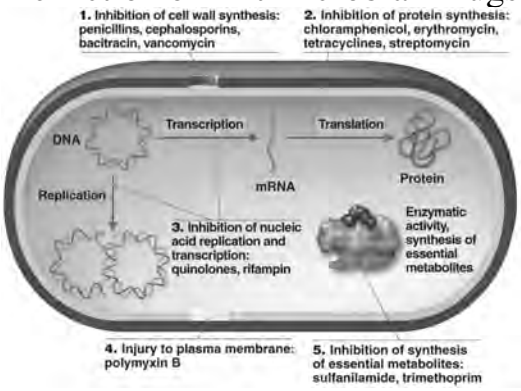


Figure 20.2

Inhibitors of cell wall synthesis

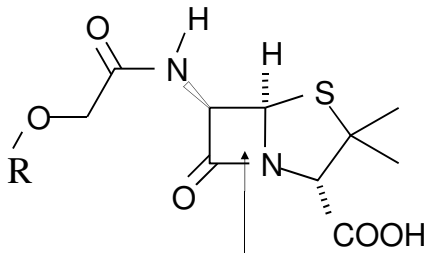
- B-lactams: penicillins, cephalosporins
- Carbapenems
- Monobactam
- Vancomycin
- Polymixins

B-Lactams - Penicillin

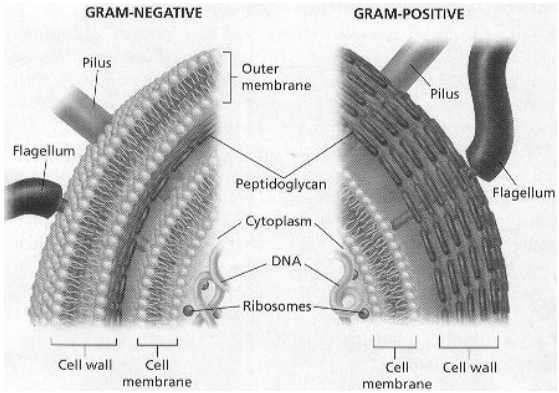
Mechanism of action

- Inhibit the final polimerization (transpeptidation reaction) of peptidoglycan synthesis
- Binds to penicillin binding proteins (PBP's):
  - induction of endogenous enzymes (autolysins)
  - inhibit proper cell wall synthesis
    - ↳ bacterial lysis

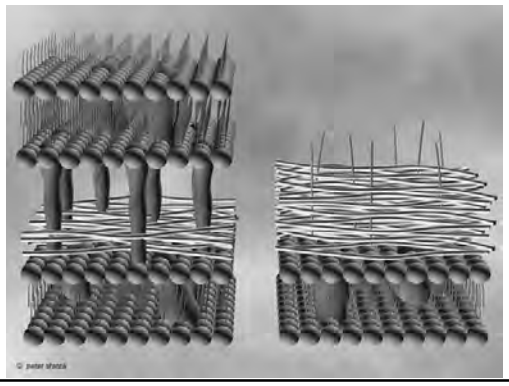
Structure of penicillin



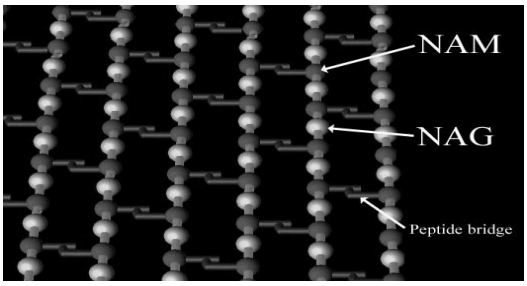
4 sided Beta-lactam ring



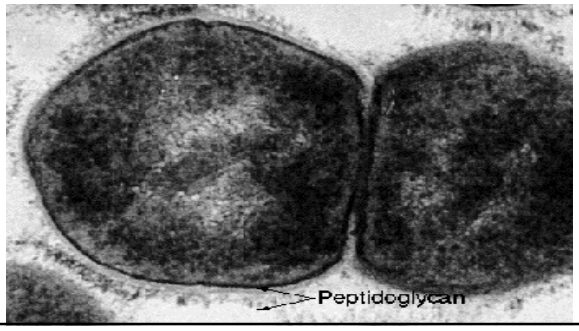
Gram neg. Gram pos



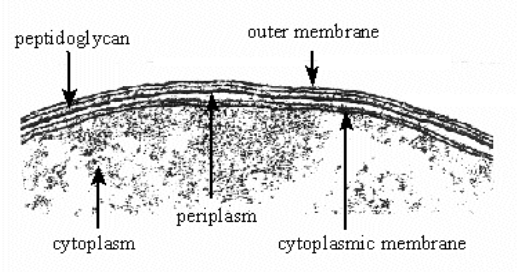
A cartoon of the peptidoglycan mesh

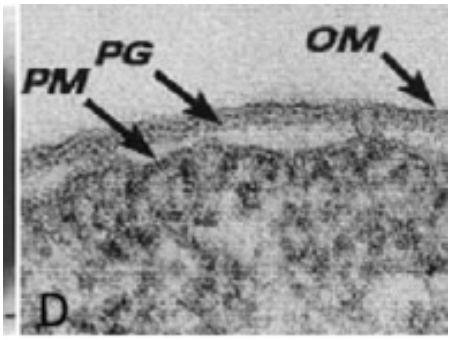


Gram + bacterial cell wall

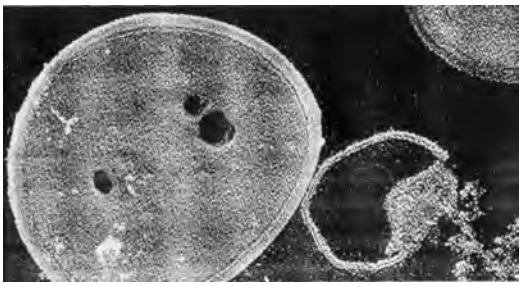


Gram - bacterial cell wall





Staphylococcus after exposure to penicillin



Acid labile (sensitive)

- **Pen-G** (Benzyl)
- t1/2 ½ - 1 hour
- Acid labile
- B-lactamase sensitive
- Narrow spectrum

Acid stable(resistant)

- **Pen-V** (phenoxymethyl)
- 1. Acid stable
- 2. Narrow spectrum
- 3. t½ ½ – 1 hour
- 4. ß-lactamase sensitive

Spectrum

Cocci
- + Strepto, pneumo, staphylococci
- - Neisseria menengitidis,gonococci

- Bacilli + Clostridium welchi/tetani
- Spirochetes: Treponema pallidum/vincenti

Broad Spectrum Penicillin's Ampicillin

- 35% oral absorption
- Concentrates in bile
- t1/2 ~ 6 hours
- Acid stable

Amoxycillin

- 70% - 90% oral absorption (not influenced by food)
- t1/2 ~ 8 hours
- Spectrum = previous + Shigella, Salmonella, H. influenza, E. coli

B-lactamase Resistant Penicillins

- Oxacillins - Cloxacillin, flucloxacillin
- Acid stable
- B-lactamase resistant
- Clavulanic acid + amoxycillin
  - Clavulinic acid binds covalent with b-lactamases inactivating it

Penicillin's activity

- Bacterial meningitis: *N meningitidis, S pneumoniae*
- Bone & joint infections: *S aureus*
- Skin & soft tissue: *S pyogenes, S aureus*
- Pharyngitis: *S pyogenes* (Pen V, amoxycillin)
- Otitis media: *S pyogenes*, H influenza (amoxycillin)
- Bronchitis: mixed infections (amoxycillin)
- UTI's: *E coli* (amoxycillin)
- Gonorrhea: amoxycillin (+ probenicid), quinolones
- Endocarditis: *S viridans, E faecalis*

Penicillin's side-effects

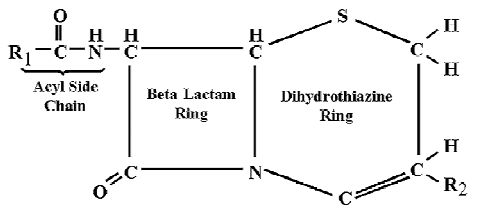
- Hypersensitivity reactions: degradation products (penicilloic acid) combine with host protein and become antigenic
- Skin rashes
- Serum sickness
- Anaphylactic shock: AAAA's
- Superinfections: GIT

Penicillin Allergy

Penicillin - Resistance

- Alteration of the PBP's
- Beta-lactamase production
- Failure to reach PBP targets (penetration)

Cephalosporins



General Structure of Cephalosporins

Cephalosporins

Mechanism of Action

- Binds to PBP → inhibits transpeptidation of peptidoglycan
- Activation of autolytic enzymes
- → inhibition of cell wall synthesis

5 Major categories of use

- Gm - infections e.g. klebsiella spp.
- Rx of mixed infections or initial Rx of unknown infections
- Prophylaxis before major surgery: GIT, pelvic, orthopedic
- Meningitis by Gm- : cefotaxime, moxalactam
- Allergy to penicillins

1st Generation

- Parenteral: Cephalothin, cefazolin
- Oral: cephalexin, cephradine, cefadroxil
- Spectrum: staphylococci (except MRSA), Streptococci (not enterococci), E. coli, Proteus, Klebsiella

2nd Generation

- Parenteral: cefamandole, cefuroxime (crosses BBB → bacterial meningitis)
- Oral: cefaclor, cefprozil, cefuroxime, loracarbef
- Spectrum:
- as for 1st generation + Haemophilus (including B-lactam producers)
- Bacteriodes: cefoxitin

3rd Generation

- Parenteral: cefotaxime, ceftriaxone
- Oral: cefpodoxime, cefbuten, cefixime
- Spectrum:
- as for 2nd generation + most other Gm- bacilli except pseudomonas
- Bacteriodes: moxalactam

4th Generation

- Parenteral: ceftazidime, cefepime, cefpirome
- Spectrum: previous generations + pseudomonas

Untoward effects

- Allergies: anaphylaxis, fever, skin rash, nephritis, cross-sensitivity with penicillins (6-18%)
- Toxic: severe pain after I.M, thrombophlebitis after I.V, renal interstitial nephritis

CARBAPENEMS

- Based on B-lactam structure (thienamycin)
- Imipenem/cilastatin: Broad spectrum
- Enterobac., pseudomonas, bacteriodes, Gm+.
- Not MRS, clostridium difficile
- Combined with cilstatin(dehydropeptidase inhibitor - prevents renal tubular degradation)
- S/E: seizures at high doses

Meropenem

- Similar to imipenem but does require cilstatin
- Less Gm+ compared to imipenem
- Alternative to cefotaxime & ceftriaxone in the management of meningitis caused by penicillin-resistant streptococcus pneumonia

MONOBACTAMS

e.g. Aztreonam

- Mechanism: based on B-lactam structure
- Active against Gm-: Rx of septicaemia and complicated UTI's
- S/E: allergic rash, GI upset, liver and marrow toxicity

VANCOMYCIN

- Mechanism: Inhibits synthesis of bacterial cell wall as well as peptioglycan polymerization
- Spectrum: multi drug resistant organisms such as methicillin-resistant staph & enteroc
- Colitis due to *Chlostridium difficile*
- Prophylaxis in dental pt's receiving prosthetic devices and also who has cardiac vulvular lesions

Vancomycin Pharmacokinetics

- Systemic use: slow I.V. Nor absorbed orally
- Inflammation allows penetration into meningis
- 90-100% excreted via glomerulas
- t1/2 ~ 6-10 hrs

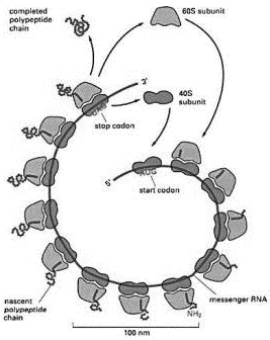
Vancomycin Adverse effects

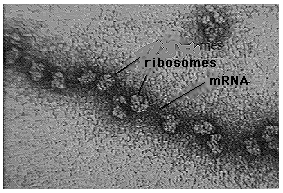
- Fever, chills, phlebitis at site of injection
- Shock can occur after rapid I.V
- Dose-related hearing loss in renal failure

POLYMIXINS

- Selective activity: Gm- Pseudomonas, coliform org.
- Bacteriocidal - decreases cell membrane function
- Topical use: wounds, burns, eyes
- I.V: Pseudomonas, bacterimia peritonitis
- Neuro-and nephro toxic, respiratory arrest

INHIBITORS of PROTEIN SYNTHESIS

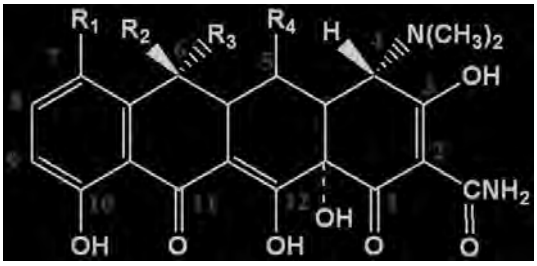




INHIBITORS of PROTEIN SYNTHESIS

- Tetracyclines
- Aminoglycosides
- Macrolides
- Chloramphenicol
- Oxazolidinones

Tetracyclines



Tetracyclines

- ***Oxytetracycline, minocycline, doxycycline***
- (t1/2 ~ 8 hrs) (t1/2 ~ 12 hrs) (t1/2 ~ 23hrs)

- Mechanism of action:
- Decreases bacterial protein synthesis by inhibiting bacterial ribosome action at the 50S sub units - static
- Increased resistance towards it

Tetracyclines Pharmacokinetics

- Route of administration: oral, parenteral, topical
- No penetration into CNS except minocycline
- Crosses placenta; appears in breast milk
- Excreted into urine & bile

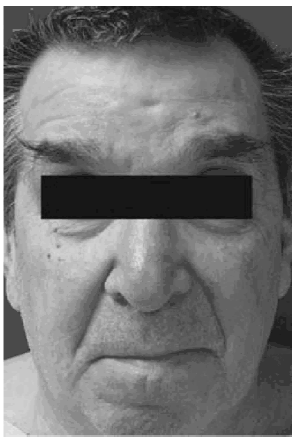
Tetracycline Clinical use

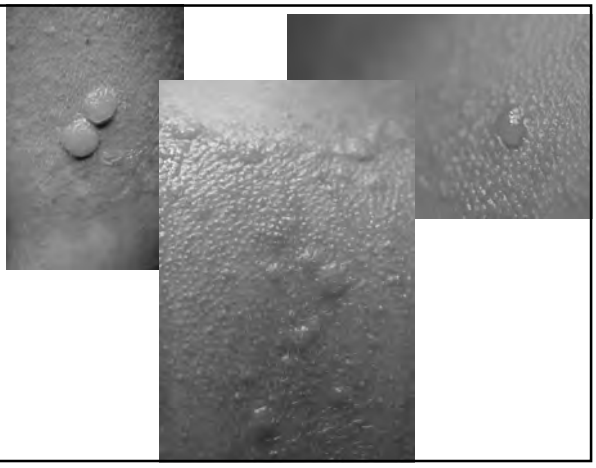
- *Mycoplasma pneumoniae*
- Chlamydiae infections
- Rickettsiae
- Vibrio cholera
- Yersinia pestis
- Brucella
- Acne: *P acnes, S epidermidis*
- Alternate to penicillin venereal disease
- Prophylaxis in meningococci contacts

Tetracycline Adverse effects

- GIT: candidiasis, enterocolitis
- Liver & kidney toxic
- Overgrowth of staphylococci
- Photosensitivity
- Vestibulo toxic
- Seldom: increased intracranial pressure, Fanconi syndrome (renal)
- Binds with Ca^{++} >> deposited into newly formed bone e.g teeth >> "Orange tooth syndrome"

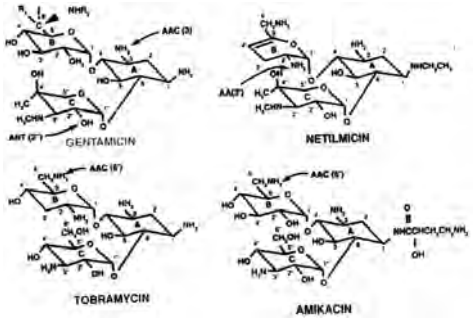
Photodermatitis





Orange Tooth Syndrome

Aminoglycoside Structures



AMINOGLYCOSIDES

- Mechanism: Inhibits bacterial ribosomal action >> decreases protein synthesis
- Spectrum: Gm- bacilli including pseudomonas, alone not active against streptococci
- Active against most staphylococci - not 1st choice & not used alone
- No activity against anaerobes

Aminoglycosides
Pharmacokinetics

- Policationic structure >> highly water-soluble, decreased oral absorption
- Decreased CNS entry
- Excreted via glomerular filtration
- Used: I.V, I.M, Topically, orally for GIT infections & sterilizes prior to surgery

Aminoglycosides

- Anti-*Enterobactericeae*, *P. aeruginosa*
  - Gentamicin
  - Netilmicin, amikacin
  - Tobramycin (esp *P. aeruginosa*)
- Anti-mycobacterial
  - Streptomycin, amikacin, capreomycin
- Anti-enterococcal (with ampicillin)
  - Gentamicin
- Anti-protozoan (amebiasis, cryptosporidiosis)
  - Paromomycin
- Anti-gonococcal
  - Spectinomycin

Aminoglycosides

- Streptomycin:
- Gm- spectrum
- Seldom used except in the Rx of TB
- Gentamycin:
- Gm-, Gm+: Rx of staph with penicillin
- Complicated UTI's
- Endocarditis
- Peritonitis
- Neonatal meningitis

Aminoglycoside Adverse Effects

- Nephrotoxicity
- Ototoxicity
  - Risk factors: age, inherited risk
  - Auditory
    - streptomycin; gentamicin>tobramycin>amikacin
  - Vestibular (most troublesome in elderly)
- *Neuromuscular blockade*
  - *Inhibition of presynaptic release of acetylcholine*
  - *Rare, preventable by slow infusion*

Risk Factors for Aminoglycoside Nephrotoxicity

- Patient factors
  - Age, volume depletion
  - Hepatic dysfunction
- Concomitant drugs
  - Vancomycin, amphotericin B
  - Foscarnet, radiocontrast
- Aminoglycoside factors
  - Specific drug
  - Size of dose and duration of therapy
  - Frequency of dosing

Factors Supporting Single-Daily Dosing of Aminoglycosides

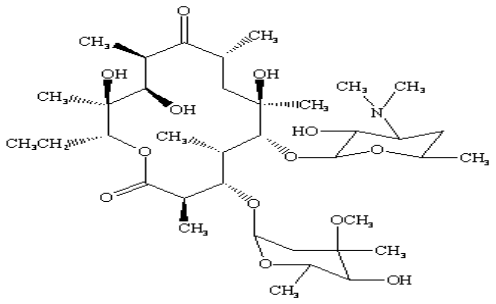
- Concentration-dependent bactericidal activity
- Post-antibiotic effect
- Avoidance of adaptive resistance phenomenon
- Reduction in nephrotoxicity in animal models

Macrolide

- History
  - 1952 Erythromycin derived from *Streptomyces erythreus*
    - Originally found from a Philippines soil sample
  - Class of agents given the name Macrolide due to the 14-member macrocyclic lactone ring
  - Newer variants: Azithromycin, Clarithromycin

Macrolide Structures

Erythromycin



Macrolide Antibiotics

- Erythromycin
- Clindamycin
- Roxithromycin
- Clarithromycin
- Azithromycin
- Telithromycin

Activity of Macrolides

- Erythromycin
  - Streptococci*, Staphylococci*
  - *Moraxella catarrhalis, Bordetella pertussis*, Corynebacteria
  - *Mycoplasma pneumoniae*, *Chlamydia* spp., *Legionella* spp.
  - *Neisseria gonorrhoeae**
  - *Campylobacter jejuni*
  - *Treponema pallidum*

*Acquired Resistance Common

Activity of Macrolides

- **Clindamycin**
- Staphylococci (including ß-lactamase & methicillin resistant strains)
- ß-haemolytic streptococci
- *Diplococcus pneumoniae*
- *Clostridium perfringes*
- *Corynebacterium acnes*
- *Actinomyces israelli*
- *Bacteroides fragilis*

Activity of Macrolides

Clarithromycin, Azithromycin, Telithromycin

- *Haemophilus influenzae, S pyogenes*
- *Helicobacter pylori* (clarithromycin), *Shigella* and *Salmonella* spp. (azithromycin)
- *S aureus, T pallidum*
- Atypical mycobacteria: *Bordetella pertussis, M. pneumoniae, M. fortuitum,, M. abscessus, M. avium, Legionella* spp

Clinical Uses of Macrolides

- Pharyngitis
- Sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated skin infections

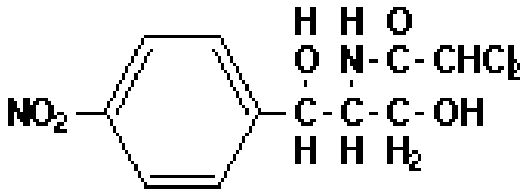
Clindamycin Selected Clinical Uses

- Pharyngitis
- Tonsillitis
- Otitis media
- Sinusitis
- Bronchitis
- Soft tissue infections
- Dental infections(periapical abscesses & gingivitis)
- Acute & chronic osteomyelitis

Adverse Effects of Macrolides

- Nausea, vomiting, abdominal pain
- Sensorineural Hearing Loss
- Pseudomembrane colitis(**Clindamycin**)
- Cholestatic hepatitis
- Prolongation of QT Interval
  - Torsades de pointes

CHLORAMPHENICOL



Chloramphenicol

Chloramphenicol
Clinical uses

- Typhoid fever
- *H. influenza* meningitis
- Mixed infections of the CNS
- Anaerobic infections
- Rickettsiae infection - alternate to tetracyclines in children and also in pregnant women

Chloramphenicol
Adverse effects

- GIT - candidiasis

Reversible, dose/duration-dependent bone marrow toxicity

•inhibition of mitochondrial protein synthesis

•anemia, leukopenia, thromboxytopenia at ~ 5-7 days after initiation

•fatalities and some cases of subsequent acute myeloblastic leukemia

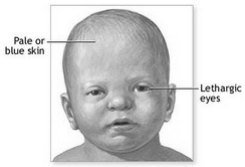
Chloramphenicol
Adverse effects

- Idiosyncratic aplastic anemia/pancytopenia incidence of 1 in 30,000
- fatality rate high if develops
- incidence of acute leukemia with recovery
- not dose related

Chloramphenicol
Adverse effects

- gray baby syndrome
  - – pre-mature babies or neonates
  - – excessive plasma chloramphenicol
    - » relatively undeveloped hepatic conjugation
    - » relatively inadequate renal elimination
  - – onset at ~ four days Rx Vomiting, respiration, green color to loose stools, hypothermic, cyanotic (gray color) and possibly death

Gray-Baby Syndrome



Linezolid

- Synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics.
- it stops the growth of bacteria by disrupting their production of proteins. Although many antibiotics work this way, the exact mechanism of action of linezolid appears to be unique to the oxazolidinone

Linezolid….

- Is active against most Gram-positive bacteria that cause disease including:
  - streptococci,
  - vancomycin-resistant enterococci (VRE), and
  - methicillin-resistant *Staphylococcus aureus* (MRSA).
- The main indications are:
- infections of the skin and soft tissues and
- pneumonia (particularly hospital-acquired pneumonia

Linezolid….

- When administered for short periods, linezolid is a relatively safe drug; it can be used in patients of all ages and in people with liver disease or poor kidney function.
- Common adverse effects of short-term use:
  - include headache, diarrhea, and nausea.
- Long-term use, however, has been associated with serious adverse affects:
  - can cause bone marrow suppression and low platelet counts, particularly when used for more than two weeks.

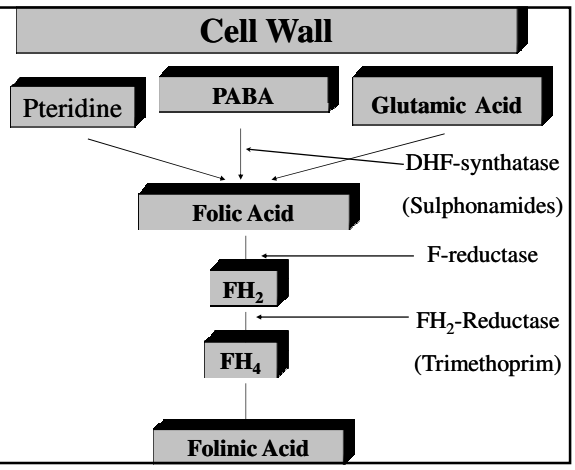
Linezolid….

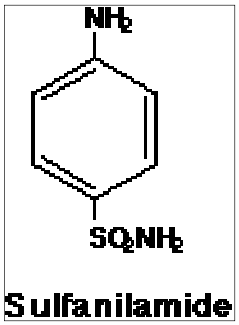
- If used for longer periods still, it may cause peripheral neuropathy (which can be irreversible),
- optic nerve damage, and
- lactic acidosis (a buildup of lactic acid in the body), all most likely due to mitochondrial toxicity

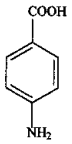
FOLATE INHIBITORS

Sulphonamides

Trimethoprim







Mechanism of Action

- Sulphonamides: inhibits DHF-synthetase
- Trimethoprim: Inhibits FH_2-reductase

Co-trimoxazole=sulphamethoxazole + trimethoprim

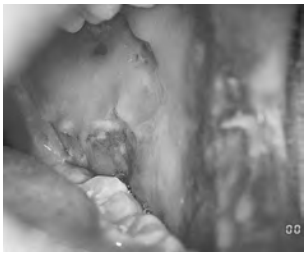
Spectrum

- Protozoa: *pneumocystis carinni* pneumonia
- GM+ cocci: *S.pneumoniae*
- GM- cocci: *N. gonorrhoea / meningitidis*
- GM- bacilli: *H. influenza L pneumophilia*
- GM- enteric: *E. coli*
  P. mirabilis
  S. typhi, Shigella

Adverse Effects

- Malaise & GI upset
- Haemolysis in G-6-P deficient pt's
- Macrocytic anaemia (folate deficiency)
- Teratogenicity (folate deficiency)
- Toxic skin reactions: Stevens-Johnson synd.

Augments antifolate effects methotrexate



INHIBITORS of NUCLEIC ACID

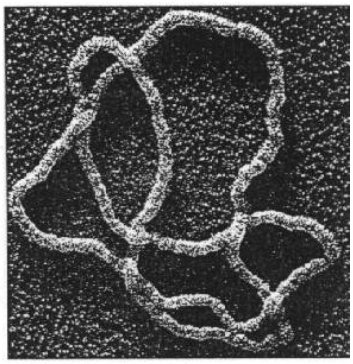
Quinolones
Rifampicin

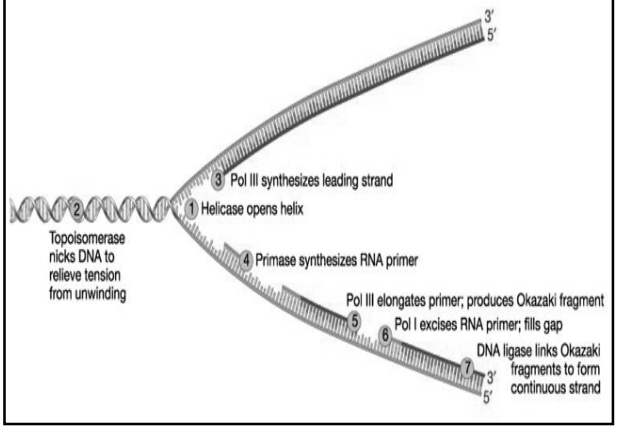
Fluoroquinolones Mechanisms of Action

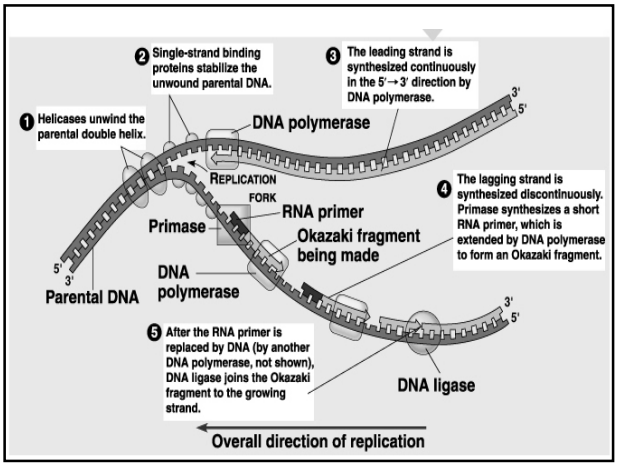
- Inhibit DNA synthesis
- Stabilize DNA strand breaks created by actions of DNA gyrase <u>and</u> topoisomerase IV by binding enzyme-DNA complexes
- Bactericidal - requires additional events after initial interaction with enzyme-DNA complexes

Mechanism of action cont…

- As a general rule, gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive bacterial activity corresponds with inhibition of DNA type IV topoisomerase.







Quinolones

First Generation:

The first-generation agents include cinoxacin and nalidixic acid, which are the oldest and least often used quinolones.

These drugs had poor systemic distribution and limited activity and were used primarily for gram-negative urinary tract infections.

Cinoxacin and nalidixic acid require more frequent dosing than the newer quinolones, and they are more susceptible to the development of bacterial resistance.

Fluoroquinolones

Second Generation.

The second-generation fluoroquinolones have increased gram-negative activity, as well as some gram-positive and atypical pathogen coverage.

Compared with first-generation quinolones, these drugs have broader clinical applications in the treatment of complicated urinary tract infections and pyelonephritis, sexually transmitted diseases, selected pneumonias and skin infections

Fluoroquinolones

2nd generation

- Second-generation agents include ciprofloxacin, enoxacin, lomefloxacin, norfloxacin and ofloxacin.
- Ciprofloxacin is the most potent fluoroquinolone against P. aeruginosa. Ciprofloxacin and ofloxacin are the most widely used second-generation quinolones

Fluoroquinolones

3rd generation

- The third-generation fluoroquinolones are separated into a third class because of their expanded activity against gram-positive organisms, particularly penicillin-sensitive and penicillin-resistant S. pneumoniae, and atypical pathogens such as Mycoplasma pneumoniae and Chlamydia pneumoniae.
- Although the third-generation agents retain broad gram-negative coverage, they are less active than ciprofloxacin against Pseudomonas species

Fluoroquinolones

3rd generation…

- Because of their expanded antimicrobial spectrum, third-generation fluoroquinolones are useful in the treatment of community-acquired pneumonia, acute sinusitis and acute exacerbations of chronic bronchitis
- The third-generation fluoroquinolones include levofloxacin, gatifloxacin, moxifloxacin and sparfloxacin

Fluoroquinolones
4th generation

- **Fourth Generation.** The fourth-generation fluoroquinolones add significant antimicrobial activity against anaerobes while maintaining the gram-positive and gram-negative activity of the third-generation drugs.
- They also retain activity against Pseudomonas species comparable to that of ciprofloxacin.
- The fourth-generation fluoroquinolones include trovafloxacin

Fluoroquinolones Spectrum of Activity

- *Enterobacteriaceae*
- *Haemophilus* spp. *Neisseria* spp.
- *Legionella, Mycoplasma, Chlamydia* [Levofloxacin, Gatifloxacin, Moxifloxacin]
- *Pseudomonas aeruginosa* [Ciprofloxacin, Levofloxacin]

Properties of Newer Quinolones

- Broad spectrum activity
  - Gram-negative bacteria
  - Improved against Gram-positive bacteria
  - Improved against Anaerobes
- Once daily dosing
- Some with apparent reduced risk of selection of resistance

Fluoroquinolones Spectrum of Activity

- Staphylococci (MSSA, MSSE) [Levofloxacin, Gatifloxacin, Moxifloxacin]
- Streptococci (+/- enterococci) [Levofloxacin, Gatifloxacin, Moxifloxacin]
- Anaerobes [Gatifloxacin, Moxifloxacin]
- Mycobacteria (*M. tuberculosis, M. kansasii, M. fortuitum*) [Ciprofloxacin, Levofloxacin, Gatifloxacin]

Clinical Uses of Fluoroquinolones

- Urinary Tract Infections
- Prostatitis
- Sexually Transmitted Diseases
- Gastroenteritis
- Intra-abdominal Infections
- Respiratory Tract Infections
- Bone & Joint Infections
- Skin & Soft Tissue Infections
- Other Broad Uses in Hospitalized Patients

Specific Uses of Fluoroquinolones

- Typhoid and enteric fever
- Prostatitis (vs trimethoprim-sulfa)
- Complicated urinary tract infections
- Community-acquired pneumonia
  - hospitalized patients (vs ceftriaxone + macrolide)
- Prosthetic joint infection
  - for salvage when prosthesis cannot be removed
  - with rifampin

Adverse Effects of Fluoroquinolones

- Gastrointestinal
  - Nausea, vomiting, diarrhea
- Central Nervous System
  - Dizziness (trovafloxacin), insomnia, seizures
- Cardiovascular
  - QT_C prolongation (sparfloxacin, others)

Adverse Effects of Fluoroquinolones

- Hepatic
  - Idiosyncratic hepatitis (trovafloxacin)
- Skin
  - Photosensitivity - UVA 320-420 nm (sparfloxacin, lomefloxacin)
- Musculoskeletal
  - Cartilage erosion in weightbearing joints (animals, ? C/I in children <18yrs)
  - Tendinitis /Tendinopathy

Cartilage erosion

The signal of the cartilage of the patella is engrossed and diffuse, indicating that a first grade osteoarthritis has developed

Quinolone Tendinopathy

- Incidence: ≈ 0.1 – 0.4% with tendon rapture in ≈ 30% especially the Achilles tendon
- the average time between the start of treatment to the onset of symptoms was 13 days, with a range of 1 to 90 day
- Risk factors:
  - >60 yrs
  - steroid use
  - Renal transplant and failure
  - Diabetes mellitus
  - Gout
  - RA
  - Chronic lung disease

A case of spontaneous rupture of the patellar ligament of a 37 year old athletic man one month after a treatment of 3 weeks with ciprofloxacin is reported by authors

Quinolone Tendinopathy…

- Mechanism unknown
  - ?Mg^{++} chelation
  - ?Mediated by NO and 5-lipoxygenase products[a]
  - A recent study provides evidence that apoptosis has to be considered as a final event in the pathogenesis of fluoroquinolone-induced tendopathies.
    - Apoptosis means programmed cell death. Cells commit suicide when receive given signals, for example signals emitted by quinolones

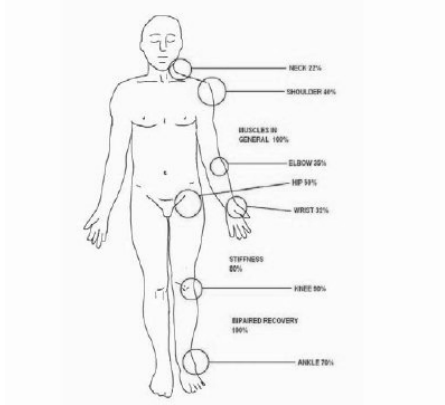
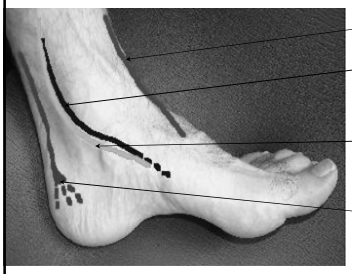


fig.1. -frequency of musculoskeletal disorders in severe reactions-

THE ANKLES: TENDONS SEVERELY HIT BY QUINOLONES



Purple: tibialis anterior

Blue: posterior tibial tendon

Green: flexor digitorum longus

Red: achilles tendon

→The achilles tendon is not the one most affected by fluoroquinolones.

→The posterior tibial tendon and the flexors of the toes are much more frequently affected, and more severely,

→but contrary to the achilles, these tendons do not tend to rupture so easily.

Dorsiflexion can cause extremely incapacitating injuries in the posterior tibial and flexor digitorum group of tendons, that require months to resolve.

This same gesture plus some pronation is done during the contact phase of a normal running activity, which from repetition can cause a devastating damage to the floxed athlete.

Rifampicin

Mechanism of action

Blocks transcription bacterial DNA-dependant RNA polymerase → inhibits RNA synthesis

Spectrum

M. tuberculosis, M. leprae,

H. Influenza (meningitis), B. Fragilis

Pharmacokinetics

Good oral absorption, penetrates most body fluids, even CNS

Elimination via bile & urine. May discolor faeces & urine pink→orange.(tears may discolor contact lenses)

Induces liver enzymes – drug interactions

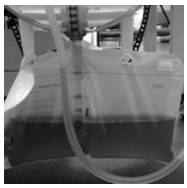
Adverse effects

Nausea, vomiting

Rash & fever

Jaundice

Rifampicin – urine discoloration



A PK/PD Approach to Antibiotic Therapy

- **Introduction**
- **Pharmacokinetics** (PK) is concerned with the time course of antimicrobial concentrations in the body, while
- **Pharmacodyamics** (PD) is concerned with the relationship between those concentrations and the antimicrobial effect.
- Antibiotic dosing regimens have traditionally been determined by PK parameters only. However, PD plays an equal, if not more important, role.
- In this age of increasing antimicrobial resistance, PD becomes even more important because these parameters may be used to design dosing regimens which counteract or prevent resistance

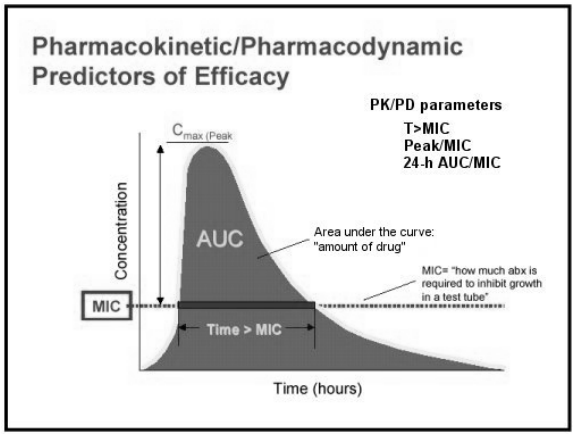
A PK/PD Approach to Antibiotic Therapy…

- The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC).
- The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.
- While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity

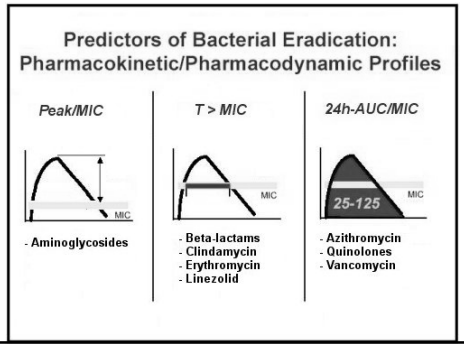
A PK/PD Approach to Antibiotic Therapy…

- PK parameters quantify the serum level time course of an antibiotic.
- The three pharmacokinetic parameters that are most important for evaluating antibiotic efficacy are:
  - the peak serum level (Cmax),
  - the trough level (Cmin), and
  - the Area Under the serum concentration time Curve (AUC).

  While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic



- Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic:



A PK/PD Approach to Antibiotic Therapy…

- The three pharmacodyamic properties of antibiotics that best describe killing activity are:
  - **Time-dependence** (the rate of killing is determined by either the length of time necessary to kill),
  - **Concentration-dependence** (the effect of increasing concentrations), and
  - **Persistent effects** (persistent effects include the Post-Antibiotic Effect (PAE). PAE is the persistant suppression of bacterial growth following antibiotic exposure.

Activity	Antibiotics	Goal of Therapy	PK/PD Parameter
TYPE I: Concentration-dependent killing and PAE	Aminoglycosides Fluoroquinolones	Maximize concentr.	24h-AUC/MIC Peak/MIC
TYPE II: Time-dependent killing and ↓ PAE	Carbapenems Cephalosporins Erythromycin Penicillins	Maximize duration of exposure	T>MIC
TYPE II: Time-dependent killing and Moderate PAE	Azithromycin Clindamycin Tetracyclines Vancomycin	Maximize amount of drug	24h-AUC/MIC

TYPE I antibiotics:
Concentration-dependent killing and prolonged persistent effects

- The ideal dosing regimen would maximize **concentration**, because the higher the concentration, the more extensive and the faster is the degree of killing.
- Therefore, the 24h-AUC/MIC ratio, and the Peak/MIC ratio are important predictors of antibiotic efficacy.
  - For aminoglycosides, it is best to have a Peak/MIC ratio of at least 8-10 to prevent resistance.
  - For fluoroquinolones vs gram negative bacteria, the optimal 24h-AUC/MIC ratio is approximately 125. Versus gram positives, 40 appears to be optimal

TYPE II antibiotics:
Time-dependent killing and ↓ PAE

- They demonstrate the complete opposite properties.
- The ideal dosing regimen for these antibiotics maximizes the **duration** of exposure.
- The T>MIC is the parameter that best correlates with efficacy. For beta-lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval

TYPE III antibiotics:
Time-dependent killing and Moderate PAE

- They have mixed properties, they have time-dependent killing and moderate persistent effects.
- The ideal dosing regimen for these antibiotics maximizes the **amount** of drug received.
- Therefore, the 24h-AUC/MIC ratio is the parameter that correlates with efficacy.
  - For vancomycin, a 24h-AUC/MIC ratio of at least 125 is necessary