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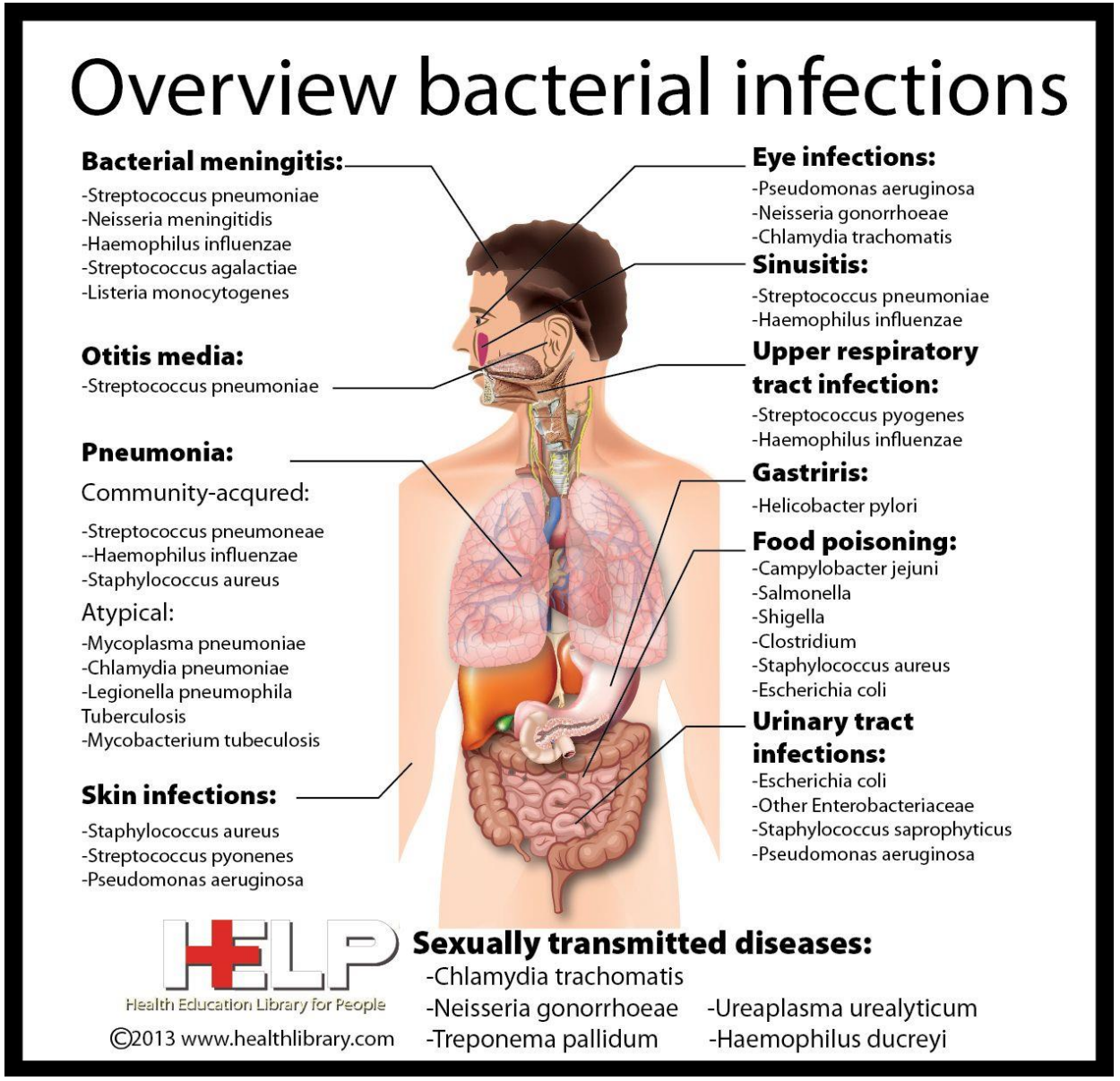
Antibiotics

Dr J Haylor,

School of Medicine,

2025



The antibiotics sessions in pharmacology are designed to complement the lectures delivered in microbiology by Dr Garcia-Lara. The introductory slide gives an overview of bacterial infections treated by antibiotic therapy occurring in a wide variety of body systems including the lung, urinary tract, gastrointestinal tract, skin, eye, ear and meninges, together with sexually-transmitted diseases such as chlamydia and gonorrhoea.

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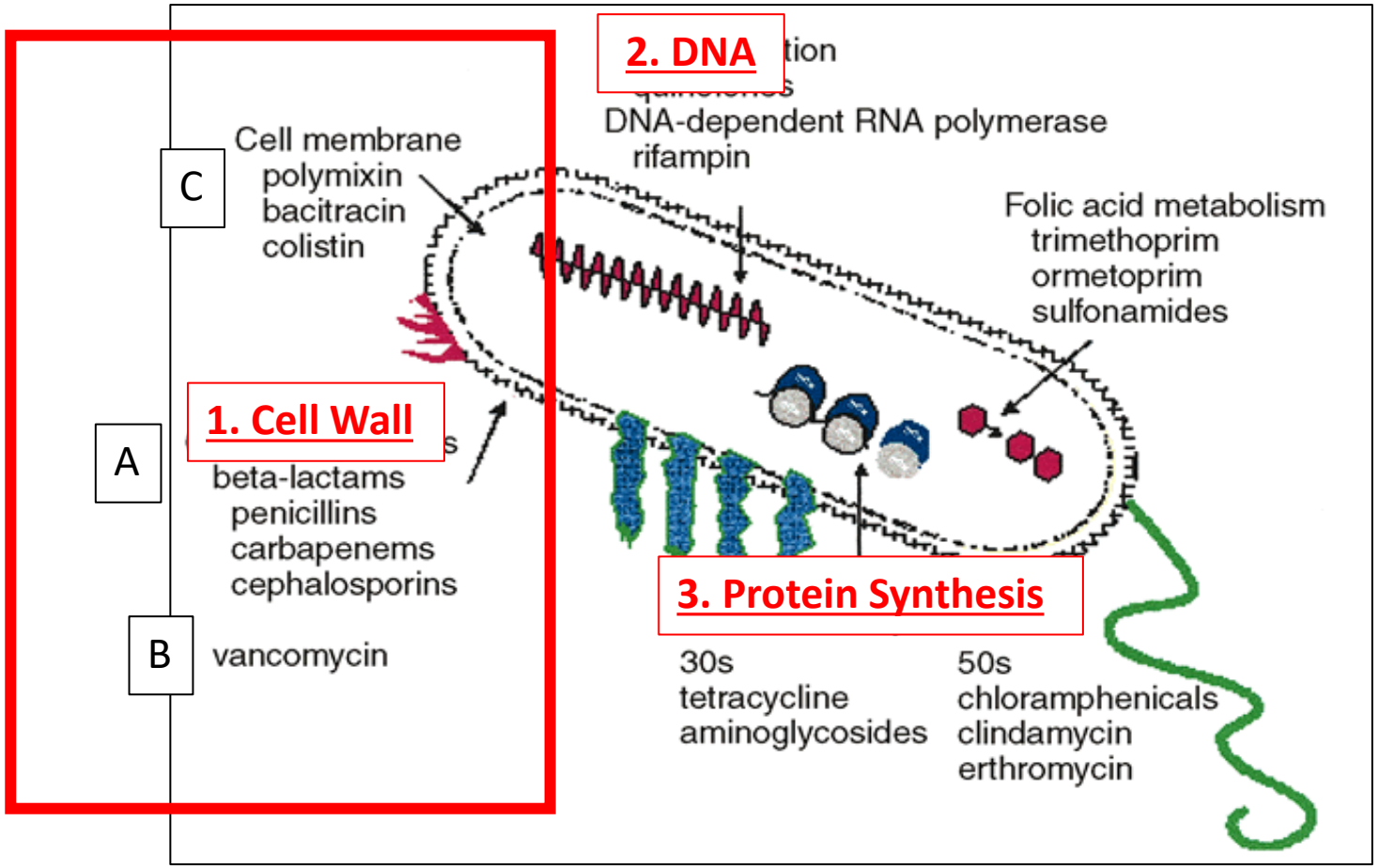
Antibiotics : 1. **Cell Wall**



Antibiotic Cell Wall Groups

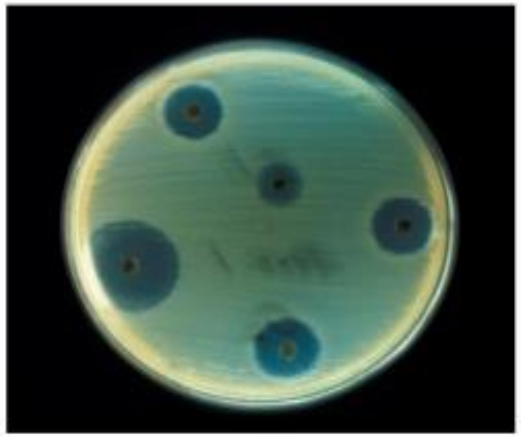
β-lactam antibiotics
Vancomycin
Bacitracin/Polymyxin
Mycobacteria

The bacterial cell wall is the only target site for antibiotics unique to bacteria and is the target site for 4 antibiotic drug groups. The major group consists of the β-lactam antibiotics which include the penicillins and cefalosporins, a second group contains vancomycin reserved for more severe or resistant bacterial infections. A third group including bacitracin and polymyxin are mainly used to treat external infections of the skin, the eye and the ear. A fourth group consists of antibiotics used in combination to treat the mycobacteria responsible for tuberculosis and leprosy, where the structure of the cell wall shows major differences to other commonly infectious bacteria. Antibiotics acting on bacterial DNA or the ribosome will be considered in a second bitesize recording.

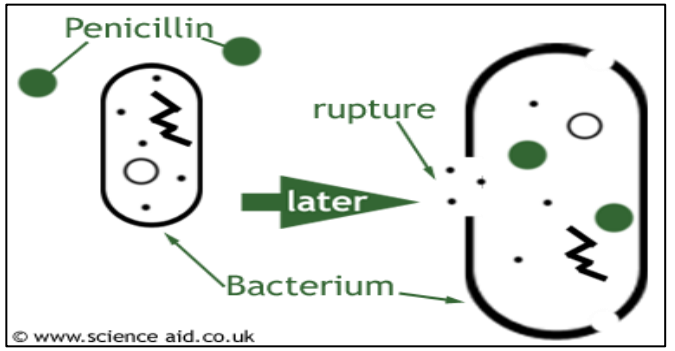
Penicillin

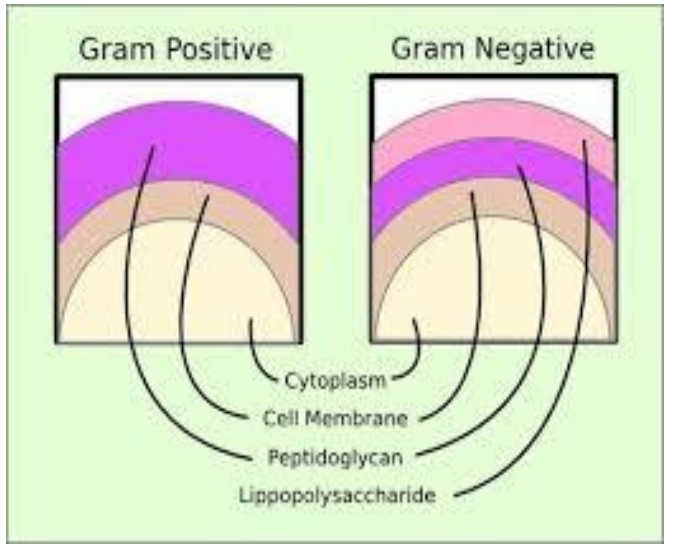
A Legendary Discovery

In the 1920's, Alexander Fleming discovers (by accident) a fungus that kills bacteria, which came to be known as Penicillin.



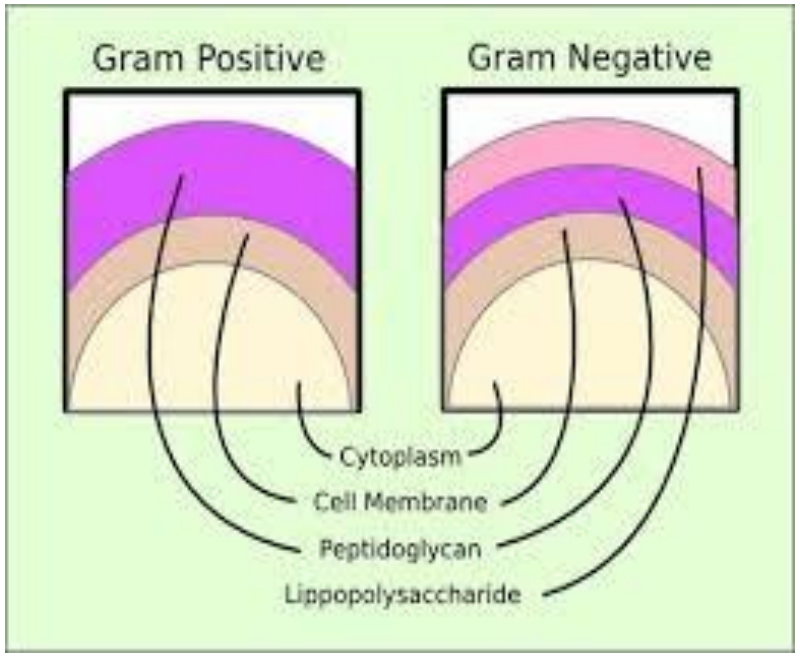
The term antibiotic literally means "against life"; in this case, against microbial bacteria.

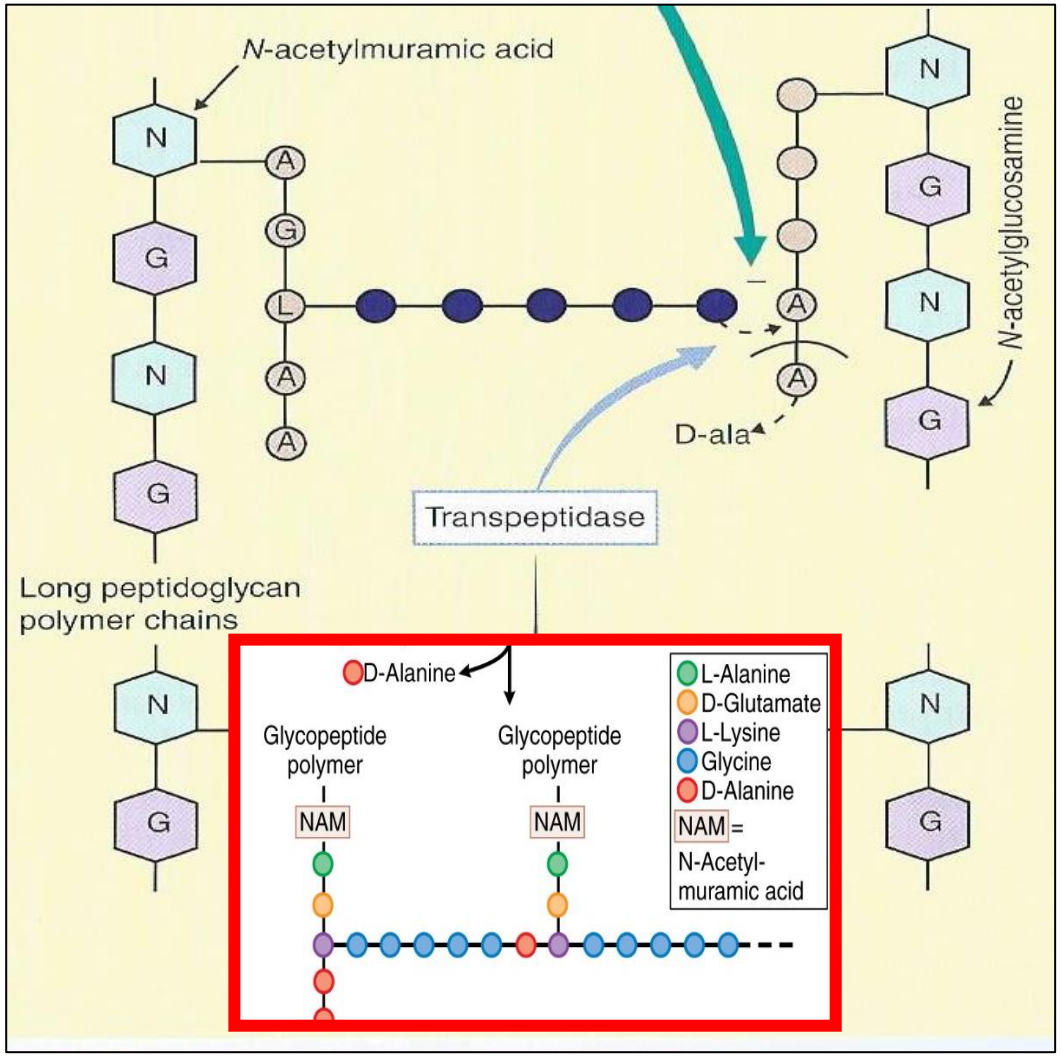




I would imagine everybody knows the penicillin story of Alexander Fleming, although the principle that moulds could inhibit bacterial growth was described by Ernest Duchesne, a French Physician some 30 years earlier. The cell wall of bacteria helps to determine their size and shape, providing tensile strength to protect against changes in their osmotic environment. Penicillin causes the rupture of the bacterial cell membrane by autolysis, targeting the peptidoglycan structure of the cell wall (shown in purple visualised using the gram stain). The presence of an outer lipopolysaccharide shell (shown in pink) in gram-negative bacteria meant the early penicillins were more effective against infection produced by gram-positive bacteria.

Cell Wall
Peptidoglycan Synthesis





To understand how penicillin produces its bactericidal effect, the structure of the bacterial cell wall must be considered in greater detail. The peptidoglycan section of the bacterial cell wall for gram positive bacteria (shown in purple) is made from up to 50 layers of peptidoglycan polymers based on the sugars N–acetylmuramic acid (N, NAM) and G-acetylglucosamine (G). Following synthesis inside the cell, these disaccharide sugar residues are exported to the outside of the cell membrane and polymerised into long peptidoglycan chains which are cross-linked to produce their final structure and strength. N-acetylmuramic acid (N, NAM) has a 5 amino acid chain, the lysine of which contains a pentaglycine bridge which cross-links with the lysine residues on the adjacent layer under the control of transpeptidase enzymes (TP) releasing the terminal alanine residue. Different bacteria have different transpeptidase enzymes located in different parts of the cell wall, which are thought to determine the final size and shape of a bacetria. S. Aureus for example has 4, E. Coli has 7. As we shall see, inhibition of different TP enzymes contributes to the selectivity of antibiotic therapy.

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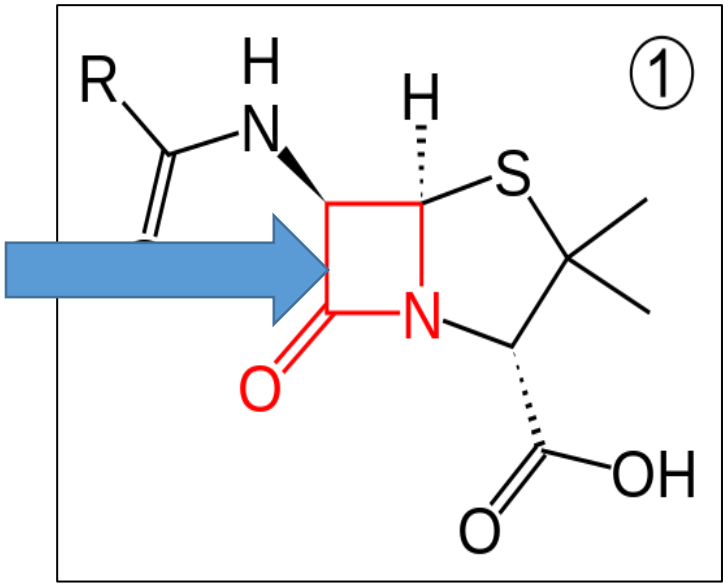
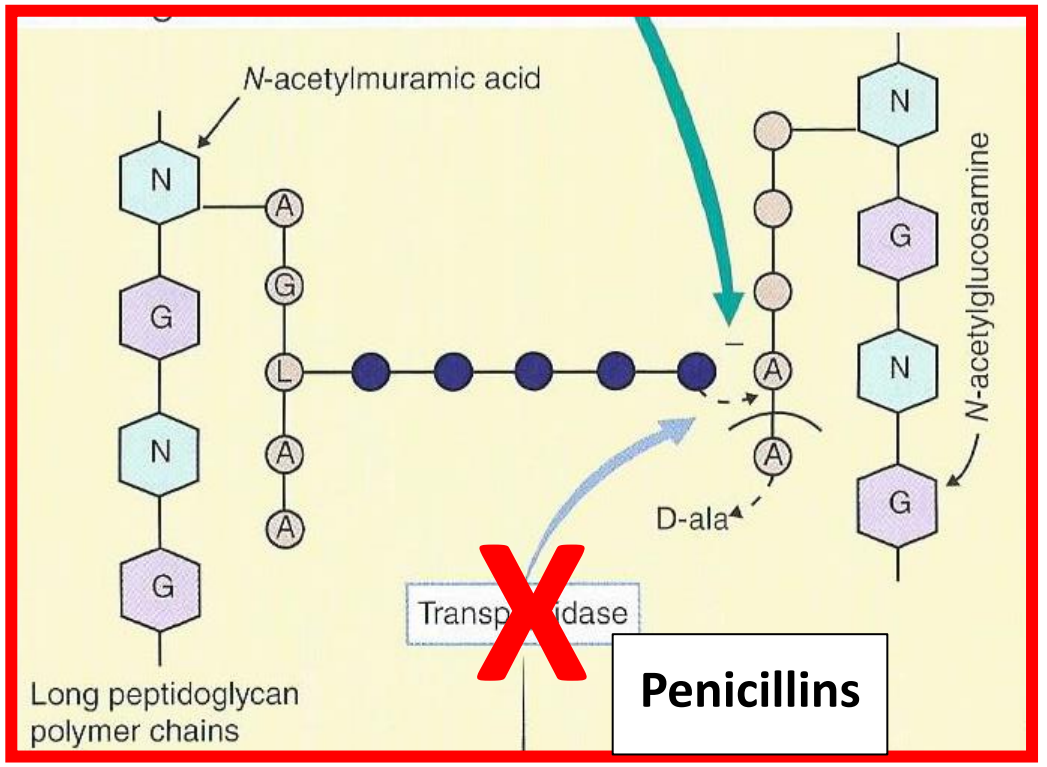
Penicillin

Mechanism of Action

β-lactam ring





Mechanism of Action: Enzyme Inhibitor

- bind covalently to a serine residue at the active site of the enzyme
- Inhibit transpeptidases (cross-linking enzymes)
- irreversible enzyme inhibitors

Today, the penicillins are described as belonging to a large group of drugs, called the β-lactam antibiotics, which inhibit the bacterial cell wall. All antibiotics in this group contain the 4 membered β-lactam ring (shown in red within the penicillin structure). It is the β-lactam ring, that binds to and irreversibly inhibits transpeptidase enzymes. β-lactam antibiotics have a surface structure which mimics that of the alanine residues attached to N-acetylmuramic acid. β-lactam antibiotics bind covalently to a serine residue at the active site of transpeptidase enzymes producing what may be called '*suicide substrate inhibition*'. However, different TP enzymes may differ in their sensitivity to the same antibiotic, an important factor in bacterial susceptibility and resistance.

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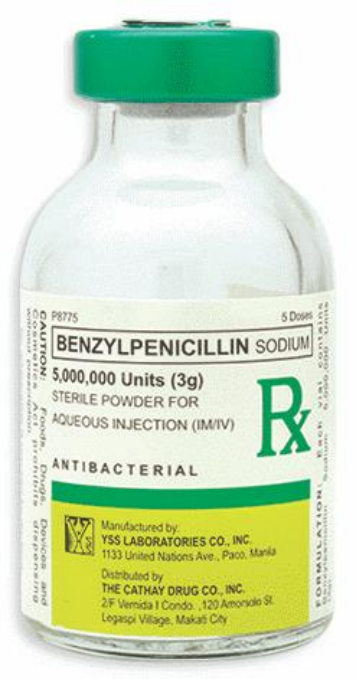
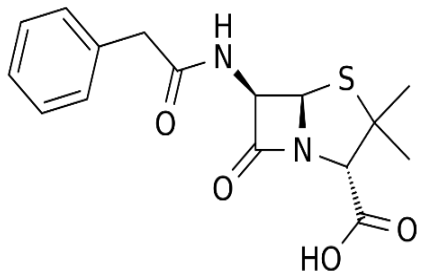
β-lactam Antibiotics : Penicillins

injection





benzylpenicillin

Benzylpenicillin (Pen G)

Penicillin nucleus effective for gram positive bacteria

Unstable in acid: parenteral administration (IV IM)

Severe infections (1.2g 4-6hly)

Streptococcal infection (pneumonia, endocarditis)

Clostridia infection (tetanus)

Meningococcal infection (meningitis, septicaemia)

Benzylpenicillin (commonly known as Pen G), was the first penicillin to be introduced and was effective principally against gram-positive bacteria. However, since benzylpenicillin is unstable in acid solution, it can only be given by injection, normally by intravenous infusion and today is reserved for the treatment of severe streptococcal infections, including pneumonia and endocarditis. Benzylpenicillin may also be useful in treating septicaemia due to meningococcal infections with penetration into the meninges, especially if they are inflamed. Penicillins are rapidly cleared from the body through the kidney and excreted in the urine.

Phenoxymethylpenicillin (Pen V)

Acid stable, orally active
but absorption unpredictable

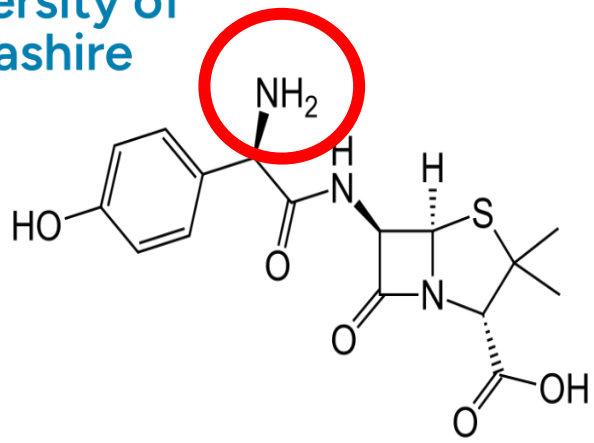
Narrow spectrum of activity

Effective for gram +ve bacteria
(less so for gram -ve)

Used in mild-to-moderate infections
such as Strep. Throat

Phenoxymethylpenicillin (commonly known as Pen V) was the first oral penicillin. It is acid stable, but has narrow bacterial spectrum, with reduced sensitivity to gram negative bacteria. However, its narrow spectrum of activity is particularly useful in treating conditions such as Strep. Throat, with symptoms of enlarged, inflamed tonsils with white/yellow patches and tiny haemorrhages to the soft palate. The variable absorption of Pen V from the GI tract restricts its use to mild-moderate infections but the narrow spectrum of action reduces potential inhibition of the gut microbiome and thereby adverse effects on the GI tract.

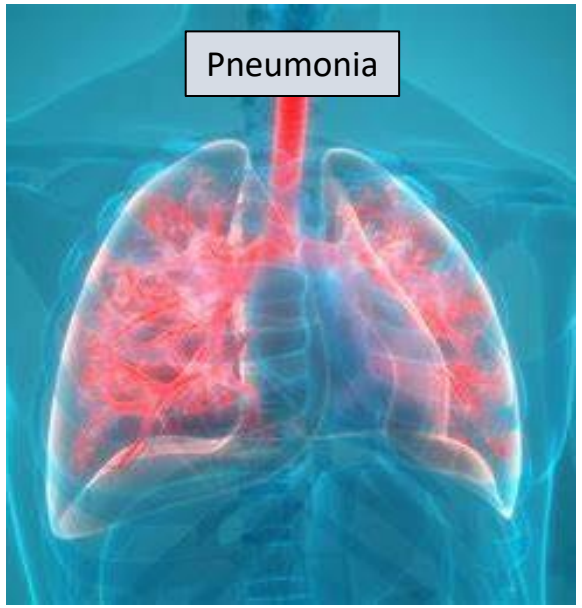
Amoxicillin

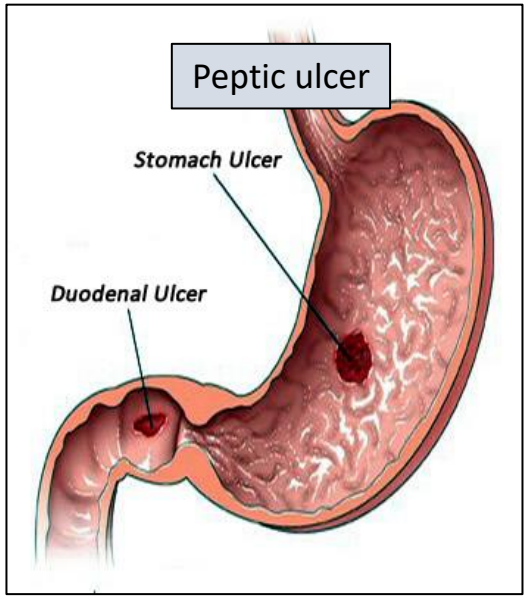


Aminopenicillin – oral broad-spectrum antibiotic
Acid stable (95% bioavailable)
Absorption independent of food intake

Adverse Effect :

diarrhoea, colitis (overgrowth *C. difficile*)





Amoxicillin has been the most frequently prescribed oral penicillin in primary care over the last 40 years. Amoxicillin is acid-stable with 95% bioavailability. The addition of an amino group (ringed in red) also provides good penetration through the lipopolysaccharide outer layer of the cell wall of gram-negative bacteria giving a broad-spectrum of activity. Amoxicillin is the first-line antibiotic used to treat a variety of infections including pneumonia and otitis media. The use of amoxicillin in the treatment of peptic ulcer, due to H.Pylori, was considered in year 1 and in secondary care its use includes the treatment of hospital acquired infections. However, as an oral, broad-spectrum antibiotic, important GI tract bacteria may also be inhibited, resulting in diarrhoea with the possibility of C. Difficile overgrowth generating colitis, inflammation of the bowel.

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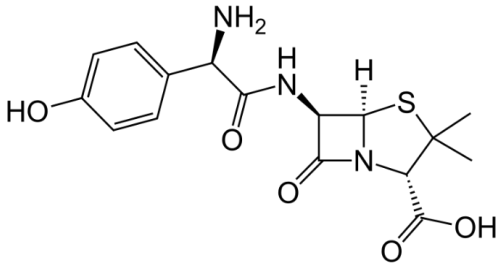
Resistance to Penicillins
β-lactamase Inhibitor

clavulanic acid
Inhibitor - binds covalently to the active site of B-lactamase
(no antibacterial activity)

amoxicillin
(substrate)



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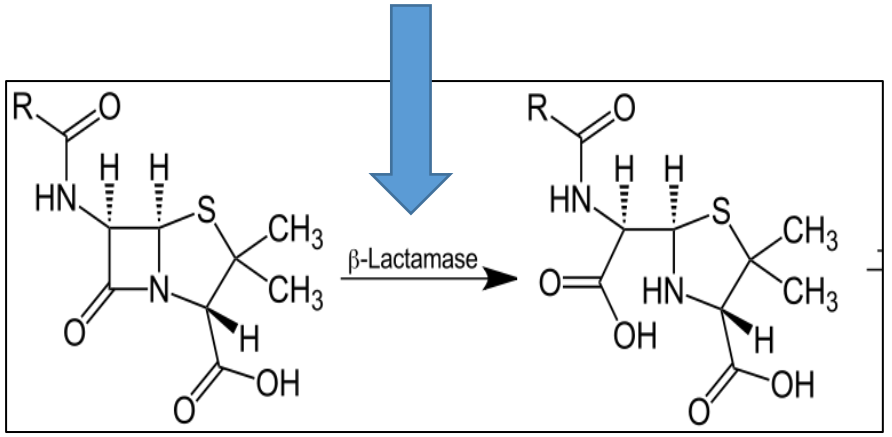

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Co-amoxiclav

Combined preparation penicillin (amoxicillin) with a β-lactamase inhibitor (clavulanic acid)

The problem of bacterial resistance to penicillin was first recognised during its development. The first β-lactamase enzyme (originally known as penicillinase) generated by bacterial infection being discovered by Ernest Chain as early as 1940. The β-lactamases are a family of enzymes which break the 4-membered β-lactam ring of the antibiotic, generating inactive metabolites. Clavulanic acid is a β-lactam analogue which binds to and inhibits the β-lactamase enzyme but without any antibacterial activity of its own. Co-amoxiclav is a combined preparation containing amoxicillin and clavulanic acid.

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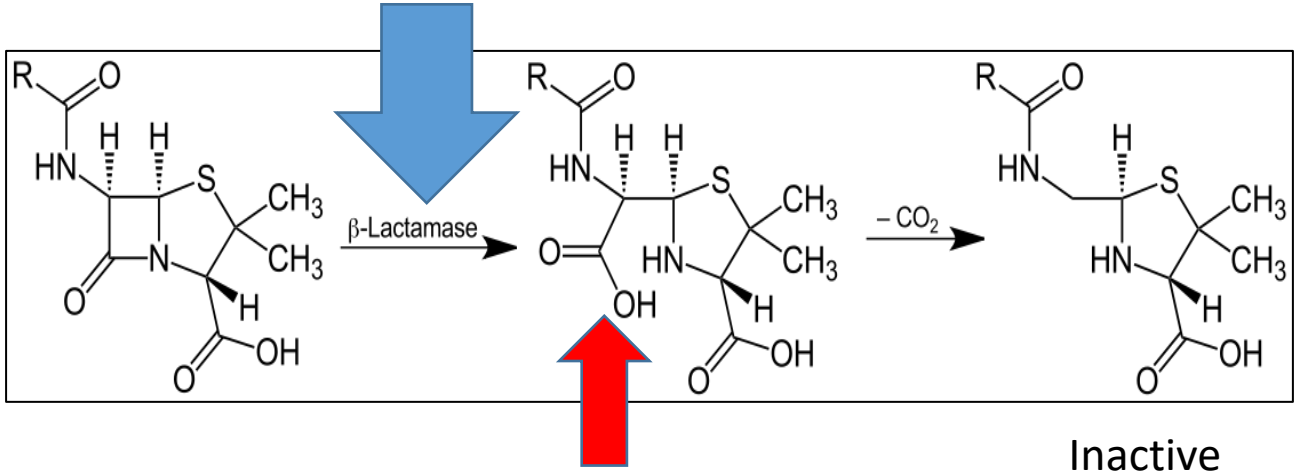
Resistance to Penicillins

β-lactamase

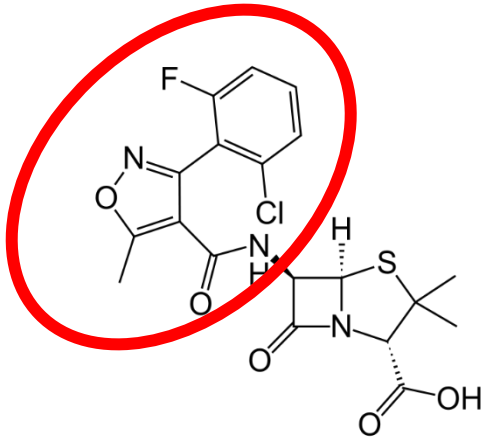
β-lactamase

Penicillin



Broken β-lactam ring

Inactive penicillin metabolite



flucloxacillin

(not substrate for β-lactamase)

An alternative approach was to modify the structure of the penicillin so it couldn't bind to the β-lactamase enzyme. Flucloxacillin, is a penicillin with a very large amine substituent (ringed in red) preventing it being a substrate for such enzymes and thereby useful in treating infections caused by β-lactamase producing bacteria, such as the staphylococcal skin infection which causes cellulitis. Unlike amoxicillin, flucloxacillin has a narrow spectrum of activity.

Penicillins : Adverse Effects

hypersensitivity

diarrhoea

nephritis

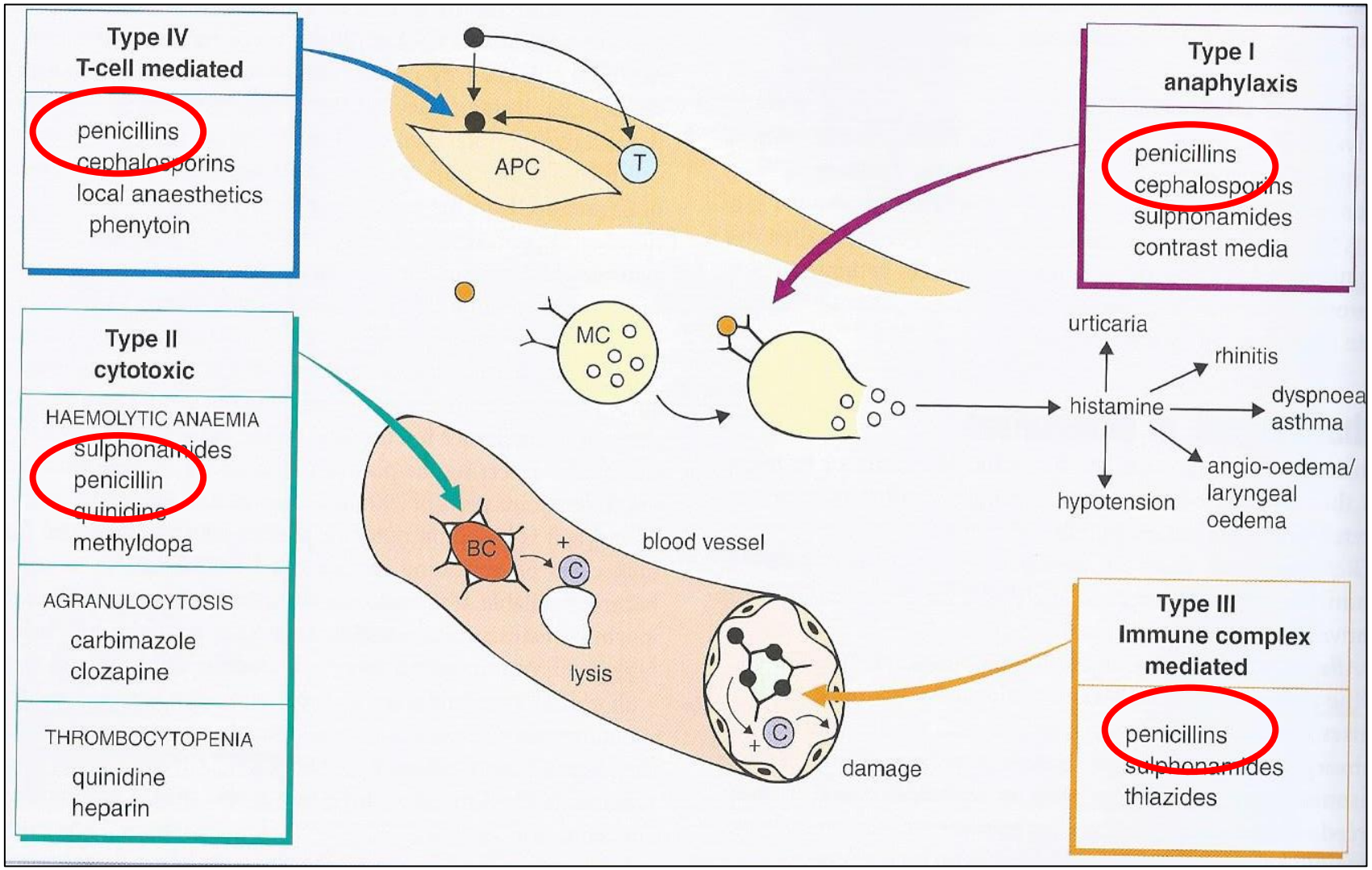
neurotoxicity

haematological toxicity

cation toxicity

The use of the bacterial cell wall (a structure absent from mammalian cells) as the target site for the penicillins results in a wide therapeutic index, making them relatively safe drugs to use. However, as water soluble drugs, their plasma concentration will be elevated in patients with renal failure, while the presence of inflamed meninges will increase their penetration into the CNS. This slide shows examples of 6 areas for potential adverse effects due to penicillins. These include sodium loading in IV infusions for patients with heart failure when the sodium salt of penicillin is employed. The GI tract problems of diarrhoea and colitis have already been mentioned but perhaps the most well-known adverse effects are hypersensitivity reactions..

Penicillin : Hypersensitivity Mechanisms



Penicillins can produce all four major types of hypersensitivity mechanism, type I anaphylaxis, type II cytotoxicity, type III immune-complex mediated responses and type IV T-cell mediated responses. The early life-threatening events of angioedema and anaphylaxis are mainly due to a type 1 response mediated by IgE and require immediate treatment to maintain the airway including the use of adrenaline (Epipen).

Penicillins **Hypersensitivity Reactions**

Adverse Effects of Penicillins

The most important side-effect is Hypersensitivity (1–10%);

The allergic reactions have been divided into 3 types:

- **Immediate Reaction** : the most severe and occurs within 20 min after parenteral administration and appears to be mediated by **IgE**.

It consists of pruritus, paraesthesia (numbness and tingling), wheezing, choking, fever, edema, and generalized urticaria and can lead to hypotension, shock, loss of consciousness, and death.

- **Accelerated Reaction** appears 1–72 hours after administration and consists mainly of urticaria.
- **Late Reaction** appears 72 hours to several weeks after drug administration. It consists mainly of skin rashes.

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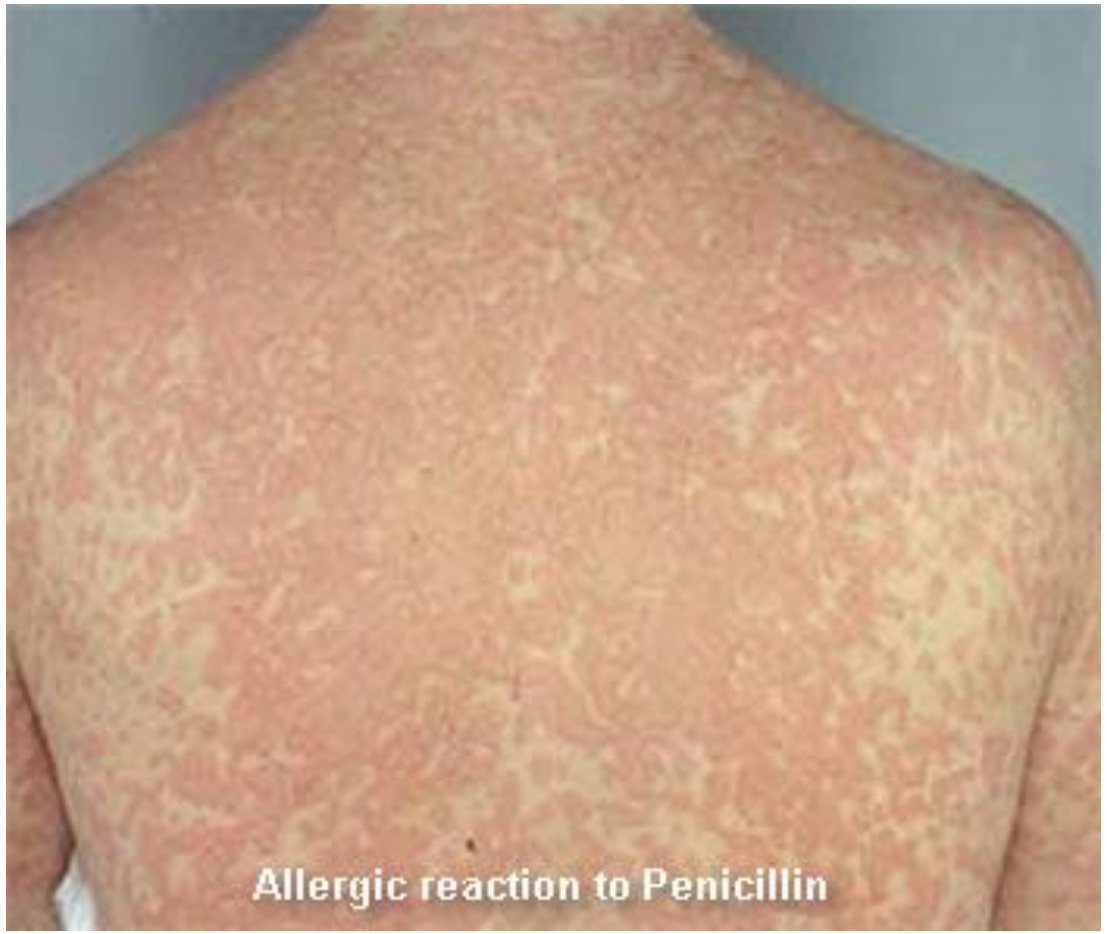

The immediate reaction to penicillins include angioedema producing wheezing and choking, pruritus, paraesthesia, hypotension, shock, loss of consciousness which can be fatal if left untreated. Accelerated symptoms of urticaria can occur in the first few days while later appearance of skin rashes may develop within weeks. An example of penicillin skin rash is shown on the right-hand slide.

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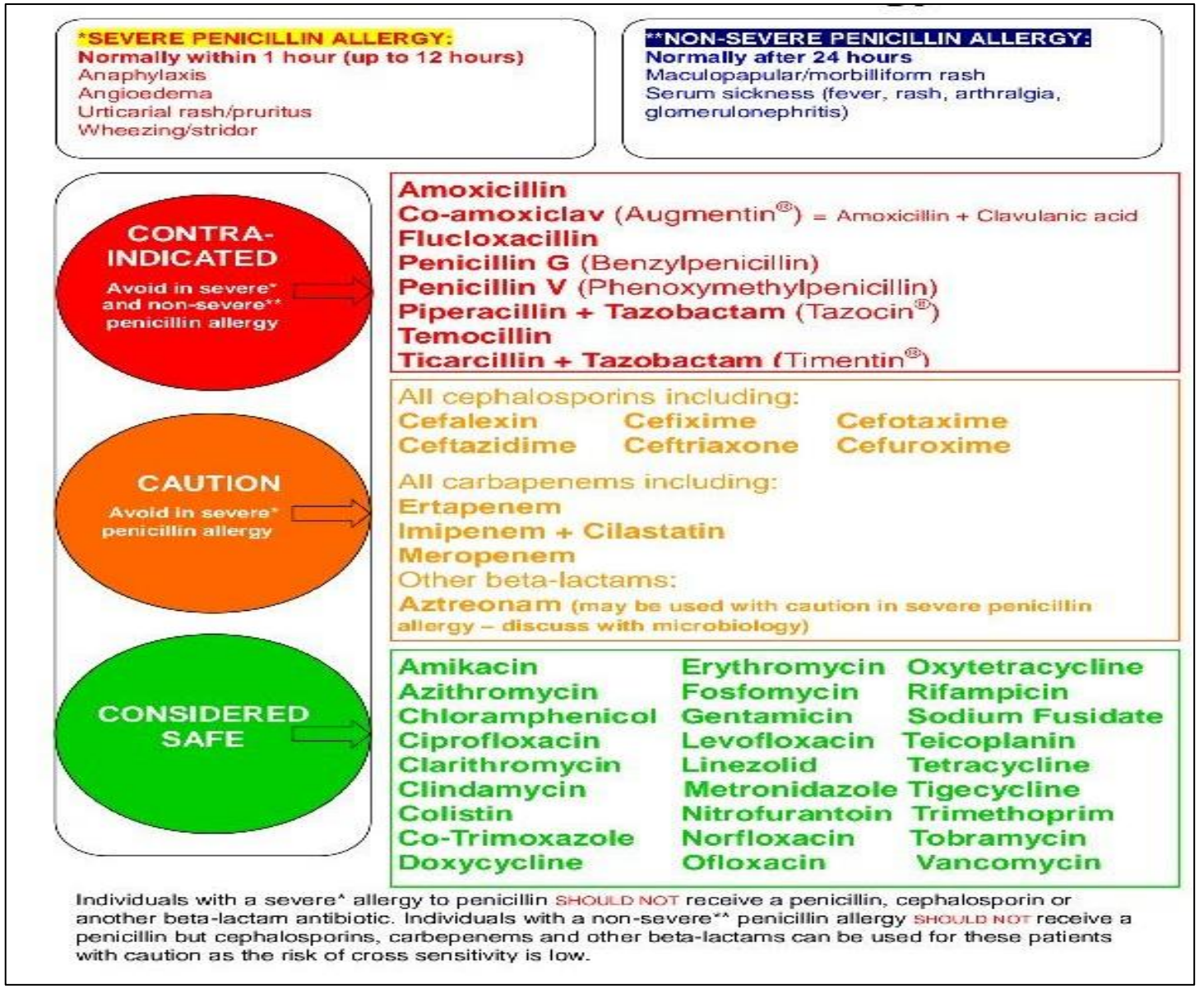
Penicillin

Cross Sensitivity



The cross sensitivity of other antibiotics in patients allergic to penicillin can be colour coded based on the severity of the expected response. These include red for contra-indication, such as with other penicillins. Orange for caution, such as with other β-lactam antibiotics and green for antibiotics considered safe to be used in patients showing penicillin allergy. Such drugs work through different cellular mechanisms targeting DNA or the ribosome to induce their antibacterial effect..

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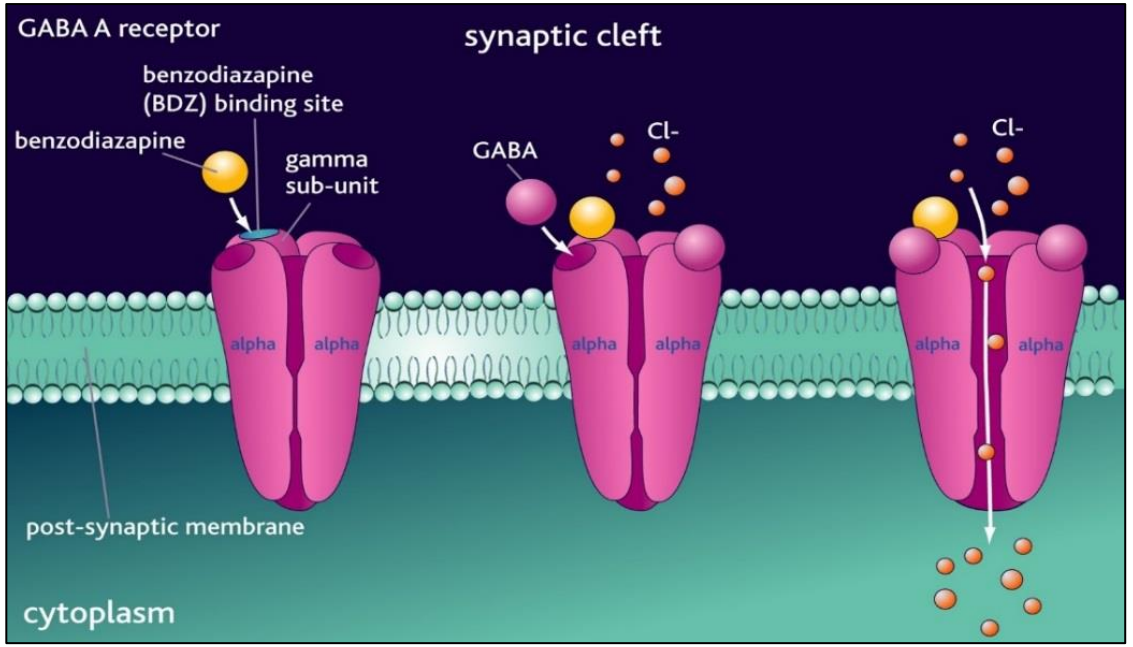
Penicillin - Neurotoxicity



β-lactam antibiotics inhibit the GABA-A receptor

Encephalopathy - seizures, myoclonus

Excess dosing
Severe renal failure/nephrotoxic drugs
Damage to BB barrier
CNS disease/drugs which lower seizure threshold
Old age

BNF

Rare but serious encephalopathy due to cerebral irritation
Do NOT give by intrathecal injection

Penicillins have a limited penetration into the CNS when given systemically although, still at high enough concentrations to use in the treatment of meningitis. Penetration is increased when the meninges are inflamed or when penicillin blood levels are increased, perhaps due to renal failure. **However it is essential to never give penicillins by intrathecal injection.** Penicillins can induce seizures and myoclonus, it is thought through antagonism of the GABA-A receptor. GABA is an inhibitory amino acid neurotransmitter, the potentiation of which contributes to the therapeutic effect of some anti-epileptic drugs. Interestingly, penicillin used to be used to induce seizures in experimental pharmacology to test the efficacy of anti-epileptic compounds.

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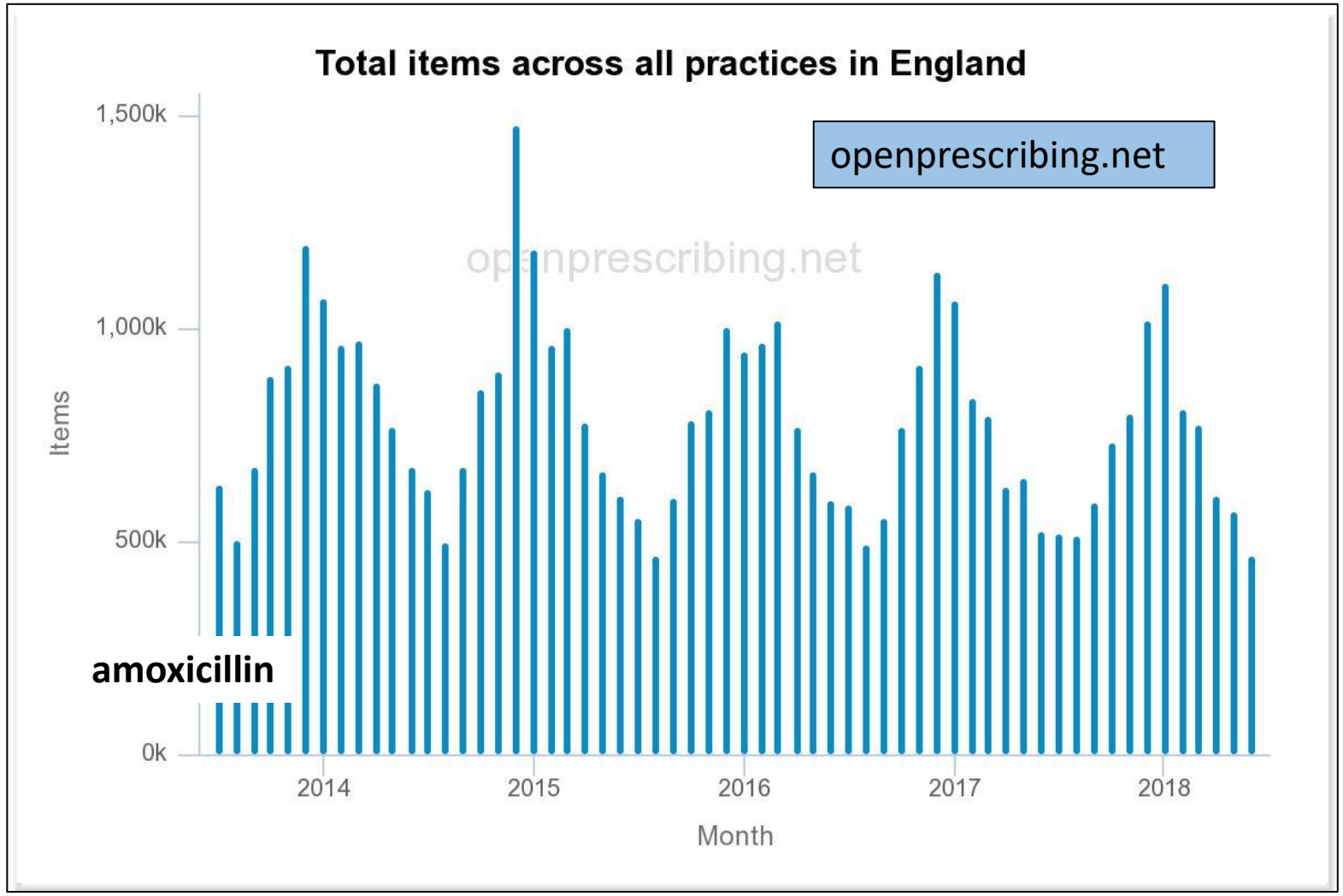
Primary Care Prescribing

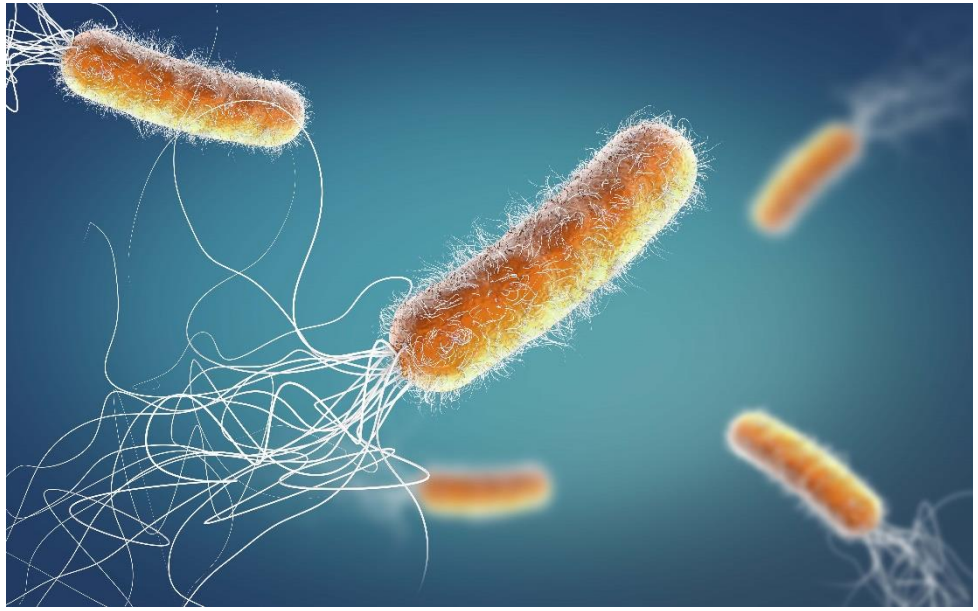
(penicillins)

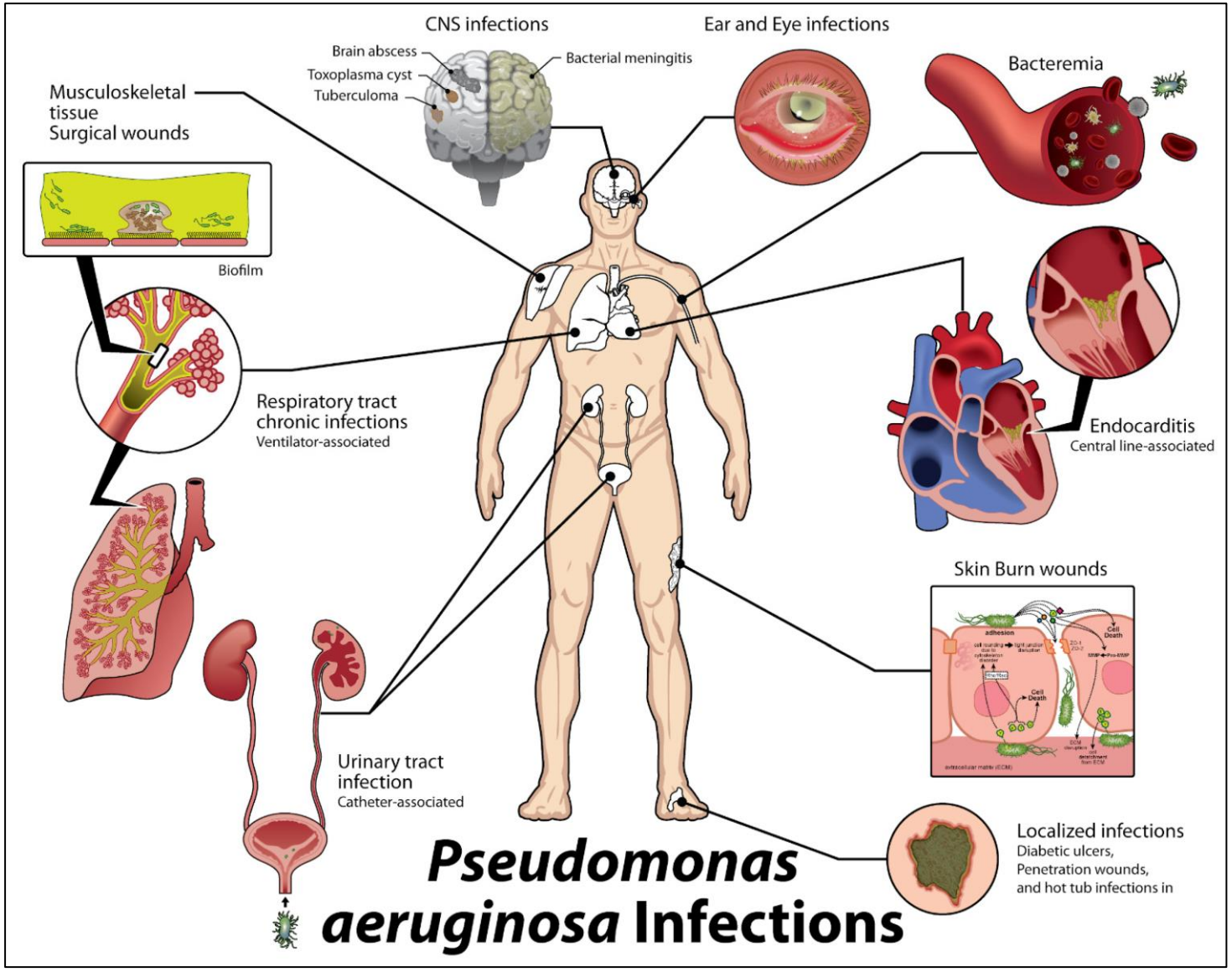
Amoxicillin	60%
Flucloxacillin	20%
Penicillin V	11%
Co-amoxiclav	8%



Data from NHS digital shows that penicillin usage in primary care is restricted to 4 drugs; amoxicillin, flucloxacillin, penicillin V and co-amoxiclav (which also contains amoxicillin). The monthly prescribing figures for amoxicillin double in the winter months (a pattern also seen with other oral broad-spectrum antibiotics) indicating a major use in the treatment of respiratory infections.

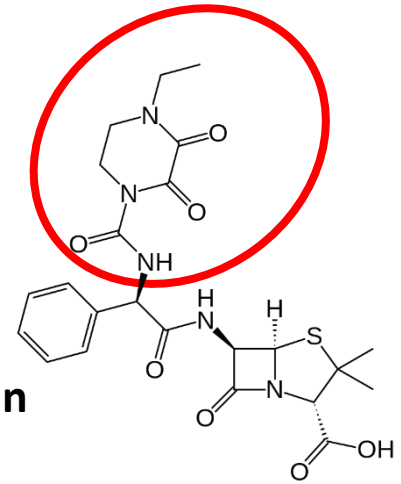
Pseudomonas Aeruginosa





Many serious gram-negative bacterial infections are not sensitive to either flucloxacillin or co-amoxiclav. An important example of such an infecting organism would be *Pseudomonas Aeruginosa* responsible for example fo infections following urinary catheterization, the respiratory infections seen in cystic fibrosis or infections associated with ventilator use in patients with Covid-19.

Penicillins : **Antipseudomonal**



piperacillin

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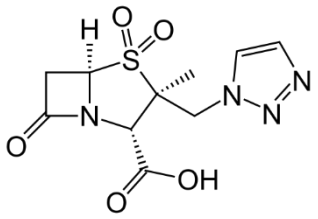

tazobactam

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Intravenous Infusion

Piperacillin - polar side chain increases gram –ve activity

Broad spectrum of pathogens (Pseudomonas Aeruginosa)

Tazobactam - B-lactamase inhibitor

Therapeutic Uses (Tazocin)

Severe Infections

Hospital acquired infection

antibiotic resistance,

immuno compromised patients

Including Lower respiratory tract

Urinary tract

Intraabdominal sepsis

Skin and soft tissue infection

The bacterial spectrum of the aminopenicillins can be further broadened, by increasing the size of its amino substituent, producing piperacillin. This enhances the penetration of the drug through the outer lipopolysaccharide layer of the cell wall of gram-negative bacteria, resulting in efficacy against *Pseudomonas Aeruginosa*. Using the same principle as with co-amoxiclav, piperacillin is combined with a different β-lactamase inhibitor, called tazobactam, in a preparation named Tazocin. Tazocin is given by IV infusion and is reserved for more complex infections in immunocompromised patients and patients with hospital acquired infections including sepsis.

Penicillins of Interest

- Benzylpenicillin (Pen G)
- Phenoxymethylpenicillin (Pen V)
- Amoxicillin
- Flucloxacillin
- Co-amoxiclav (amoxicillin + clavulanic acid)
- Tazocin (piperacillin + tazobactam)

Amoxicillin is one of three major oral broad-spectrum antibiotics used in the UK together with doxycycline and clarithromycin. Both phenoxymethylpenicillin and flucloxacillin have a narrow spectrum of activity. Amoxicillin is also present in co-amoxiclav together with the β-lactamase inhibitor, clavulanic acid. A second drug combination named tazocin has enhanced activity against gram-negative organisms such as *Pseudomonas Aeruginosa.*

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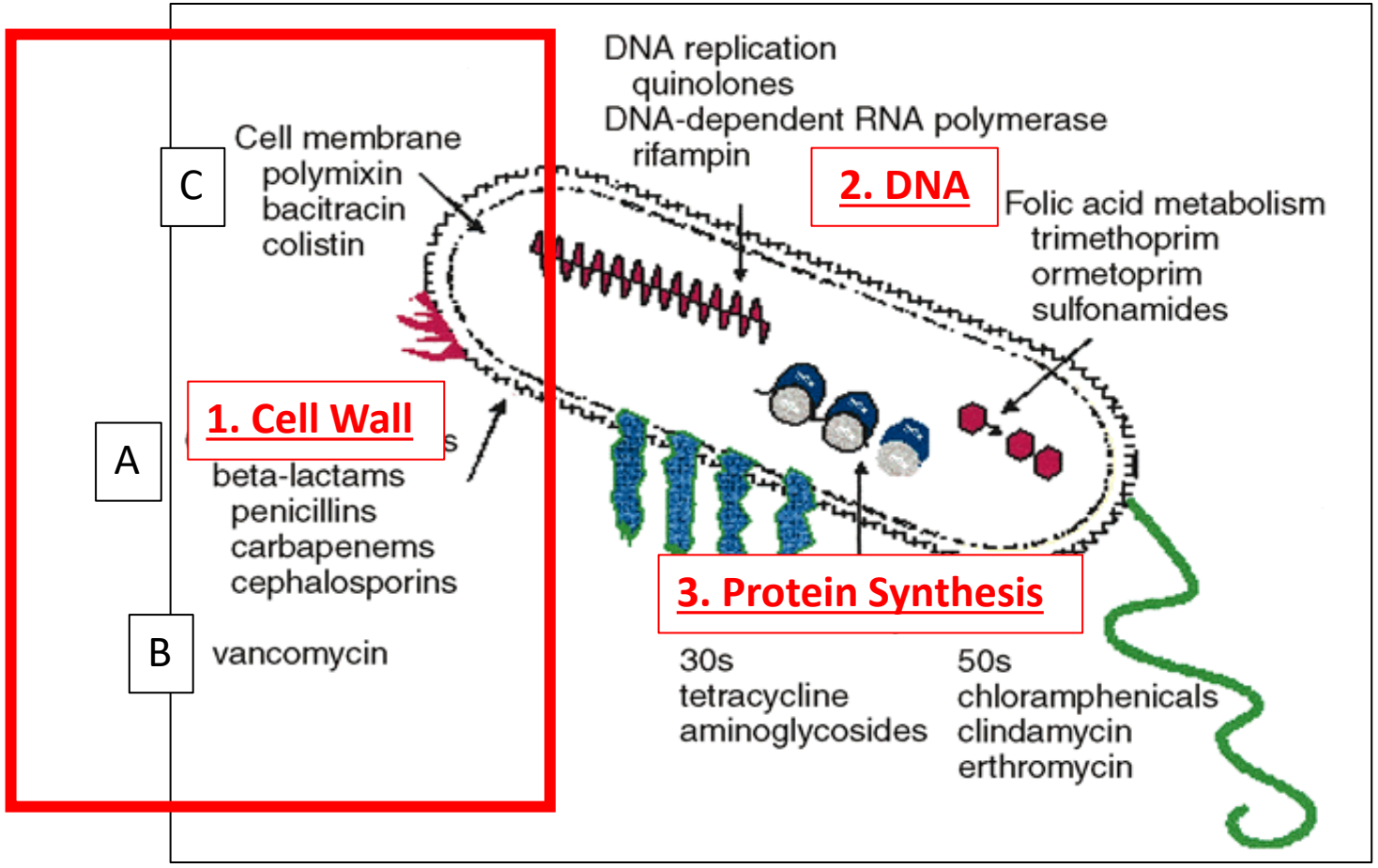
Antibiotics **Cell Wall 2**

Other B-lactam antibiotics and alternative targets



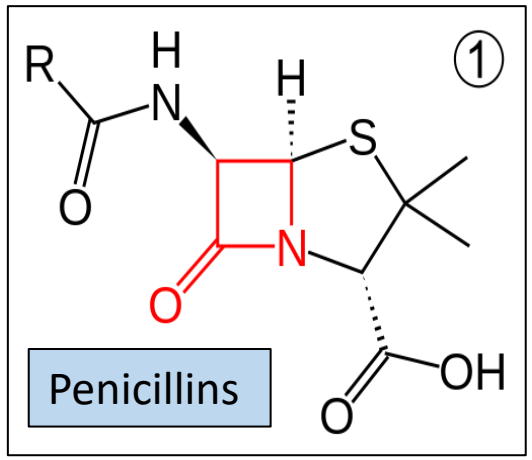
Antibiotic Cell Wall Groups

β-lactam antibiotics
Vancomycin
Bacitracin/Polymyxin
Mycobacteria

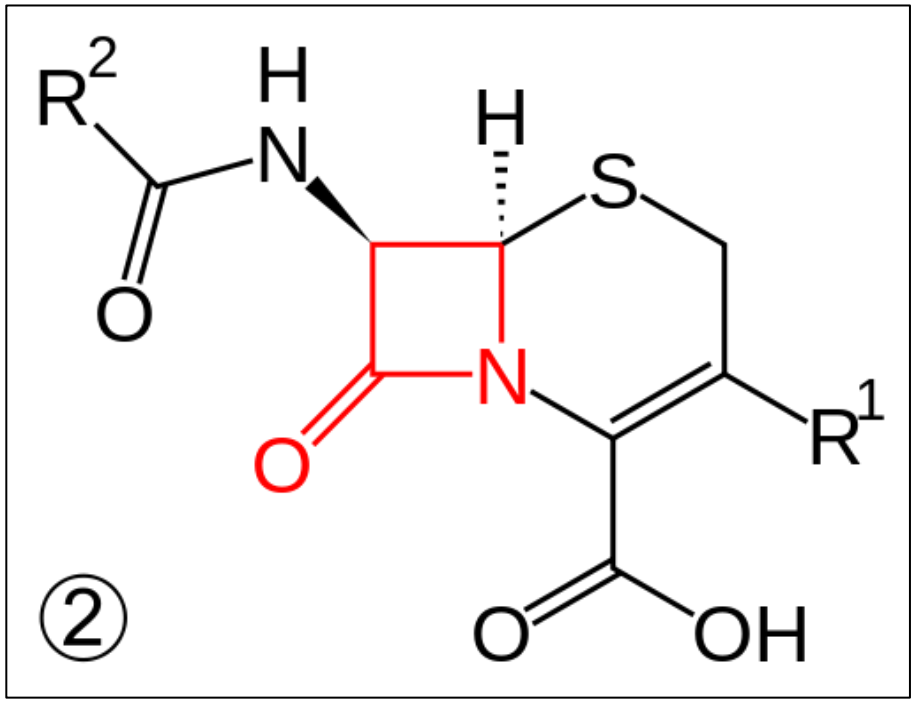
Dr J Haylor,
Medicine,
2025

The first recorded session on antibiotics and the cell wall considered the penicillins, the first of the β-lactam antibiotics. In this second recorded session on antibiotics and the cell wall, other β-lactam antibiotics including the cefalosporins, the carbapenems and the monobactams are discussed. In addition, 3 other antibiotics with different targets in the bacterial cell wall mediating their bactericidal or bacteriostatic effects will be considered. Vancomycin, which is reserved for more severe/resistant gram-positive infections, bacitracin and polymyxin which are mainly used for external infections of the skin/eye/ear. Antibiotics used to inhibit the mycobacteria responsible for tuberculosis, where the structure of the cell wall shows major differences to other commonly infectious bacteria will be consider together with rifampicin under DNA and protein synthesis.

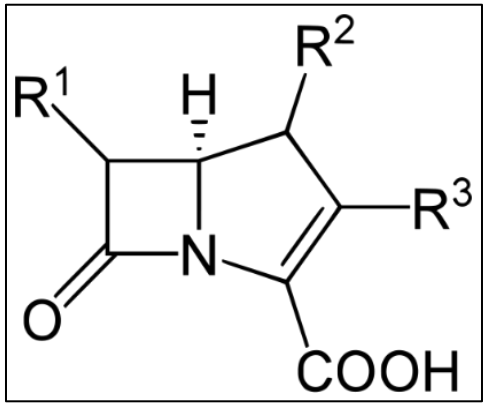
β-lactam antibiotics



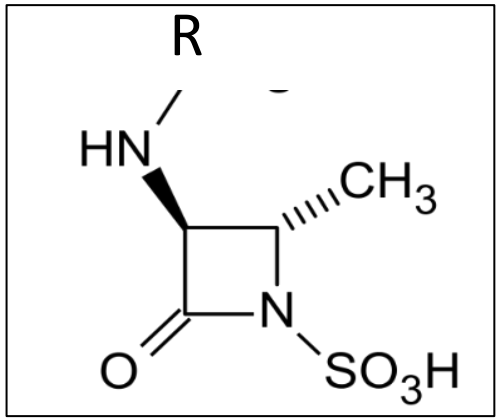
Penicillins



Cefalosporins



Carbapenems



Monobactams

Other β-lactam antibiotics have been developed which contain the same β-lactam ring as penicillin. The cefalosporins have the advantage of a reduced sensitivity to β-lactamase enzymes., giving a broader spectrum of activity. Carbapenems have both reduced β-lactamase sensitivity and the ability to directly inhibit β-lactamase enzymes. While the monobactams, very interestingly, inhibit a transpeptidase enzyme which is only present in gram-negative bacteria such as *Pseudomonas Aeruginosa,* but are ineffective in treating infections due to gram-positive bacteria.

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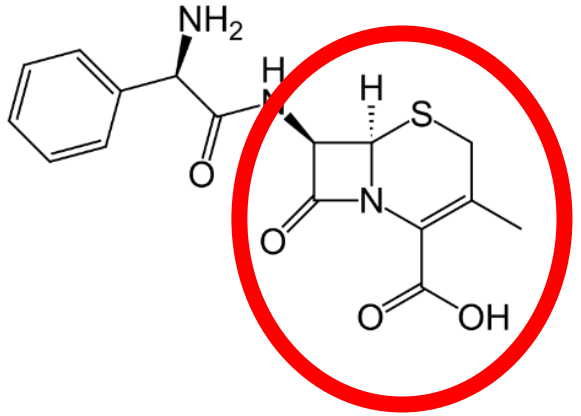
Cefalexin (1st Generation)

Cefalosporins

β-lactam antibiotics inhibit cell wall peptidoglycan cross-linking *BUT Less susceptible to β-lactamase*

- 5 generations of drugs based on increasing resistance to β-lactamases broadening the pattern of bacterial susceptibility
- Change from oral to injectable only drugs



Cefalexin

Adverse Effects

- Nausea, diarrhoea (C.difficile colitis more likely with 2/3 generation agents)
- Hypersensitivity
- Seizures
- Dose reduction in renal impairment

Cephalexin (1st generation)

Orally active

Commonest cefalosporin prescribed in primary care

Second-line therapy

pneumonia, urinary tract, skin/soft tissue infections

The cefalosporins, are β-lactam antibiotics containing the 4-membered β-lactam ring but, with a different side arm from the penicillins (structure ringed in red). All β-lactam antibiotics have the same mechanism of action, inhibiting peptidoglycan cross-linking in the cell wall but may vary in their sensitivity to different transpeptidase enzymes (also known as penicillin binding proteins). The adverse effects of cefalosporins are similar to the penicillins including diarrhoea, hypersensitivity and seizures with dosage reduction required in patients with renal failure. Five generations of cefalosporins have now been developed based on increasing resistance to different types of β–lactamase enzyme, broadening their bacterial spectrum of action. The first generation cefalosporin, cephalexin, is orally active with a major use in 2nd-line treatments of common bacterial infections. Cefalexin is the most widely prescribed cefalosporin in primary care (over 95%) albeit, at only some 5% of the level of prescribing for amoxicillin.

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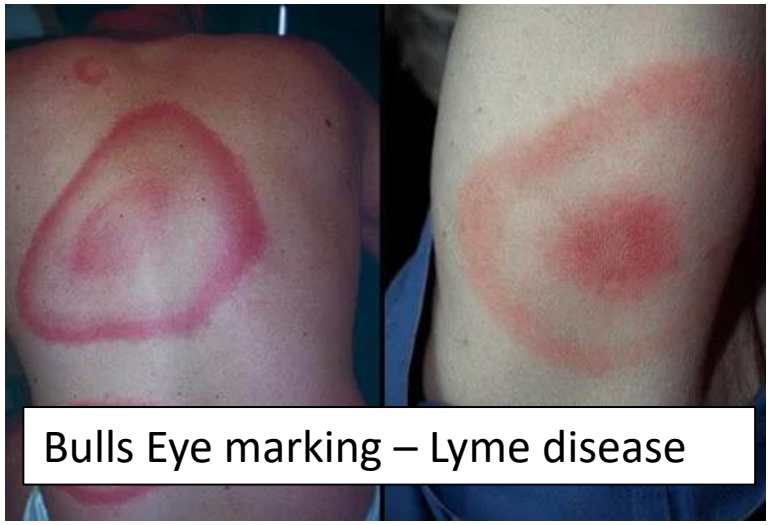
Ceftriaxone (3rd Generation)

Ceftriaxone (Injection only)
Pneumonia
Community acquired meningitis
Gonococcal infections
Lyme disease
Highly active against Enterbacteriaceae
(Klebsiella & E Coli)
H. Influenzae & Neisseria

No effect *Pseudomonas A or MRSA*



Bulls Eye marking – Lyme disease

Penile discharge - gonorrhoea

A wide variety of cefalosporins are available for use in secondary care to treat sepsis, respiratory, urinary tract and GI tract infections of which, two will be considered in further detail. Ceftriaxone is a third generation cefalosporin, only available as an injection (IV infusion/IV injection/deep IM injection), used to treat difficult gram-negative infections. Ceftriaxone has a greater resistance to β-lactamases, enhancing effectiveness against gram-negative compared to gram-positive organisms. For example, ceftriaxone is used in the second line treatment of Lyme disease caused by *Borrelia burgdorferi* in deer ticks *(NG95).* The typical Bulls Eye marking following a tick bite is shown in the right-hand diagram. A single dose of ceftriaxone (1g IM) is also used to treat gonorrhoea when antimicrobial sensitivity is unknown. However, ceftriaxone is without an effect on *Pseudomonas A*. or *MRSA* (methicillin resistant staph aureus).

Ceftaroline (5th generation)

Ceftaroline fosamil

(2010)

Prodrug

IV infusion

Effective Gram +ve MRSA (PBP-2A)

Such as skin infections

Broad spectrum (weaker gram-ve)

Ceftaroline fosamil, a 5th generation cefalosporin, is a liver-based prodrug delivered by intravenous infusion. Ceftaroline fosamil has a broad spectrum of action but is important since, unlike other cefalosporins, it inhibits PBP-2A, the transpeptidase enzyme present in MRSA (methicillin resistant Staph. Aureus). Ceftaroline is effective at treating MRSA skin infections resistant to flucloxacillin, such as cellulitis shown in the left leg (right-hand diagram).

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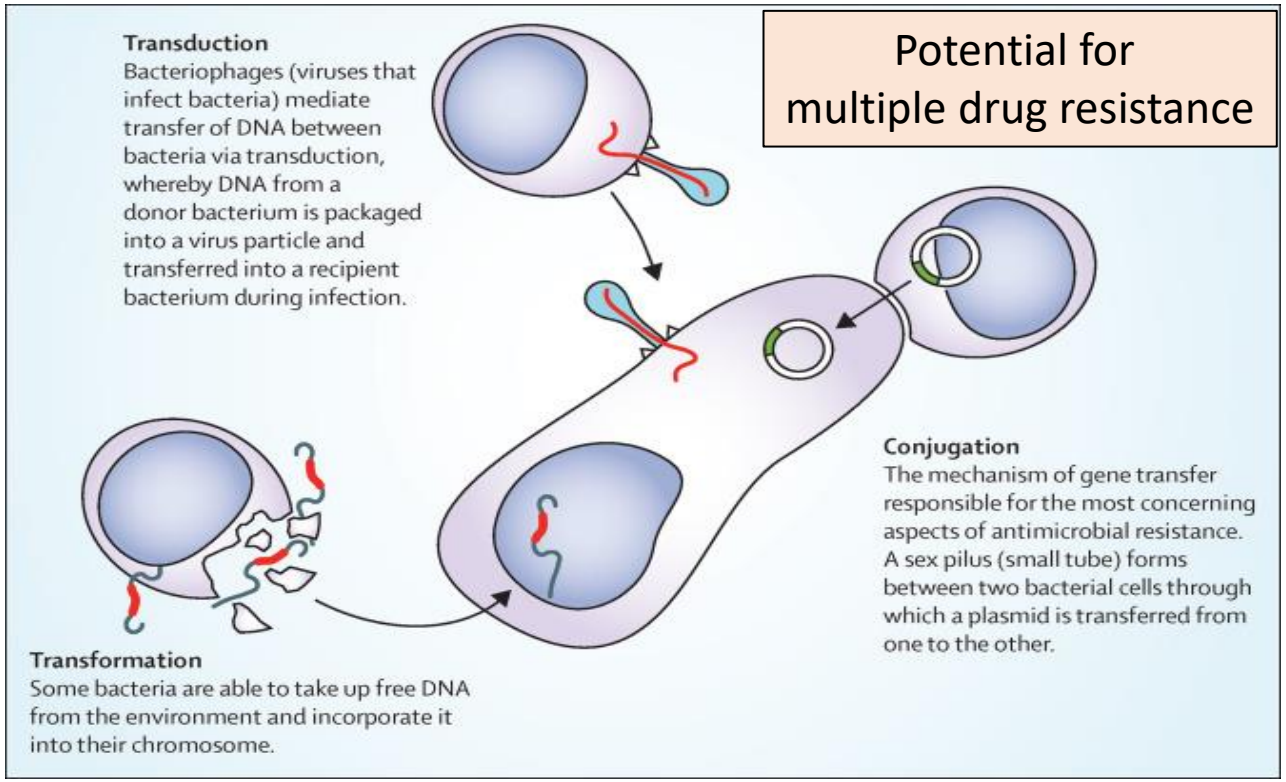
B lactam antibiotics : **Carbapenems**

β-lactamase resistance + β-lactamase inhibition



Potential for multiple drug resistance

Meropenem (1996)

Highly resistant to B-lactamases
I/V only - ultra-broad spectrum (Gram +/- ve)
Both *Pseudomonas A.* & anaerobic bacteria
Reserved for complicated infections
Including multiple drug resistant (MDR) patients

Ertapenem (1999)

Less broad spectrum
(ineffective against Pseudomonas A.)
Longer half life - protein bound
I/V infusion - once daily

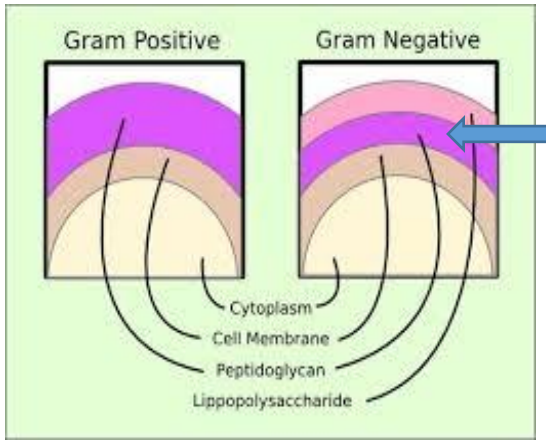
Antibiotic resistance may be transferred from one bacteria to another by mechanisms of conjugation, transduction or transformation as shown on the left-hand side of the slide. The carbapenems are β-lactam antibiotics with the additional ability to inhibit β-lactamase enzymes directly but can only be delivered intravenously. Carbapenems have similar adverse effects to the cefalosporins including a risk of C. Difficile infection, allergy, seizures and dosage reduction in renal failure. **Meropenem** has an ultra-broad spectrum of activity, including activity against *Pseudomonas* A**.** Meropenem is reserved for very severe or complex infections and its use requires the approval of a microbiologist, where the concept of antibiotic stewardship is an important consideration. Infections include those produced by multiple drug-resistant organisms. The short half-life of meropenem however, means it must be administered 3 times a day. **Ertapenem** although with a narrower bacterial spectrum, has the advantage of once daily treatment being more extensively bound to plasma protein, making IV outpatient treatment a possibility.

β-lactam Antibiotics : **Monobactams**

aztreonam

1. Very high affinity for PBP-3
2. Effective in gram –ve iinfections ie *Pseudomonas A*
3. Very poor binding to Gram+ve/anaerobic
4. No effect on Gram +ve bacteria
5. IV/IM/inhaled dosage forms

* Useful in penicillin/aminoglycoside allergy



PBP-3

Nebuliser for aztreonam in cystic fibrosis

In marked contrast to the carbapenems, the monobactams are not distinguished by their β-lactamase sensitivity but by their selectivity for only one form of transpeptidase enzyme, penicillin binding protein 3 (PBP-3) resulting in an unusual selectivity for gram-negative bacteria. Aztreonam is the only monobactam in clinical use. It has no effect on gram-positive bacteria but, as shown in the right-hand diagram, its use includes delivery by inhalation to treat *Pseudomonas A* infections in the lung of patients with cystic fibrosis. The lack of cross-sensitivity to penicillin makes aztreonam useful in appropriate patients with penicillin allergy.

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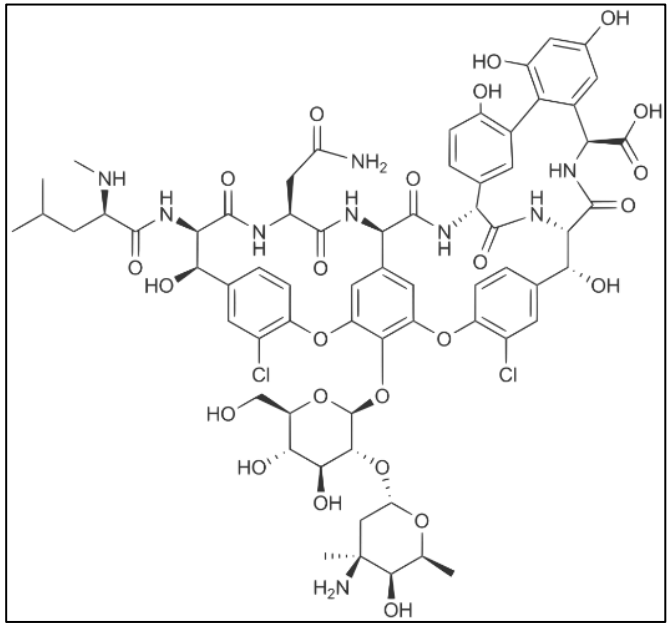
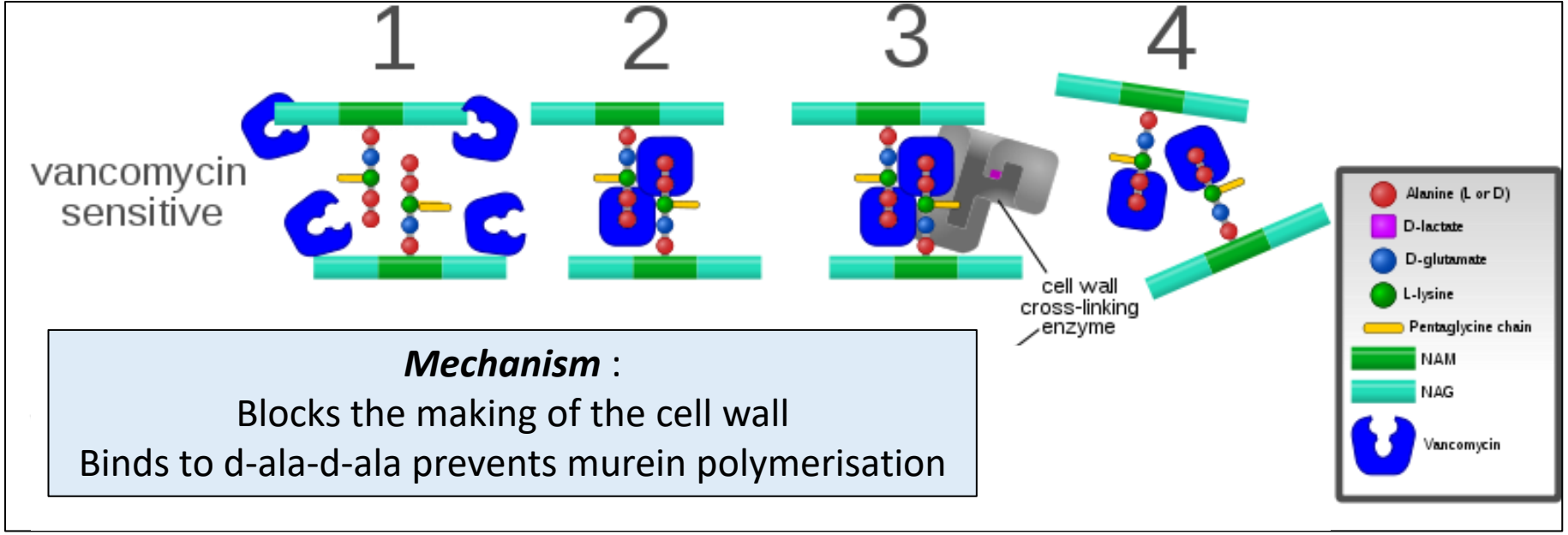
B. Vancomycin





Mechanism :
Blocks the making of the cell wall
Binds to d-ala-d-ala prevents murein polymerisation

Structure: Branched chain tricyclic glycopeptide
Origin Borneo soil sample (Amycolatopsis Orientalis)
Product: Vaconin, Lilly 1958

The first non-β-lactam antibiotic to consider is vancomycin. Vancomycin was introduced in 1958 at a time when the importance of penicillin resistance was just being recognised. It was originally thought that vancomycin could take the place of the penicillins as a widely used antibiotic. However, poor oral absorption and potential ear/kidney adverse effects meant the aminopenicillins, such as amoxicillin, were developed instead. Vancomycin (shown in blue) combines with the 2 terminal alanine residues of the cross-link mechanism. Unlike the β-lactam antibiotics, vancomycin does not inhibit transpeptidase enzymes. Instead, because of its large molecular size, vancomycin acts at an earlier step than peptidoglycan cross-linking, inhibiting polymerisation of the murein sugar monomers by steric hinderance, thus preventing the formation of peptidoglycan chains.

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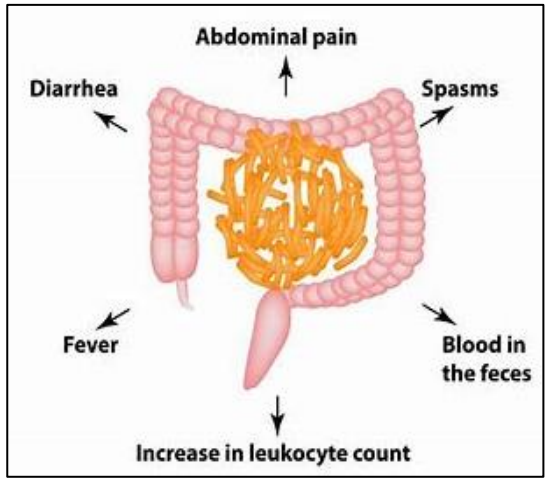
Vancomycin

Indications

- ***Intravenous:*** severe/resistant gram-positive infection ie endocarditis, MRSA.
- ***Oral*** : C difficile colitis – poor oral absorption



Adverse Effects

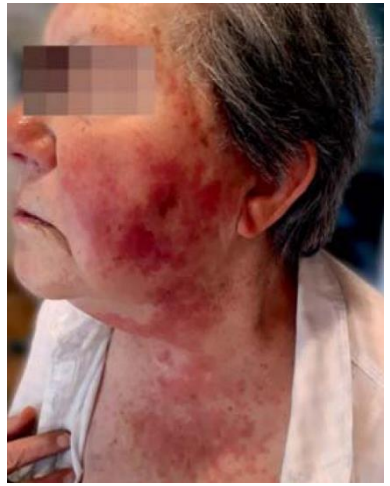
Acute : Rapid IV infusion :

thrombophlebitis,

red neck syndrome

(mast cell degranulation).

Chronic : ear and kidney toxicity



During a Course of Treatment

Therapeutic Drug Monitoring : trough levels 10-15 mg/L

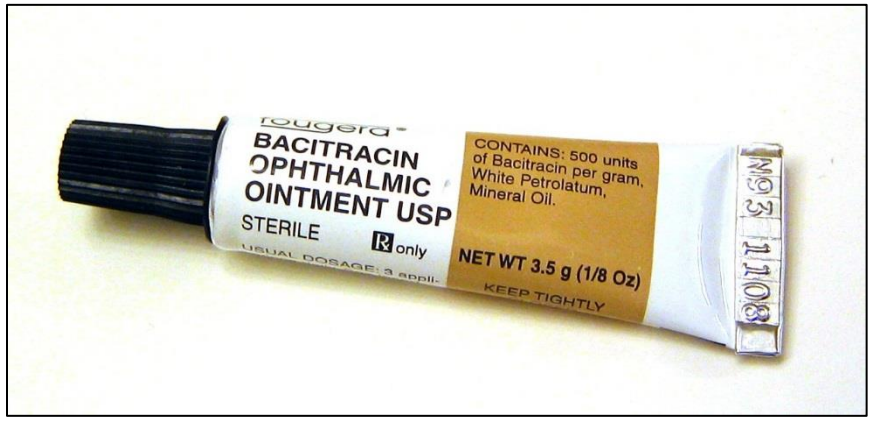
Nephrotoxic - acute renal failure

Ototoxic – high wavelengths

Similar Drugs : **Teicoplanin** similar mechanism/ therapeutic use

Due to its large molecular size, vancomycin is unable to penetrate the gram-negative bacterial cell wall. Vancomycin is only effective against gram-positive bacteria and is given by injection for severe or resistant infections such as endocarditis. Due to the potential to induce renal and ototoxicity the drug plasma levels require monitoring to keep within their therapeutic range. Rapid IV infusion can however result in mast cell degranulation leading to a red neck syndrome. In marled contrast, oral vancomycin has a completely different use. The poor oral absorption of vancomycin allows its oral use in the treatment of GI tract infections, such as the colitis produced by the overgrowth of C. Difficile following oral broad-spectrum antibiotics such as amoxicillin, without systemic effects. Teicoplanin has very similar pharmacology to vancomycin. Not being beta-lactam antibiotics, neither vancomycin nor teicoplanin are degraded by beta-lactamase enzymes.

C. Bacitracin



Structure :
Polypeptide - mixture of over 10 cyclic peptides

Origin :
Bacillus subtilis derived (1945) from compound fracture of Margaret Tracey

Sensitivity :

Bactericidal for both Gram +ve and Gram -ve bacteria

Mechanisms :

Inhibits peptidoglycan cell wall synthesis

Inhibits dephosphorylation of an enzyme involved transferring peptidoglycan building blocks (murein monomers) from the inside to outside of the cell membrane

Uses

Topical use eye/ear/skin

After care – tattoos/circumcision

Resistant infection BUT - Nephrotoxic

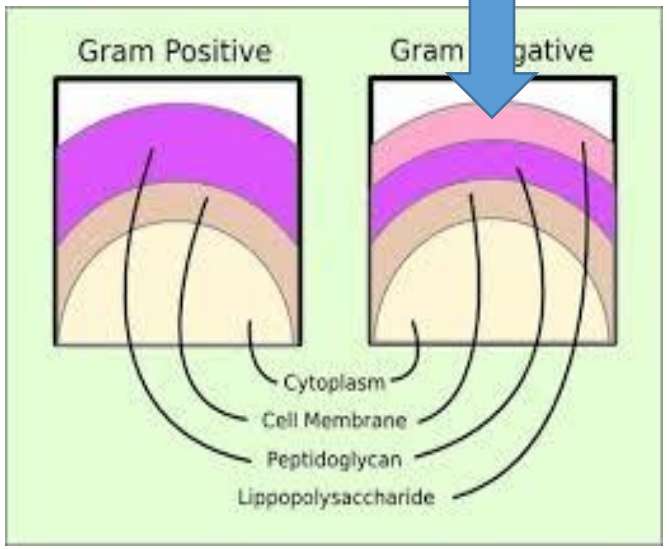
The third group of antibiotics to inhibit the bacterial cell wall, which includes bacitracin and polymyxin, work by different mechanism but, their greater toxicity means their activity is reserved for topical rather than systemic use. Bacitracin does also inhibit peptidoglycan synthesis but at an earlier step, inside the bacterial cell. Bacitracin inhibits a prenylation step, which attaches the forming murein sugar monomers to the inside of the bacterial cell membrane thus preventing these building blocks from being transported to the outside of the cell membrane to form the peptidoglycan structure of the cell wall. The major use of bacitracin is topical for infections of the eye, ear and skin. Bacitracin is unusual in that it was first discovered in bacteria present in a compound fracture leg wound. Although bacitracin is highly nephrotoxic, it occasionally has a systemic use as an antibiotic of last result

D. Polymyxin Antibiotics

- Cyclic nonapeptides with hydrophobic tail
- **Polymyxin B**

  Polymyxin E (colistin)

  colistimethate (prodrug)
- Made by gram +ve bacteria *Paenibacillus polymyxea*
- Binds to lipopolysaccharide (LPS) in outer cell membrane act as detergents disrupting the phospholipid components of cell
- Triple antibiotic ointment with neomycin & bacitracin.



- Bactericidal for gram-negative bacteria
- Treatment of external infections in eye/ear/skin
- Not absorbed from GI tract - used to sterilise gut
- Nebuliser/powder inhalation for P.Aeruginosa infection in cystic fibrosis

  * IV use as antibiotic of last resort (neurotoxic nephrotoxic)

The polymyxin antibiotics are frequently grouped together with bacitracin and used in combination for external use in topical formulations to treat ear, eye and skin infections. However, the polymyxins work in a **completely** different way from bacitracin and are the only example of an antibiotic that is selective for the outer lipopolysaccharide layer of the cell wall of gram-negative bacteria, with a detergent-like effect. This difference in mechanism makes the combination very useful. The lack of oral absorption for the polymyxins, similar to vancomycin, allows an additional use to sterilise the GI tract. The effectiveness against gram-negative bacteria such as *Pseudomonas A*. also allows a further use, when delivered by inhalation, like aztreonam, to treat lung infections in patients with cystic fibrosis.

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Antibiotics & Cell Wall: Formulary drug names

β-lactam antibiotics

Benzylpenicillin (Pen G)
Phenoxymethylpenicillin (Pen V)
Amoxicillin
Flucloxacillin
Co-amoxiclav (amoxicillin + clavulanic acid)
Tazocin (piperacillin + tazobactam)

Cefalexin
Ceftriaxone
Ceftaroline fosamil
Meropenem
Aztreonam

Other Cell Wall Antibiotics

Vancomycin

Bacitracin
Polymyxin

Isoniazid
Ethambutol

The following antibiotics which work by inhibiting the bacterial cell wall are included in the year 2 drug formulary. Isoniazid and ethambutol used in the treatment of tuberculosis, will be considered in a following bitesize recording on antibiotics and DNA together with rifampicin.