# Antibiotics

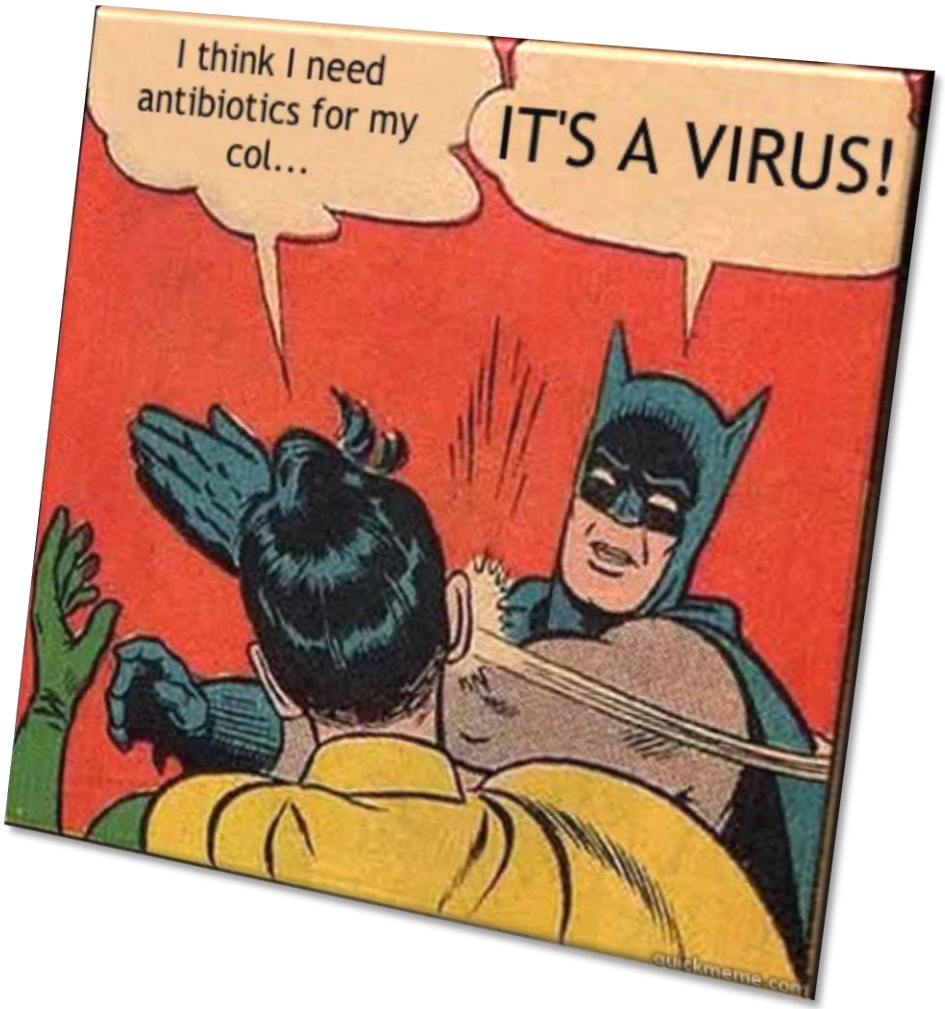
Dr Andrew Smith

# Overview

- Introduction

- Principles of Use
- Bacterial Classification
- Resistance
- Antibacterial Drugs
- Drug Choice

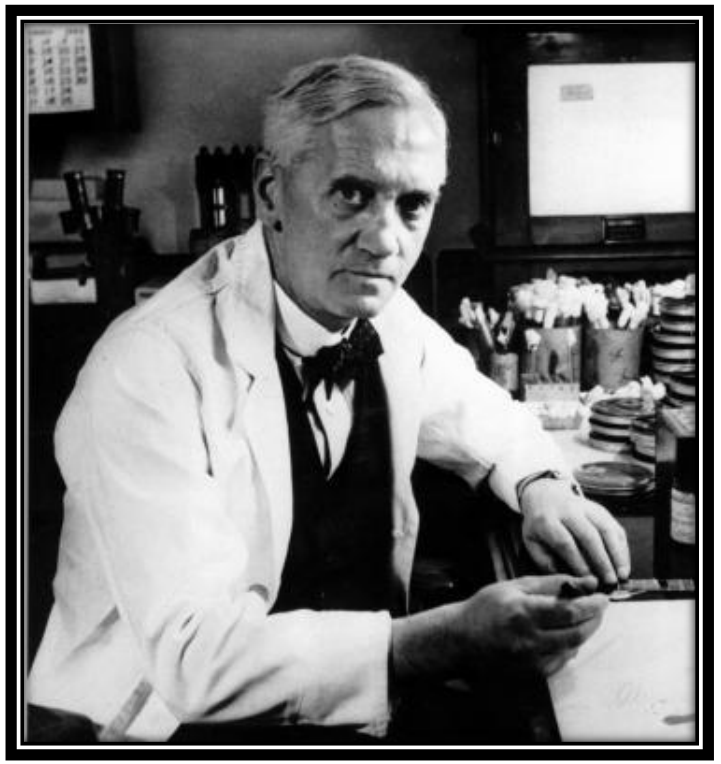
- Summary




SIMPLY FINALS

# Introduction

- Natural products with antimicrobial properties were used millennia ago.
- It was not until the late 19th century that Pasteur and Koch began to describe the effects of certain compounds against microbes.
- The most famous discovery was that of the antimicrobial effect of the mold *Penicillium*, made by Alexander Fleming *(a colleague of Grandad Dooley!)* in 1928.
- Nowadays there are a vast number of antibiotics in use, and bacterial resistance is of growing concern.

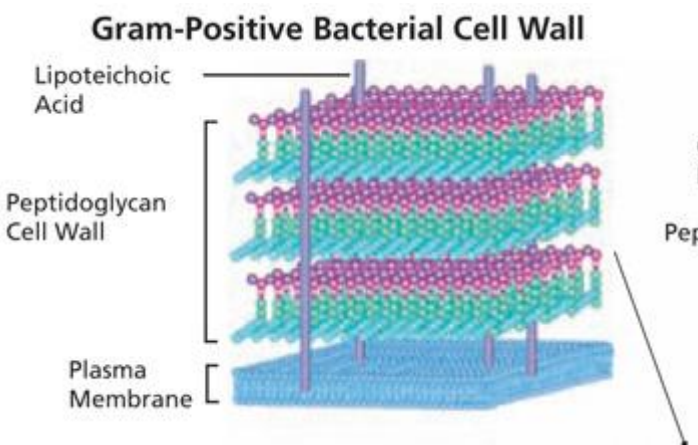


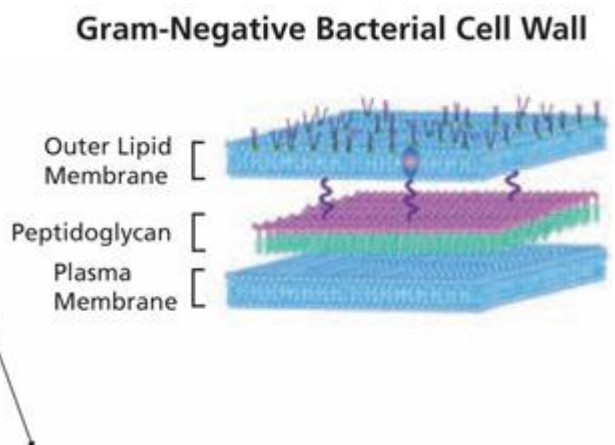
SIMPLY FINALS

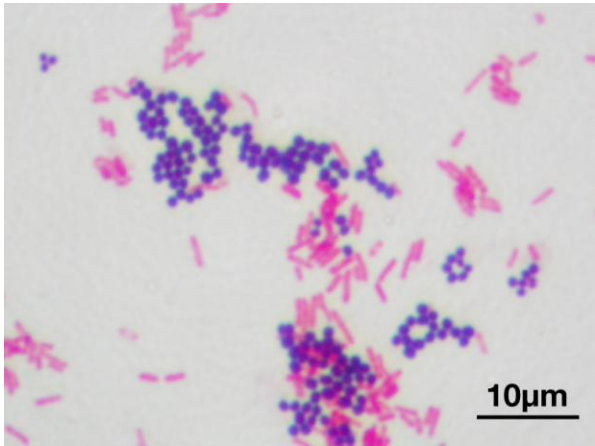
# Simple Bacterial Classification

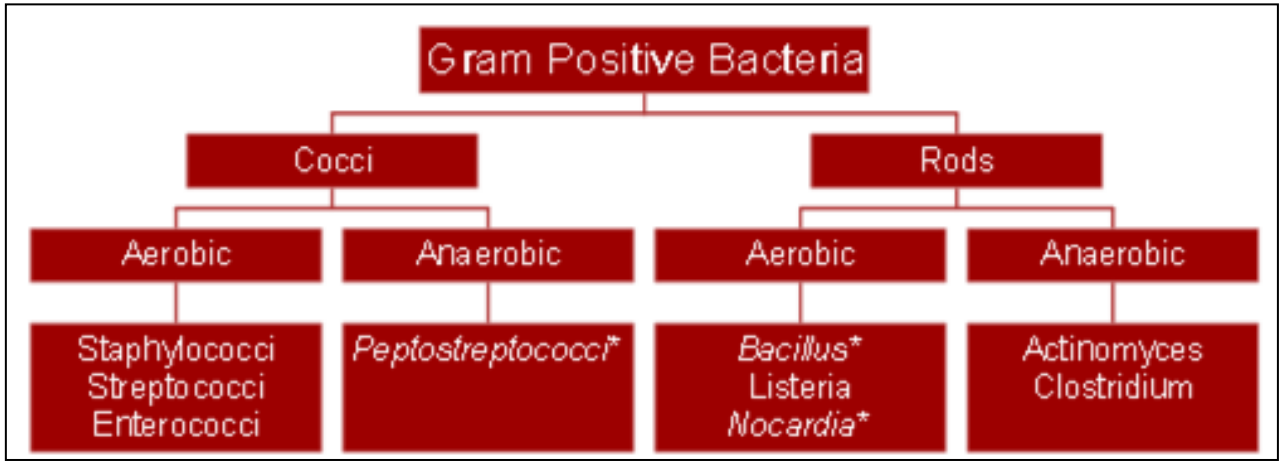
- **Shape:**
  - Cocci – spheres
  - Bacilli – rods
  - Spirochaetes

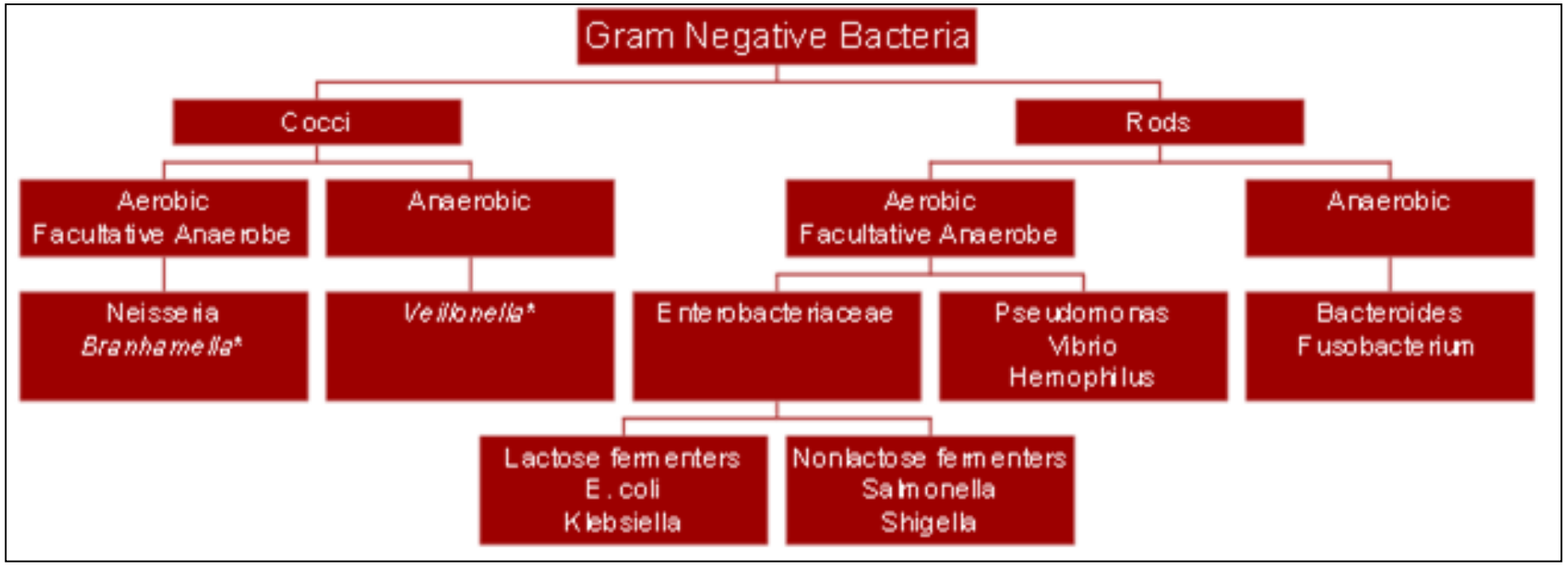
  Diplo – two bacteria
  Strep – line of bacteria
  Staph – cluster
- **Aerobic, facultative or strict anaerobic**
- Also by virtue of staining characteristics:
  - **Gram-Positive** – Have a large peptidoglycan rich cell wall – stain purple on the gram stain.
  - **Gram-Negative** – have a thinner cell wall so do not absorb as much stain – appear pink.
  - **Special Stains** e.g. Acid-fast
- Genetic profiling, biochemical tests, serology etc.

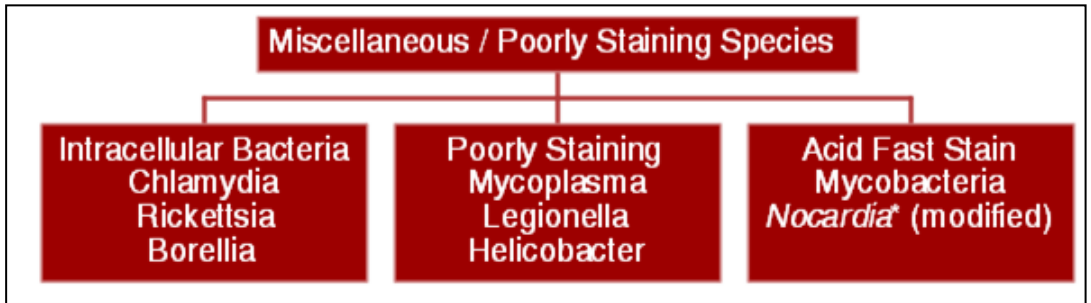




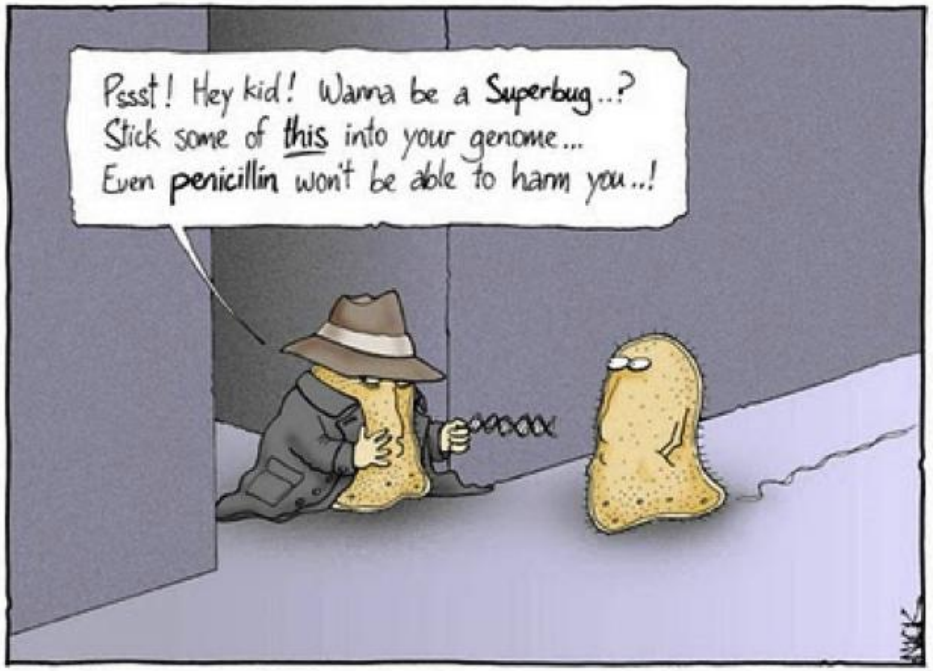



# Principles of Use

- In most cases antibiotics should only be prescribed when there is clinical evidence of infection.
  - Exceptions include prophylaxis (e.g. Pre-surgery, post-splenectomy)
  - If treating blind, broad-spectrum antibiotics should be used .
- Cultures (local and/or blood) should be taken before initiating therapy.
  - Exceptions may include presumed meningitis (i.e. In the community)
- Consideration must be given to:
  - **Dose** - will depend on age, renal/hepatic function, weight, site/severity of infection)
  - **Route** – Oral, IV (expensive), IM (painful), Intra-thecal etc.
  - **Duration** – Often depends on clinical judgement but good evidence exists for certain infections
- Where possible, hospital guidelines should be used.

# Resistance

- Not all microbes are sensitive to all agents.
- Previously sensitive microbes may develop resistance due to the acquisition of resistance genes, via:
  - Random mutation
  - Genetic transfer (e.g. Plasmids)




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

- Resistance may be due to:
  - Impermeable membranes
  - Metabolism/destruction of the drug
  - No active sites
- Resistance is increased by poor prescribing and compliance.

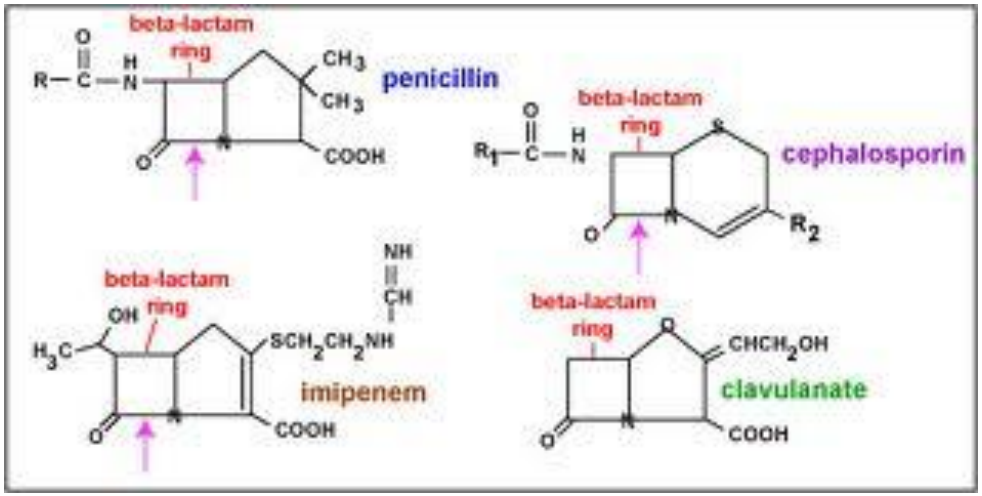
# Classification of Antibiotics

- Although of dubious clinical significance, they can be broadly classified as:
  - Bacteriocidal – actively kill bacteria
  - Bacteriostatic – inhibit bacterial growth
- They are better thought of in terms of their class and their spectrum of activity.

# ß-lactams

- Named because they contain a ß-lactam ring.
- They interfere with bacterial cell wall synthesis, inhibiting the peptidoglycan link formation
- They are bacteriocidal agents.

- The class includes the:
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - (Monobactams)

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# ß-lactams - Penicillins

- Effective against a wide variety of bacteria including the streptococci, meningococci and pneumococci species. Resistance varies to *S. aureas*.

- **Benzylpenicillin** – used in a number of situations (e.g. meningitis)
- **Penicillin V** – mainly used for strep throat and prevention of rheumatic fever
- **Ampicillin/Amoxicillin** – Broad spectrum penicillins which have some action against Gram-Negative bugs too. Not effective against ß-lacatmase producing organisms.
- **Flucloxacillin** – a penicillinase resistant drug which is active against *S. aureus* (not MRSA). Useful in skin infections
- **Piperacillin/Ticarcillin** – semi-synthetic which have activity against *Pseudomonas* also.
- **ß-lactamase inhibitors** – These protect against enzymes of resistant bacteria and increase the spectrum to cover gram-negatives and anaerobic organisms. They're combined with standard antibiotics, e.g.
  - Clavulanic acid and Amoxicillin – ***Coamoxiclav***
  - Tazobactam and Pipericillin - ***Tazocin***

# ß-lactams - Cephalosporins

- Are more resistant to ß-lactamases than the penicillins.
- They are generally classed in 'generations' with new generations having wider gram-negative cover.
- They have poor oral availability, but good CSF penetration if given parenterally.
- They increase the risk of *C. difficile* infection.
- **First Generation**
  - e.g. Cefalexin, good against staph and strep,
- **Second Generation**
  - e.g. Cefuroxime, better against gram-negs (e.g. *E. coli, Klebsiella, Proteus spp.*), worse against gram-positives.
- **Third Generation**
  - Cefotaxime, Ceftriaxone (long-half life), Ceftazodime, Cefixime – penetrate the CSF well. More potent against anaerobic gram-negs. Useful in severe sepsis.
- **Fourth** – Cefepime
- **Fifth** - Ceftobiprole

# ß-lactams - Carbapenems

- Stable against Extended-Spectrum ß-lactamases (ESBLs) although not active against MRSA
- **Imipenem** – broad spectrum and used in severe sepsis. Good against enterococci. It is neurotoxic and is metabolised by the kidney.
- **Meropenem** – good in CNS infections

# Macrolides

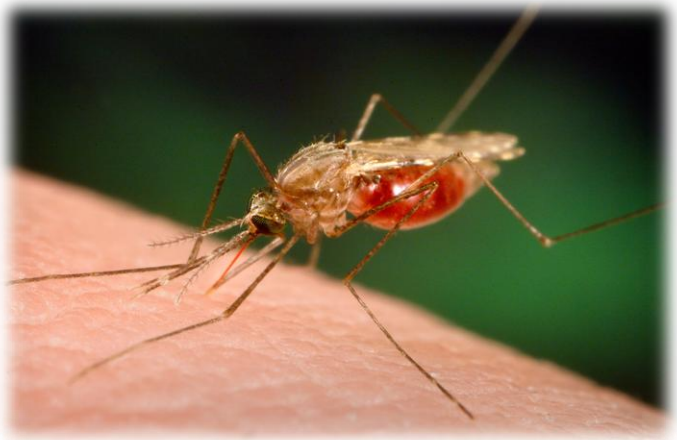
- Bind to the 50S subunit of bacterial ribosomes and inhibit protein synthesis. They are bacteriostatic.

- **Erythromycin** – similar range to penicillin so are often used in pen-allergy. Active against *Mycoplasma* and *Legionella* species.
- **Clarithromycin** – has higher tissue concentration than erythromycin.
- **Azithromycin** has good intracellular penetration so useful *Salmonella typhi* and *Chlamydia* infections

# Tetracyclines

- Bind to the 30S subunit of the ribosome and are bacteriostatic.
- Have a wide spectrum of action against both gram positives and negatives including some rarer organisms such as *Borrellia*, *Coxiella* and *Rickettsia spp.*.
- Are all typically given orally and have similar profiles. They can cause photosensitivity and are deposited in growing bone and teeth.

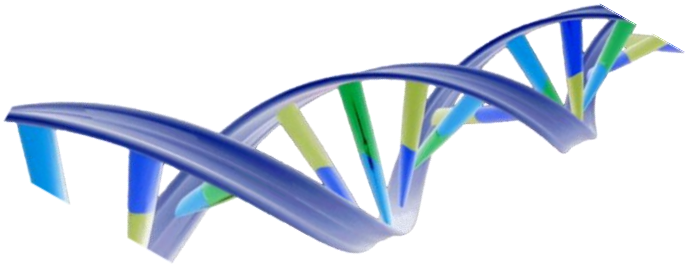
- **Tetracycline**
- **Doxycycline**
- **Minocycline**



# Quinolones

- These affect bacterial DNA synthesis by inhibiting topoisomerases – they are bacteriocidal.
- Given orally or IV.
- There is growing resistance.
- There is an increased risk of *C. difficile* infection and other more serious effects include toxic epidermal necrolysis and prolongation of the QT interval.

- **Ciprofloxacin** – mostly active against gram-negatives. Typically used in UTIs, GI infections and gonorrhoea.
- **Moxifloxacin** – growing role in the treatment of TB.
- **Norfloxacin**
- **Levofloxacin**



# Aminoglycosides

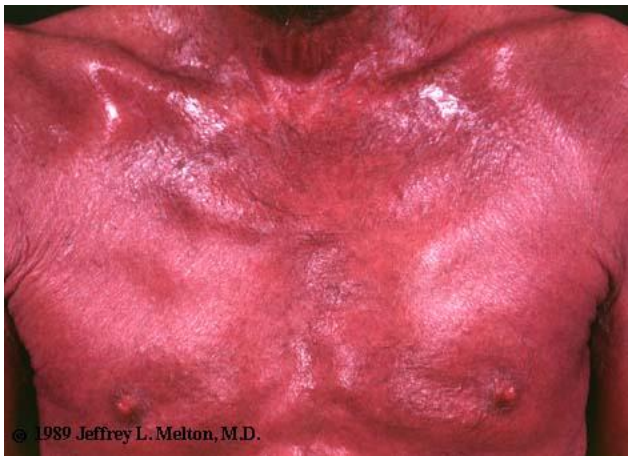
- Bind to the 30S subunit of the bacterial ribosome, therefore interfere with protein synthesis
- They are bacteriocidal.
- Poor oral availability so must be given parenterally.
- Mainly active against gram-negatives, but *S. aureus* is often sensitive as well. Poor action against the strep and enterococci.
- Resistance to Aminoglycosides does occur, but it is drug specific.
- Rarely used as monotherapy.
- Drug level monitoring is required due to nephro and oto toxicity.

- **Gentamicin and Amikacin** are the most widely used.
- **Streptomycin** is a second line anti-TB drug.
- **Tobramycin** – similar to Gentamicin but also used as inhaled therapy against *P. aeruginosa* in Cystic Fibrosis.

# Glycopeptides

- These interfere with bacterial cell wall synthesis and are bacteriocidal.
- Some enterococci are now resistant (GRE).
- Therapeutic drug monitoring is required due to nephrotoxicity. Vancomycin can also cause profound histamine release causing ‘red-man syndrome’.

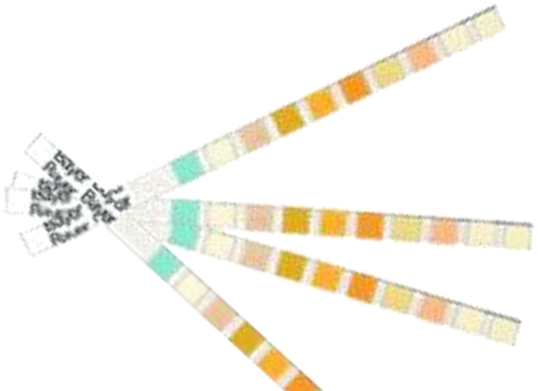
- **Vancomycin** – active only against gram-positive organisms. Usually given IV, but given PO to treat *C. diff* infection. It is reserved for when other antibiotics cannot be used and is effective against MRSA.
- **Teicoplanin** – given IV



# Other antibiotics - Trimethoprim

- **Trimethroprim** is a synthetic diaminopyrimidine which inhibits dihydrofolate reductase (involved in folate synthesis). It has good bacteriocidal action against aerobic organisms. Typically used to treat UTIs.

- It can be combined with a sulphonamide drug (sulfamethoxazole) to create **Co-trimoxazole** which is used to treat rarer infections such as Whipple's disease and *Pneumocystis jeroveci* pneumonia (PCP) in the immunocompromised.



SIMPLY FINALS

# Other antibiotics

- **Metronidazole** destabilises DNA and is active against anaerobic and protozoal infections. It is often used in the treatment of *C. difficile*, bacterial vaginosis and tetanus; as well as part of *H. pylori* eradication.
- It has a disulfiram-like reaction if used with alcohol.

- **Chloramphenicol** inhibits protein synthesis by binding to the 50S subunit of the ribosome. Rarely used systemically nowadays (unless in multiple allergies), but is used for topical treatment of eye infections.

# Other antibiotics

- The **Polymyxins** (e.g. **Colistin**), are only active against Gram negative bacteria.
- They have poor oral absorption, but can be used topically, i.e. to treat ear infections, nebulised in cystic fibrosis, or as bowel decontamination in neutropaenic patients.

- **Clindamycin** is a liconsamide antibiotic inhibiting ribosome translocation and is given IV in severe infections. It has good action against gram-positives, especially staph and strep, as well as anaerobes. Topical treatment is also used for bacterial vaginosis.
- Can increase the risk of *C. diff.*

# Other antibiotics

- **Nitrofuantoin** is a nitrofuran drug which is used in UTIs. It can cause brown urine and more severe effects such as pneumonitis, lung fibrosis and peripheral neuropathy.

- **Fusidic Acid** is most active towards gram-positives, especially *S. aureus*. It shouldn't be used as monotherapy, but can be added in serious infections such as osteomyeltis.

- **Linezolid** is a newer antibacterial agent which is only effective against gram-positives. Only used for MRSA or GRE infections.

# Other antibiotics – Anti-TB drugs

- **Rifampicin** is a rifamycin that inhibits RNA synthesis and is typically used as an anti-TB drug. However, it has wide spectrum against bacteria as well as some protozoa (and even some viruses). Hepatotoxicity can occur. It stains bodily excretions red.

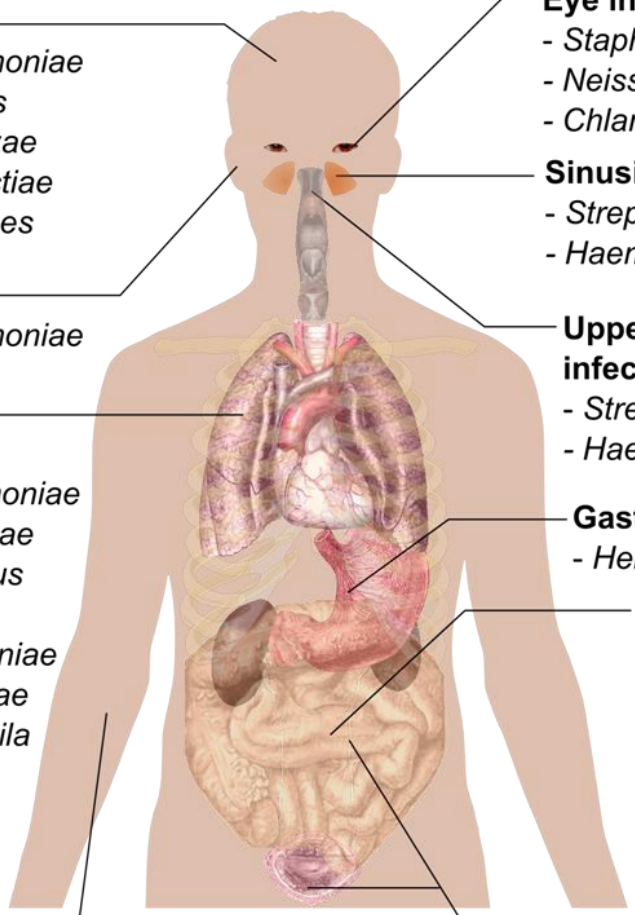
- **Isoniazid** is an anti-TB drug which inhibits mycobacterial cell wall synthesis. Can be used as a single drug for prophylaxis of TB contacts. Hepatotoxicity and peripheral neuropathy are risks.

- **Ethambutol** acts against typical and atypical mycobacteria, inhibiting cell wall synthesis. Can cause optic neuritis so visual acuity should be tested. Colour recognition can decrease.

- **Pyrazinamide** is only active against TB and its mechanism of action is not fully understood, but likely due to interfering with fatty acid synthesis. Hepatotoxicity can occur.

Overview of

# Bacterial infections



**Bacterial meningitis**
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Streptococcus agalactiae*
- *Listeria monocytogenes*

**Otitis media**
- *Streptococcus pneumoniae*

**Pneumonia**
Community-acquired:
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

Atypical:
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*

Tuberculosis
- *Mycobacterium tuberculosis*

**Skin infections**
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*

**Sexually transmitted diseases**
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Treponema pallidum*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*

**Eye infections**
- *Staphylococcus aureus*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*

**Sinusitis**
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

**Upper respiratory tract infection**
- *Streptococcus pyogenes*
- *Haemophilus influenzae*

**Gastritis**
- *Helicobacter pylori*

**Food poisoning**
- *Campylobacter jejuni*
- *Salmonella*
- *Shigella*
- *Clostridium*
- *Staphylococcus aureus*
- *Escherichia coli*

**Urinary tract infections**
- *Escherichia coli*
- Other Enterobacteriaceae
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*

Drug Choice depends on:
- Site
- Likely organism
- Severity
- Co-morbidity
- Local policy

SIMPLY FINALS

# Sepsis - Definition

- Sepsis is present when there is **a high suspicion** of, or **proven infection and** 2 or more of the following SIRS (systemic inflammatory response syndrome) criteria:
  - 1. Heart rate > 90 beats/min
  - 2. Temperature < 36 °C or > 38 °C
  - 3. Respiratory rate > 20 breaths/min or, PaCO2 less than 4.3Kpa
  - 4. White blood cell count < 4 x109 or > 12 x109 cells/L, or > 10% band forms
- **Severe Sepsis:** Sepsis **plus** acute organ dysfunction &/or hypotension
- **Septic Shock:** severe sepsis despite adequate fluid resuscitation

- Treatment must be initiated quickly (the golden hour).
- It will depend on likely source.

# Sepsis – **Antibiotic** Treatment

Example regimes:

- Broad-spectrum penicillin (e.g. Coamoxiclav), with a cephalosporin (e.g. Cefuroxime/Cefotaxime) plus Gentamicin.
- Other options would include (especially in neutropaenic sepsis) a Broad-spectrum anti-pseudomonal penicillin (e.g. Tazocin),

- If MRSA presumed, add Vancomycin
- If anaerobic organism presumed, add Metronidazole
- If hospital acquired, consider a carbopenem (e.g. Imipenem)

# Community Acquired Pneumonia

- Commonly caused by *Strep pneumoniae, Haemophilus influenzae.* More rarely *Mycoplasma pneumoniae, Legionella spp, Chlamydia spp, Coxiella burnetii.* Also consider *Staph. aureus* if recent influenza infection*;* TB if no response to treatment or in at risk group.

- CURB-65 can be used (but use clinical judgement)
- Treatment is typically 5-10 days. Longer in *Staph* infections.

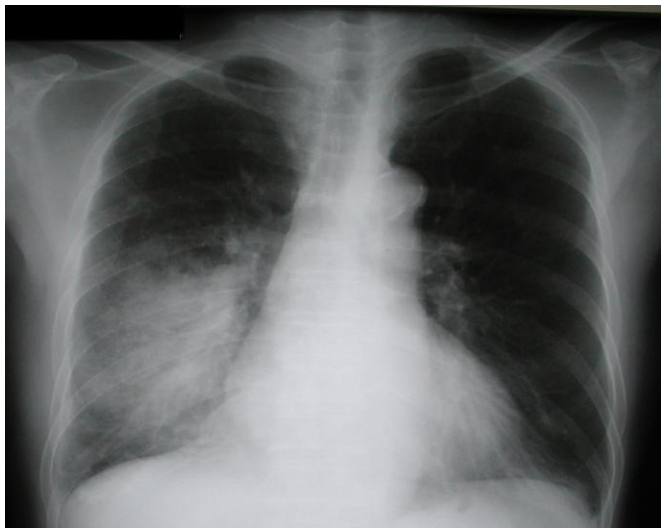
**Mild/Moderate**

- Amoxicillin +/- a Macrolide (e.g. Clarithromycin) or Doxycycline

**Severe**

- Coamoxiclav and Clarithromycin, or;
- Benzylpenicillin and Clarithroymycin, or;
- Cephalosporins can also be used.

- Vancomycin can be used in penicillin allergy



# Hospital Acquired Pneumonia

- Can be similar organisms to CAP, but also gram-negatives and multi-resistant organisms.

- **Treatment:** Tazocin (or a cephalosporin). If MRSA, add Vancomycin.

# Aspiration Pneumonia

- May be chemical rather than infective.
- Anaerobes are common (e.g. *Klebsiella*).

- **Add Metronidazole**

"The patient in the next bed is highly infectious. Thank God for these curtains."

# Infective Exacerbation of COPD

- Antibiotics have been shown to be effective ONLY if there is a history of at least 2 of the following:
  - increased dyspnoea
  - increased sputum purulence
  - Increased sputum volume

**Treatment**

- Add a tetracycline (Doxycycline) or macrolide (Clarithromycin)

- If recent course of first line therapy, consider alternative combinations.

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# Urinary Tract Infections

- Commonly caused by *E.coli*, other coliforms, enterococci, *Staph. Saprophyticus* (in young women)

**First line**

- Trimethroprim or Nitrofurantoin. 3 days is usually enough in women, longer for men.
- Amoxicillin or cephalosporin is an alternative.

- Add Gentamicin if catheter is *in situ*
- Note: All catheters become infected so a positive urine dip is not indication for treatment without clinical infection.

**In Pyelonephritis**

- Coamoxiclav (or Gentamicin if pen-allergic)
- 10-14 days treatment

# Infective Endocarditis

- Depends on risk factors for each individual patient. Commonly for native valve endocarditis, oral streptococci, *Staph. aureus (including MRSA),* enterococci, less commonly *Coxiella burnetii (Q fever),* HACEK organisms

- Diagnosis by Modified Dukes Criteria
- Treatment 4-6 weeks – involve microbiology!

**Simple Endocarditis**
- Amoxicillin +/- Gentamicin

**Acute presentation**
- Benzylpenicillin, Flucloxacillin and Gentamicin

**Pen-Allergy (or prosthetic valve):** Vancomyicin, Rifampicin and Gentamicin

# Acute Meningitis/Encephalitis

- Causative agent depends on age and risk factors for each individual patient. In adults, commonly *Strep. pneumoniae, Neisseria meningitides, Haemophilus influenzae,* enteroviruses. Less commonly *Listeria monocytogenes,* Herpes viruses, TB. With underlying immune compromise: *Cryptococcus neoformans.*

- Length of treatment varies from 7-21 days.

**Treatment**

- Benzylpenicillin (given in community)

- Cephalosporin (Cefotaxime/Ceftriaxone) 1st line in hospital +/- amoxicillin.

- Pen-allergy: Vancomycin and Chloramphenicol

*(consider adding Acyclovir)*

SIMPLY FINALS

# Acute Cellulitis (and friends)

- Commonly Group A Strep, *Staph aureus (including MRSA).* Less commonly coliforms, anaerobes.
- Staged using modified Enron criteria. Treatment is for 7-10 days.

**Mild/Moderate**

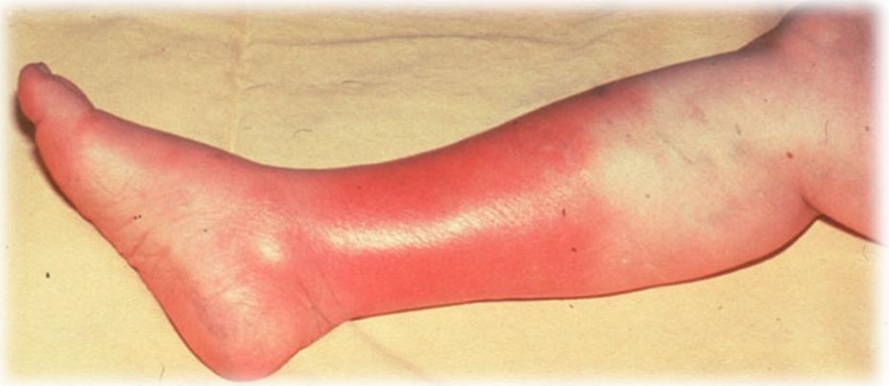
- Flucloxacillin (po/iv)

**Moderate/Severe**

- Flucloxacillin and Benzylpenicillin

**Severe**

- As above plus Clindamycin



- If penicillin allergy: Clarithromycin (+/- Clindamycin).
- If MRSA colonised Vancomycin +/- Fusidic Acid
- If evidence of shock, add Gentamicin

- ***The above is generally applicable to peripheral/central line infections and wound infections also.***
- ***Flucloxacillin, Fusidic Acid and Clindamycin form the basis of osteromyeltis and septic arthritis treatment.***

# Gastro and friends

**Gastroenteritis**

- Typically due to viruses so antibiotics not indicated. Even bacterial infections are often self-limiting. If indication to treat, however:
- *Salmonella*, *Campylobacter* and *Shigella* can be treated with Ciprofloxacin or a cephalosporin

***Clostridium difficile* infection** – Metronidazole +/- Vancomycin

***Helicobacter pylori*** eradication regimens, Omeprazole with:

- Clarithromycin and Amoxicillin, *or;*
- Metronidazole and Clarithromycin.

- These should be given for 7 or 14 days.

**Intra-abdominal infection** (e.g. Post-surgery) is typically treated with Tazocin/Coamoxiclav +/- Gentamicin

# Summary

- There are many factors that influence the choice of antimicrobial.

- Some very general thoughts:
  - If it's mild, start with oral and simple/common drugs, e.g. Amoxicillin, Trimethorprim.
  - Staph/Skin = Flucloxacillin
  - If it's more severe, convert to IV and add in extra drugs, e.g. Metronidazole, a cephalosporin
  - If evidence of sepsis, consider Gentamicin, Tazocin and/or a carbopenem (e.g. Imipenem).
  - If MRSA or *C. diff*, add in Vancomycin.

# Thank-you

## Any Questions


**Bibliography**
Medical Management and Therapeutics – Kumar, Clark
Oxford Handbook Clinical Medicine – Longmore et.al.
The BNF
Barts Health antimicrobial guidelines

SIMPLY FINALS