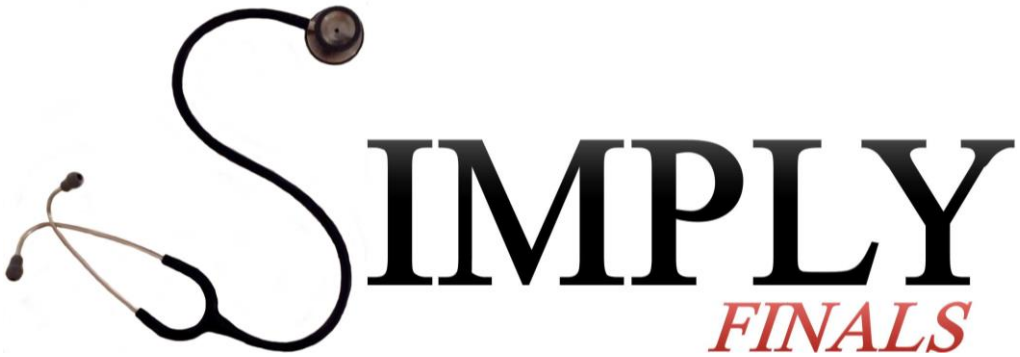
Antibiotics

Dr Andrew Smith

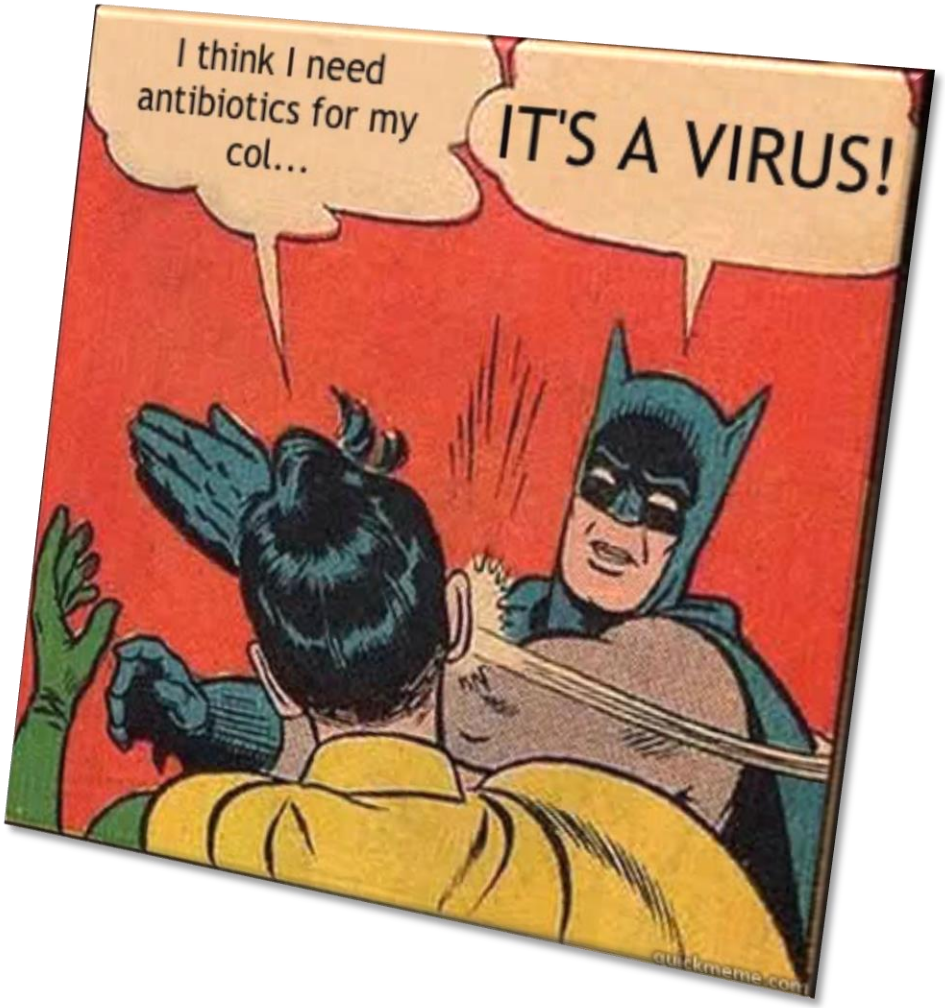


Overview

- Introduction

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

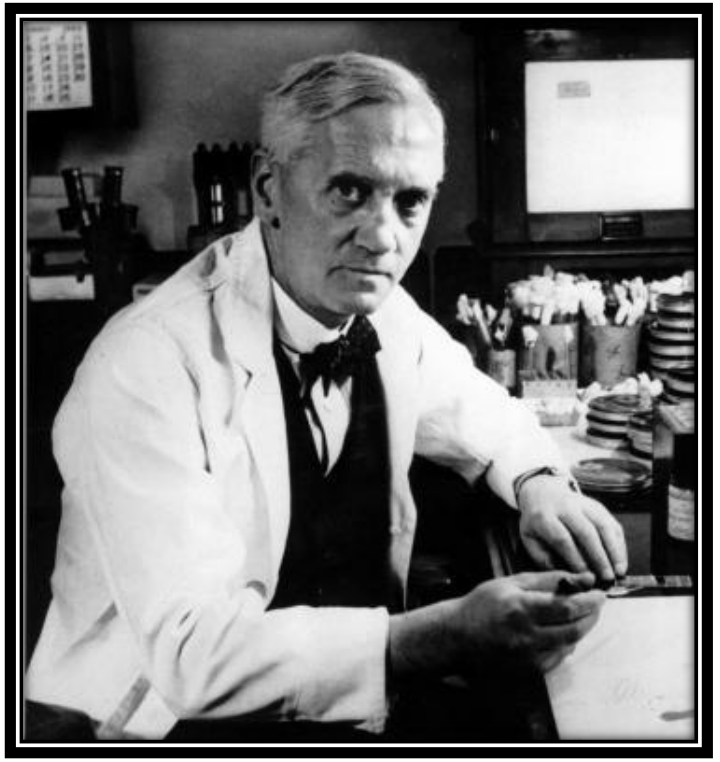
- Summary



SIMPLY FINALS

Introduction

- Natural products with antimicrobial properties were used millennia ago.
- Late 19th century - Pasteur and Koch described effects of compounds towards microbes
- 1928 - Alexander Fleming *(a colleague of Grandad Dooley!)* discovered the antimicrobial effect of the mold *Penicillium*.



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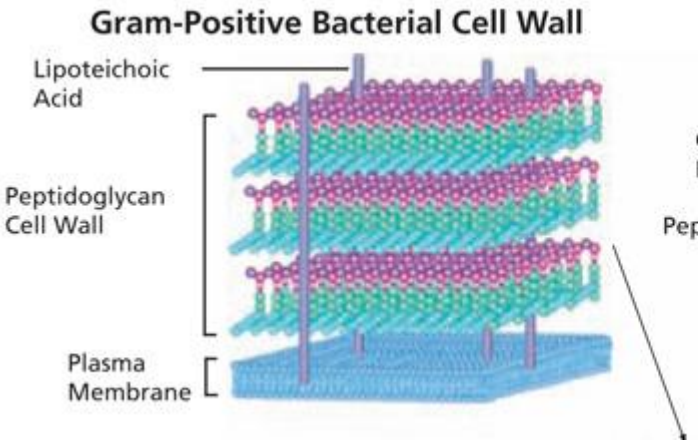
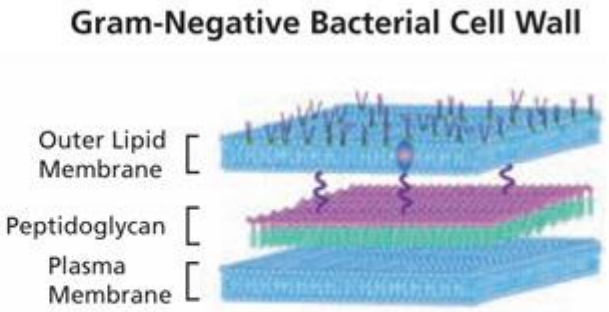
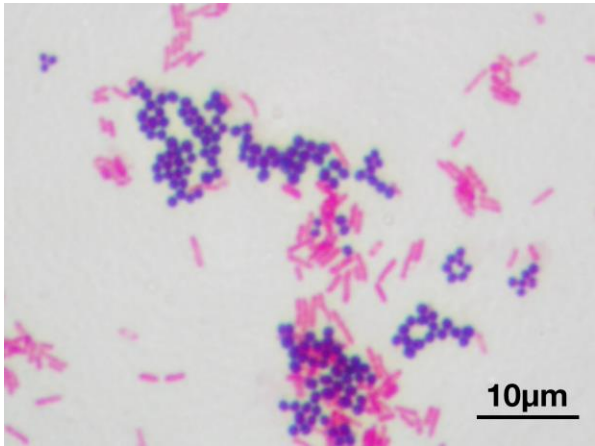
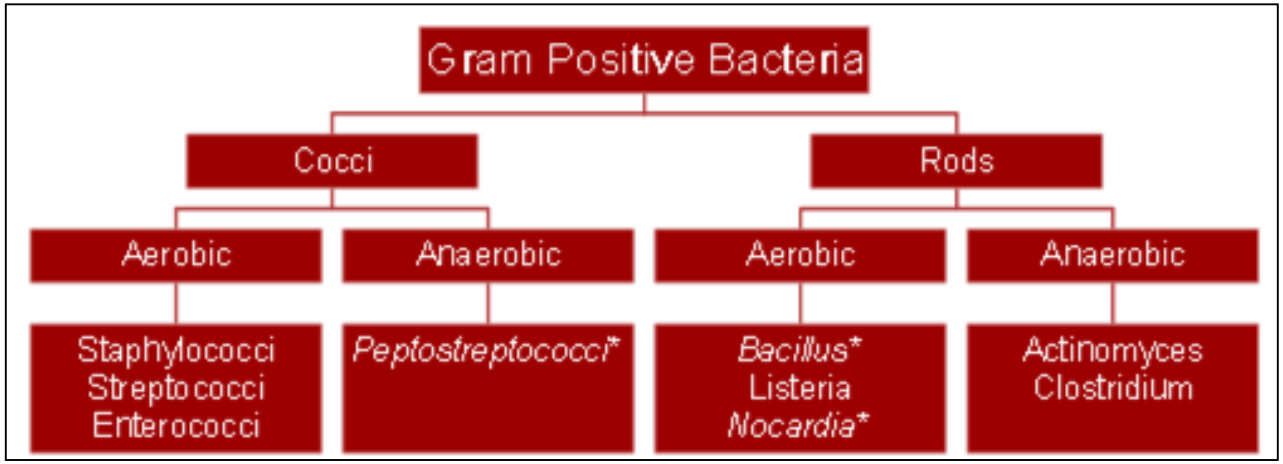
Simple Bacterial Classification

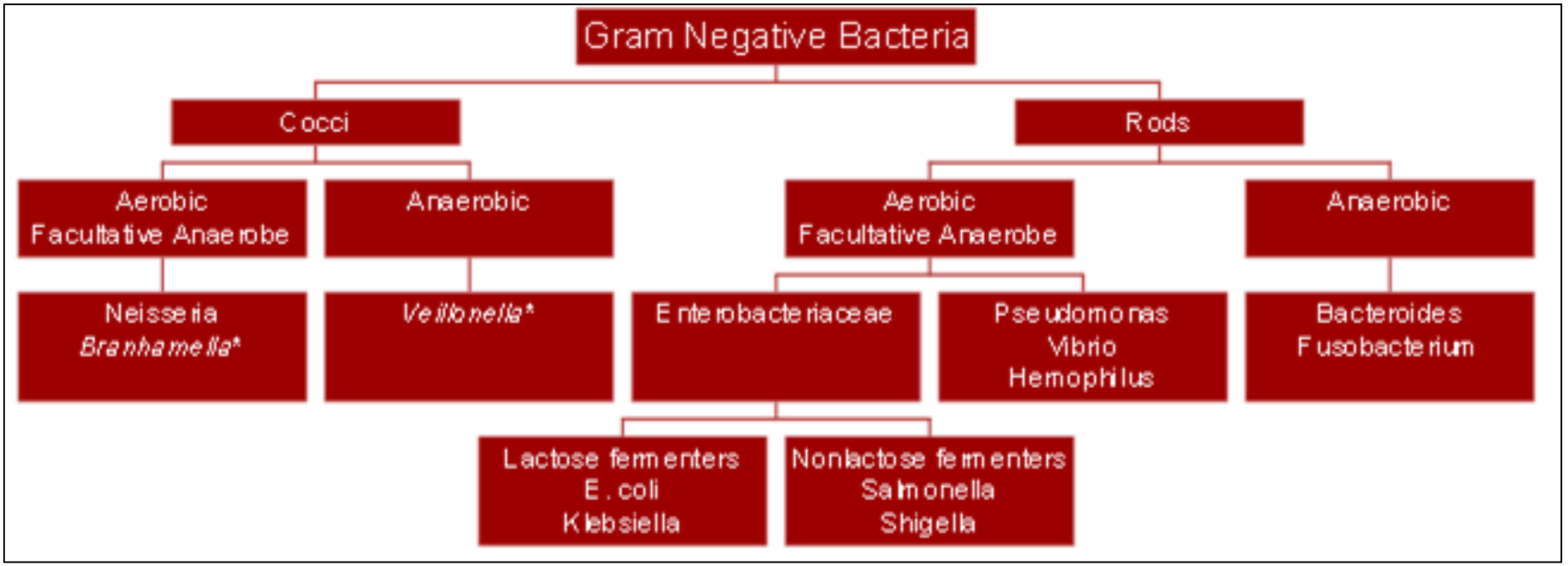
- **Shape:**
  - Cocci – spheres
  - Bacilli – rods
  - Spirochaetes
  - Diplo – two bacteria
  - Strep – line of bacteria
  - Staph – cluster
- **Aerobic, facultative or strict anaerobic**
- Also by virtue of staining characteristics:
  - **Gram-Positive** – Have a large peptidoglycan rich cell wall – 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.

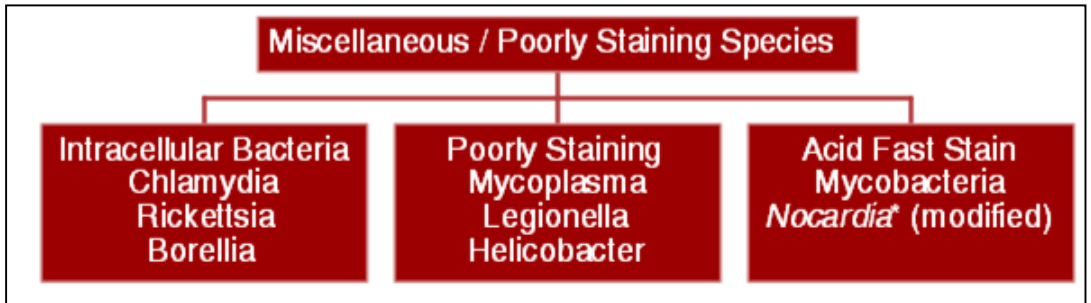










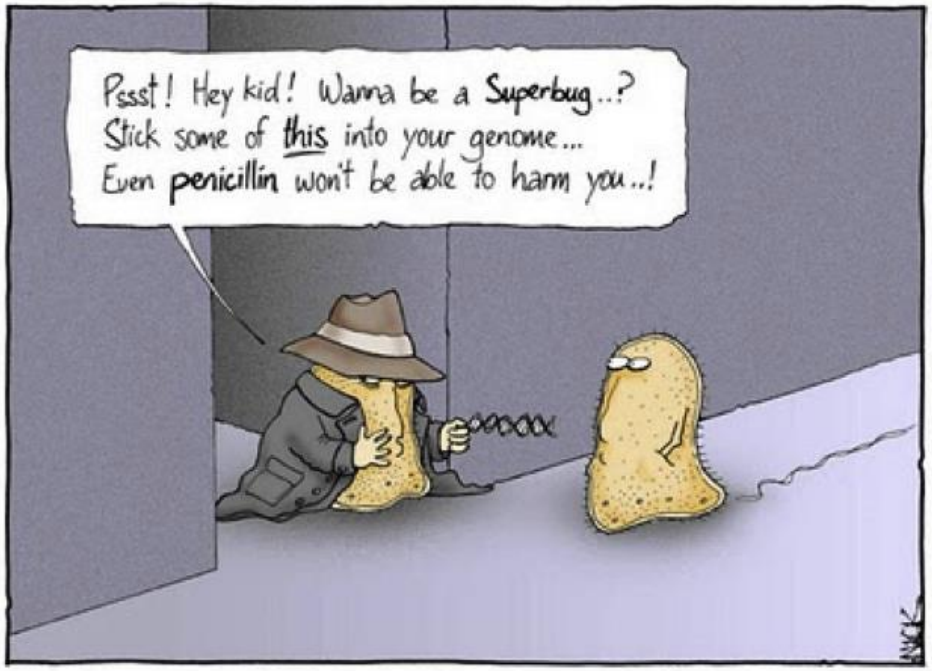


Principles of Use

- Antibiotics should only be prescribed with clinical evidence of infection.
  - Exceptions include prophylaxis (e.g. Pre-surgery, post-splenectomy)
- 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.

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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.

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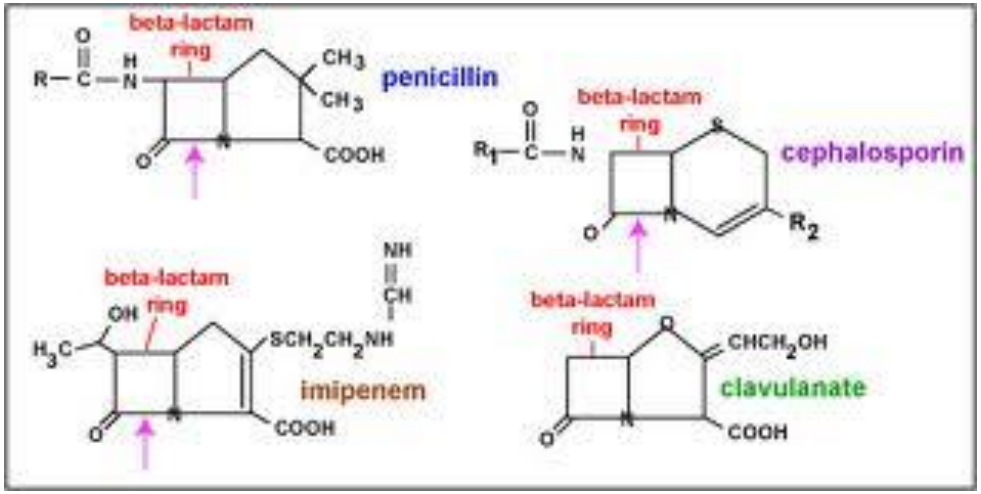
ß-lactams

- 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

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Macrolides

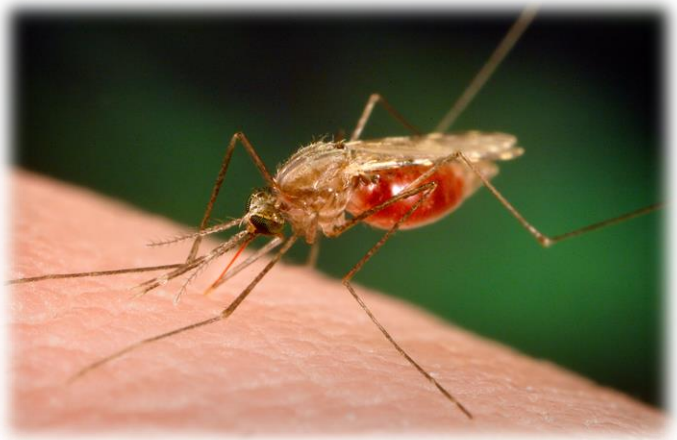
- Bind to the 50S subunit of bacterial ribosomes and inhibit protein synthesis. They are bacteriostatic.

- **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.

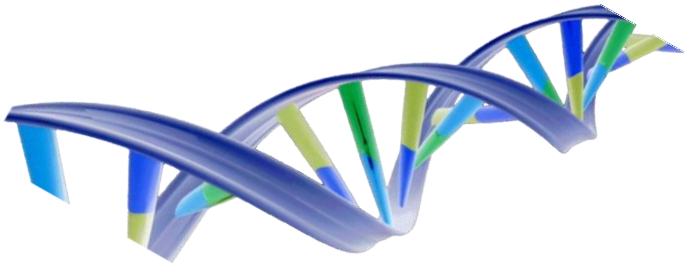
- **Tetracycline**
- **Doxycycline**
- **Minocycline**



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

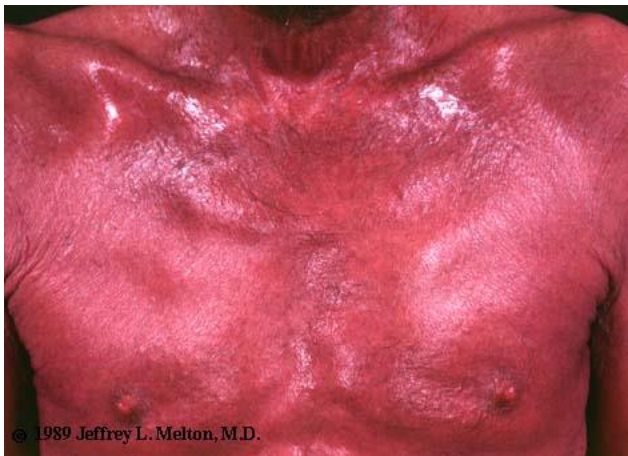
- Bind to the 30S subunit of the bacterial ribosome, therefore interfere with protein synthesis
- They are bacteriocidal.
- Poor oral availability so most be given parenterally.
- Mainly active against gram-negatives, but *S. aureus* is often sensitive as well. Poor action against the strep and enterococci.
- 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’.

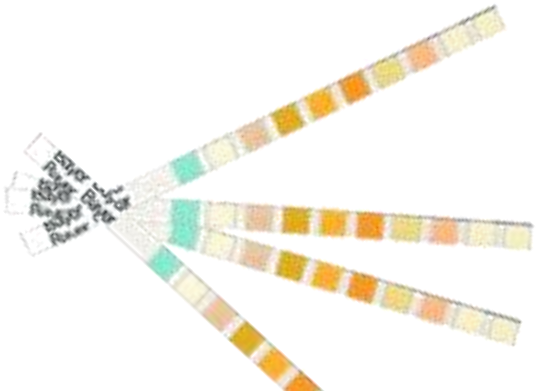
- **Vancomycin** – active only against gram-positive organisms. Usually given IV, but given PO to treat *C. diff* infection. It is reserved for when other antibiotics cannot be used and is effective against MRSA.
- **Teicoplanin** – given IV



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.



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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.

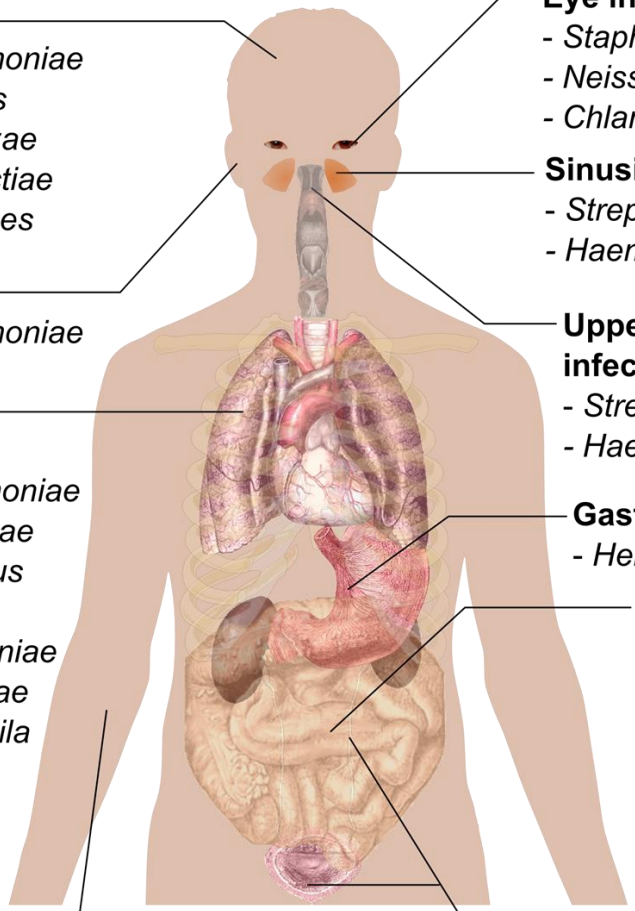
- **Isoniazid** is an anti-TB drug which inhibits mycobacterial cell wall synthesis. Can be used as a single drug for prophylaxis of TB contacts. Hepatotoxicity and peripheral neuropathy are risks.

- **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*

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

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

Gastritis
- *Helicobacter pylori*

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

Sinusitis
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

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

Drug Choice depends on:

- Site
- Likely organism
- Severity
- Co-morbidity
- Local policy

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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

If source is known, treatment should be targeted to that.

Sepsis of Unknown Origin

Example regimes:

- Broad-spectrum penicillin (e.g. Coamoxiclav) or Cephlasporin (e.g. Ceftriaxone) ***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.

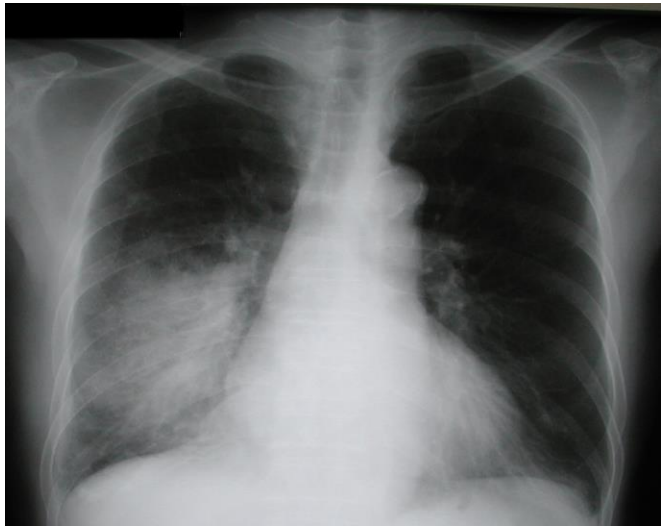
Mild/Moderate

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

Severe

- Coamoxiclav and Clarithromycin;
- Cephalosporins can also be used.

- Vancomycin/Levofloxacin can be used in penicillin allergy



Hospital Acquired Pneumonia

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

- Coamoxiclav plus Gentamicin
- Alternative, Tazocin (or a cephalosporin).
- If MRSA, add Vancomycin.

Aspiration Pneumonia

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

- May need to 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

- Tetracycline (Doxycycline), macrolide (Clarithromycin), Coamoxiclav

- 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 a 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

- Gentamicin +/- penicillin
- 10-14 days treatment (can switch to oral)

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

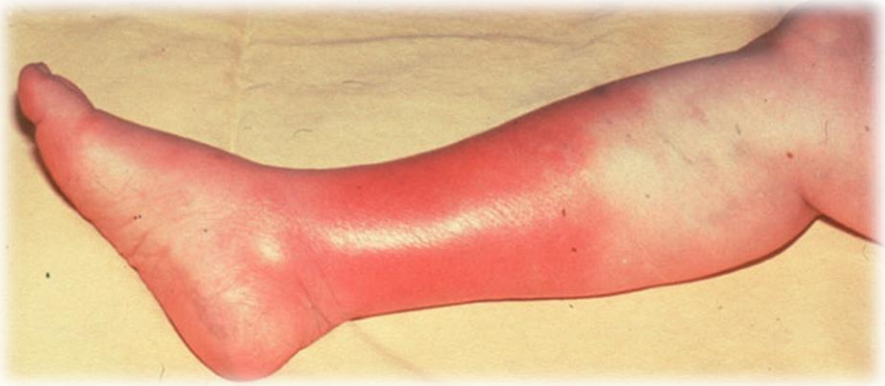
- Flucloxacillin (po/iv)

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** – oral 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 +/- Metronidazole

Summary

- There are many factors that influence the choice of antimicrobial (e.g. site/severity).

- Some very general thoughts:
  - If it's mild, start with oral and simple/common drugs, e.g. Amoxicillin, Trimethorprim.
  - Skin = Flucloxacillin
  - Coamoxiclav will serve you well…
  - If infection not responding, you can convert to IV and add in extra drugs, e.g. Gentamicin, Metronidazole
  - If evidence of severe sepsis 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 and BHRUT Antimicrobial Guidelines

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