Introduction to antibiotic therapy

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Overview of session

How do antibiotics work?

Factors in choosing an antibiotic

Some important antibiotic groups

A few words on *Clostridioides difficile*

What antibiotics do you know?

How do antibiotics work?

Remember bacteria are prokaryotes and we are eukaryotes – lucky! – magic bullet concept

Commonest targets in bacteria:

- cell wall (peptidoglycan) synthesis
  - eg penicillin/beta-lactams
- protein synthesis
  - eg gentamicin
- DNA/RNA
  - eg ciprofloxacin
- folate synthesis
  - eg trimethoprim

Choosing an antibiotic

1. What is the likely source of infection?

   (clinical assessment)

2. What organisms are likely to cause infection in that source?

   (basic knowledge of microbiology)

3. What antibiotics do those organisms respond to? - In general choose narrow spectrum agent where possible

   (understanding of antibiotic spectra)

Antibiotic spectra

- Broad vs narrow
  - Always use narrowest spectrum antibiotic possible – to reserve broad spectrum antibiotics for when really needed
- For example:
- Gram-positive organisms?
- Gram-negative organisms?
- Anaerobes?

Choosing an antibiotic

Choosing an antibiotic

- Penetration into site of infection
  - e.g. central nervous system/bone
- Side-effects e.g. antibiotic–associated diarrhoea/ *C. difficile*
- allergies
- Interactions
- intravenous vs oral
  - Some achieve blood/tissue concentrations orally equivalent to intravenous
- Pregnancy/lactation
- Guidelines/local policies
- Cost

Downsides of antibiotic treatment

- Toxicity (‘side-effects’)
- Allergy – mild rash to life-threatening anaphylaxis
- *Clostridioides difficile*
- Development of RESISTANCE

Some important antibiotic classes

Class	Examples	Target
Beta-lactams	Penicillin, flucloxacillin, cephalosporins, meropenem	Cell wall synthesis
Tetracyclines	Tetracycline, doxycycline	ribosome
Glycopeptides	Vancomycin	Cell wall synthesis
Macrolides	Erythromycin, clarithromycin	ribosome
Quinolones	ciprofloxacin	DNA gyrase
aminoglycosides	gentamicin	ribosome
trimethoprim	Trimethoprim	Folate synthesis

A closer look at 2 important antibiotic classes

- Beta-lactams
- Aminoglycosides

Beta-lactams

- Penicillins
- Cephalosporins
- Carbapenems

Flucloxacillin

Beta-lactam class

Main use: staphylococcal infections

Gram positive cover	4
Narrow spectrum - great for Staphylococcus aureus	
Gram negative cover	0
Toxicity (allergy)	2
Ease of administration (Frequent dosing required)	6

Cephalosporins

Beta-lactam class

Main use: varied, broad spectrum

Gram positive cover	7
Decreases down generations	
Gram negative cover	7
Increases down generations	
Toxicity (allergy)	2
Ease of administration	5
Mainly i.v.	
****BEWARE**	*C.difficile*

Carbapenems

Beta-lactam class

Main use: critical care broad spectrum

Gram positive cover	8
Gram negative cover	9
Toxicity (allergy)	2
Ease of administration	4 – iv only
****Extra superpower**	**Kills anaerobes**

NB Do not cover MRSA

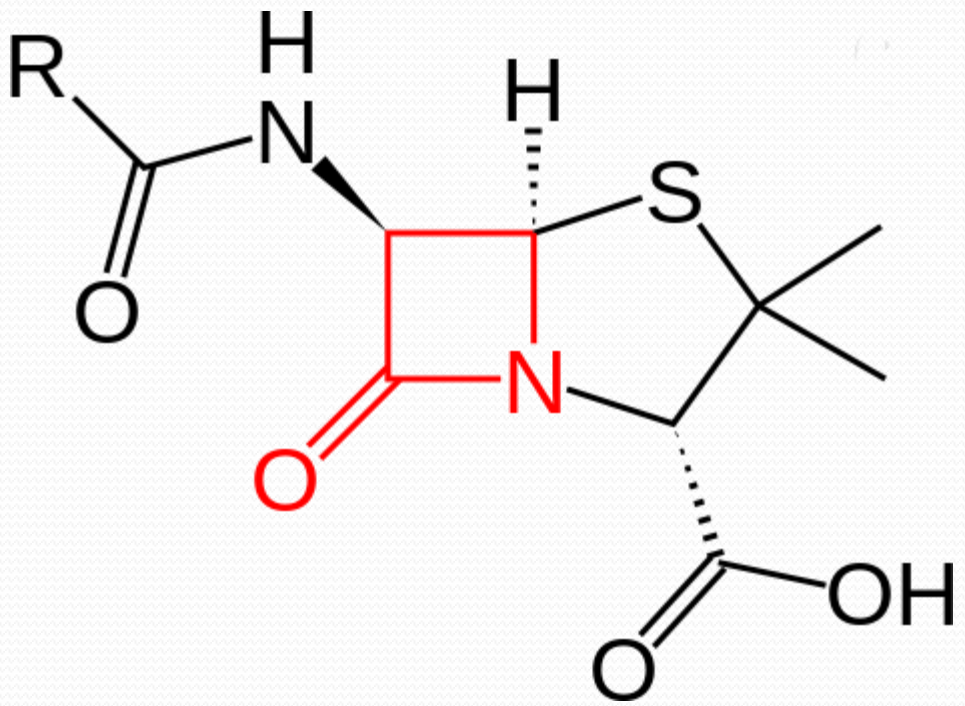
Penicillin

Beta-lactam group

Main use: tonsillitis; skin infections

Gram positive cover	4
Streptococci	
Gram negative cover	1
Toxicity (allergy)	2
Ease of administration	6
Oral or i.v. but frequent dosing required	

Beta-lactam ring



Beta-lactams: penicillins

- **Penicillin**
  - Narrow spectrum - streptococci
- **Flucloxacillin**
  - Narrow spectrum - *Staphylococcus aureus*
- **Ampicillin/amoxycillin**
  - Broader spectrum penicillin

Flucloxacillin

- Methicillin was the first penicillin developed through rational drug modification
- In the UK we use flucloxacillin

- Narrow spectrum
- Developed specifically to treat *Staphylococcus aureus*

Beta lactams: cephalosporins

- Discovered from *Cephalosporium* mould from Sardinian sewage 1945
- Widely introduced in 1980's
- Broad spectrum, G+ and G-
- Reputation for causing *C. difficile* disease

Beta-lactams: carbapenems

- Imipenem, meropenem
- **Very broad spectrum**
  - G+ and G-
- Critical care ‘big guns’
- ICUs/bone marrow transplant/chemotherapy units now very reliant on them

Aminoglycosides

- Example: gentamicin
- Discovered in 1963 – product of *Micromonospora* sp.
- On WHO list of essential medicines
- inexpensive

Gentamicin

Aminoglycoside class

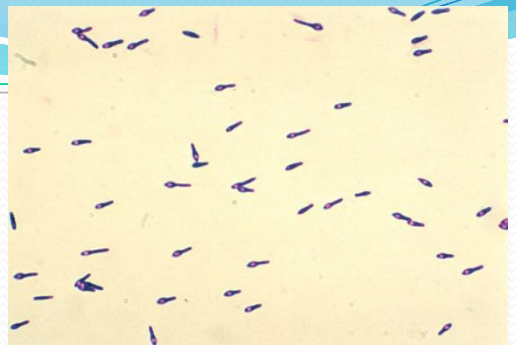
Main use: serious Gram negative sepsis

Gram positive cover	2
Gram negative cover	9
Toxicity	10
Deafness	
Kidney toxicity	
Ease of administration	1
i.v. only; check levels	

Aminoglycosides continued

- Spectrum: usually used for **Gram-negatives**
- Toxicity: kidneys and inner ear hair cells (nephrotoxic and ototoxic)
- Nonetheless being used increasingly again because of rising antimicrobial resistance and less propensity to cause *C. difficile* (?)
- Need to measure blood levels to avoid toxicity
- once daily dosing is usually preferred

Clostridioides difficile



- Use of broad spectrum antibiotics kills normal flora and allows *C. difficile* to proliferate in gut
- Spores spread in the hospital environment
- Government targets
- Ward cleaning is important as well as handwashing and disinfecting equipment
- **Antibiotic stewardship**
  - avoid unnecessary antibiotics
  - avoid prolonged courses of antibiotics
  - Use hospital antibiotic policies

Clostridioides difficile infection

- Infectious diarrhoea caused by the gut bacterium *Clostridioides difficile*
  - Symptoms range from mild diarrhoea to severe life-threatening inflammation of the colon

- **Often provoked by antibiotic therapy**
  - Any antibiotic may increase risk
  - Risks additive with multiple antibiotics
  - Risk increases with course length
  - ?Risk may vary between agents

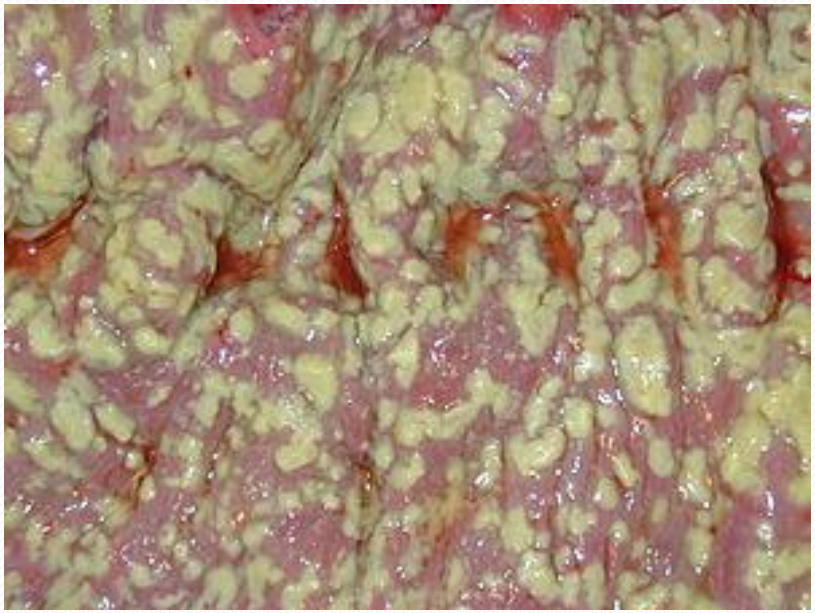
Clinical aspects of *C. difficile*

- Diarrhoea is caused by a toxin
- May lead to toxic megacolon/pseudomembranous colitis and bowel perforation
- Treatment:
  - Stop other antibiotics

  if possible

  Treat with specific antibiotics

  (oral vancomycin)



https://en.m.wikipedia.org/wiki/Clostridioides_difficile_infection

Decreasing antibiotic use has also been shown to result in lower incidence of *C. difficile* infections.

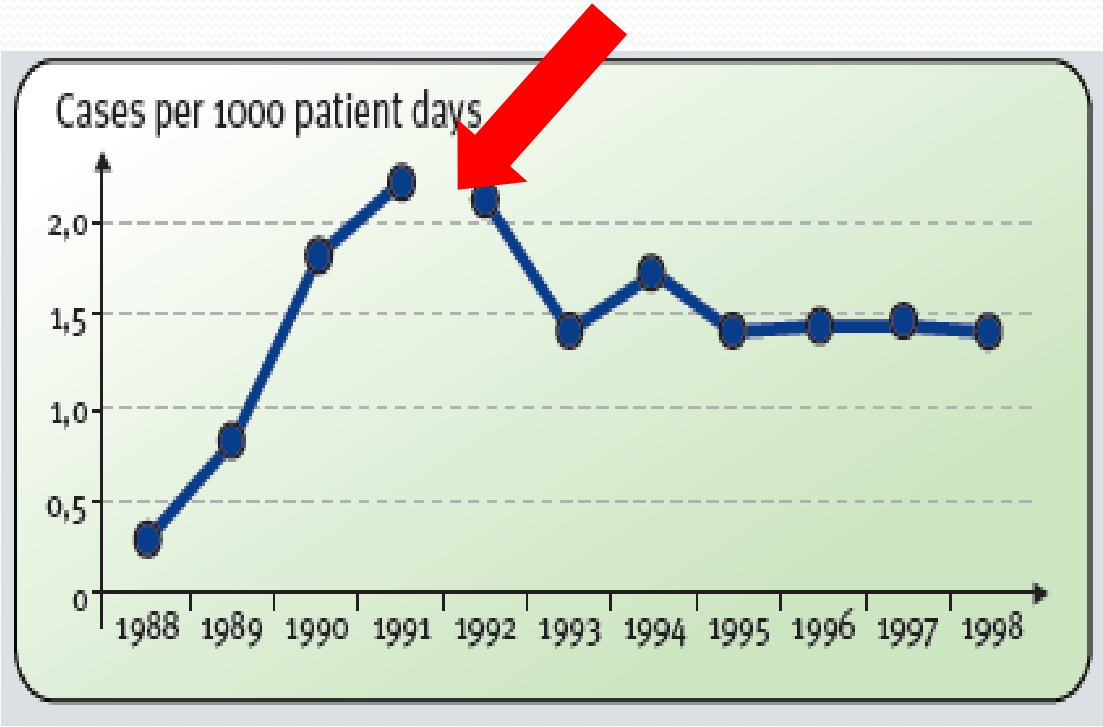


Figure 7: Rates of nosocomial *C. difficile*, expressed per 1,000 patient-days, before and after implementation of the antibiotic management program.

Carling P, et. Al. Infect Control Hosp Epidemiol. 2003 Sep;24(9):699-706.