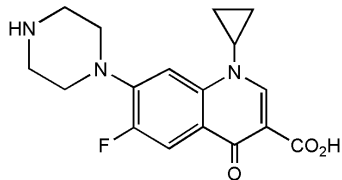
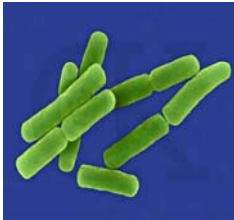


Antibacterial and Antifungal Agents

06763 Dr AN Boa



Ciprofloxacin



Antibacterial & Antifungal Agents

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<http://www.hull.ac.uk/php/chsanb/teaching.html>

Course summary

1. Introduction
Background and historical aspects
2. Bacteria and structure of the bacterial cell wall
Gram-positive and Gram-negative bacteria
3. Antibacterial drugs
Focus on the penicillin class of drugs
4. Antifungal drugs
Focus on the azole class of drugs
5. Drug resistance

Microbes

- fungi and bacteria can be *saprophytes* (living on dead so causing the decay of foods, fabrics and timber etc)
- many are *parasites*, some of which are *human parasites*
- we mostly co-exist happily with these microbes, but they can proliferate on or in the outermost layers of skin causing *irritation or growths* (fungi), and *in extreme cases serious infection*.
- (also viruses, protozoa, spirochaetes etc - not covered in this course)

2

Microbial infections

- *first recorded account of a human fungal infection* was by *Hippocrates* (460-377 B.C.) - a case of oral candidiasis - known as '*thrush*' from around the time of *Samuel Pepys*
- '*Diseases and Casualties of the Week*', a London bulletin dated 12th of September to the 19th, 1665 reported the following causes of deaths, including the *first documented case of a fatality due to a fungal infection*

"Consumption 129, Feaver 332, Plague 6544, Thrush 6"

3

Identification of microbes

- **Robert Hooke** - first detailed examination of a fungus reported in *Micrographia* (1665).

*'The blue and white and several kinds of hairy mouldy spots.....are all of them nothing else but several kinds of **small and variously figur'd Mushrooms**,which will not be unworthy of our serious speculation and examination as I shall by and by shew.'*



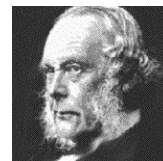
- **Anton van Leeuwenhoek** identified bacteria by microscopy in the same century



4

Key advances in the development antimicrobial chemotherapy

- 19th century: **Louis Pasteur**
 - link between bacteria and disease
- 19th century: **Robert Koch**
 - identified micro-organisms for tuberculosis, cholera and typhoid
- 1867: **Joseph Lister**
 - proponent of “germ theory of disease”

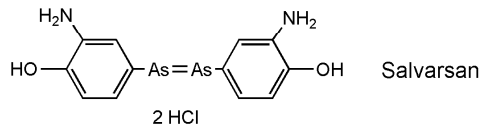


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Paul Ehrlich



- the “father of modern chemotherapy”.
- used chemicals against infection and was the originator of the “Magic bullet” theory.
- Nobel prize 1908
- developed the first fully synthetic drug ‘salvarsan’ (1910)



- not very good against bacteria as intended but useful for sleeping sickness and syphilis.

6

Non-specific antimicrobial agents

- Disinfectants:
 - Formulations where the agent is too toxic or corrosive for topical use. Limited to inanimate objects (sinks, toilets, floors)
- Preservatives:
 - Additives used in food and pharmaceutical products, as well as biological specimens, to prevent biodeterioration (by bacterial action or growth)
- Antiseptics:
 - Formulations that can be safely applied to the skin (topical use)

7

Disinfectants

- *Bleach*
 - NaOCl (sodium hypochlorite)
 - e.g. Domestos: "kills all known germs dead"
- *Hydrogen peroxide*
 - H₂O₂
- *N-chloro compounds*
 - slow release of chlorine, e.g. for use in swimming pools

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Preservatives

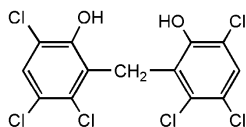
- *NaCl* – salt has been used to preserve food products since ancient times.
- *Formaldehyde* – for biological tissue samples etc. aqueous formaldehyde is called 'formalin'.
- *Mercury compounds*:
 - highly toxic to bacteria, plants, fungi and animals.
 - organo mercury compounds less irritating than simple salts, but still toxic. Examples include *penotrane* and *thimersol*.
 - limited uses up to the 1950s as plant fungicides and for the preservation of leather, textiles and timber.
 - not used widely nowadays due to the toxicity of the mercury.
- *Nisin* - a 34 residue polypeptide produced by *Streptococcus lactis*.

9

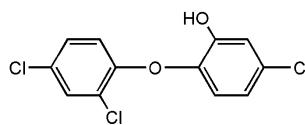
Antiseptics

Phenols / Alkylhalophenols:

- *Phenol* used by Lister – too corrosive and toxic.
- *4-Chloro-3,5-dimethylphenol* - active ingredient of *Dettol*.
- *Hexachlorophene* – was used in toothpastes and deodorants. Now banned due to CNS damage
- *Triclosan* – used modern toothpastes and other products.



Hexachlorophene



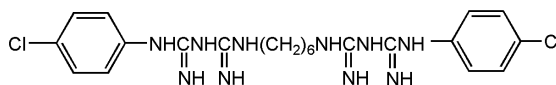
Triclosan

10

Antiseptics

Quaternary ammonium salts (cationic surfactants)

- *Chlorhexidine gluconate*, a guanidine derivative



Chlorhexidine (Hibitane)

- *Cetrimide* or CTAB ($C_{16}H_{33}NMe_3Br$)
- *Roccal®*, used as a general disinfecting agent for pre-operative skin preparation.
- *Bradosol®*, $PhOCH_2CH_2^+N(Me)_2CH_2(CH_2)_{10}CH_3 \cdot Br^-$
 - still available as an antiseptic in throat lozenges, British National Formulary (Sept. 1997) states that "there is no convincing evidence that antiseptic lozenges.....have a beneficial action, and they sometimes irritate and cause sore tongue and sore lips".

11

Chemotherapy

- **Chemotherapy** is "the use of **chemicals (drugs)** to prevent, control or eradicate **disease/infection**"
 - Applications in medicinal, veterinary and agricultural chemistry.
- **Why study antimicrobial chemotherapy?**
 - Many bacteria are pathogens, *i.e.* agents of disease in man, animals and plants
- **Why study chemotherapy further?**
 - 'new' infectious agents (e.g. *Borrelia burgdorferi*)
 - resurgent pathogens (e.g. *Mycobacterium tuberculosis*)
 - multidrug resistance, e.g. 'Superbugs' (e.g. *Staphylococcus aureus* - MRSA)
 - opportunist Gram-negative pathogens [hospital-acquired (nosocomial) infections] (e.g. *Clostridium difficile*)