Antibacterial Drugs

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Principle of antibacterial chemotherapy

- Bacteria are a common cause of disease, but have beneficial as well as harmful effects. For example, the **gastrointestinal** bacterial flora of the healthy human assists in preventing **colonization** by pathogens. The widespread use of **antibacterial** drugs has led to the appearance of **multiresistant** bacteria which are now a significant cause of **morbidity** and **mortality** in the UK. Consequently, antibacterial therapy should not be used **indiscriminately**. A distinction is conventionally drawn between bactericidal drugs that kill bacteria and **bacteriostatic** drugs that prevent their reproduction, elimination depending on host defence. This difference is relative, as bacteriostatic drugs are often bactericidal at high **concentrations** and in the presence of host defence mechanisms. In clinical practice, the distinction is seldom important unless the body's defence mechanisms are depressed. Antibacterial drugs can be further classified into five main groups according to their mechanism of action.
- The choice of antibacterial drug, together with its dose and **route** of administration, depend on the **infection** (in particular the responsible pathogen(s), but also anatomical site and severity), **absorption** characteristics of the drug, and patient factors (in particular age, weight, renal function).

Classification of the antibacterial agents

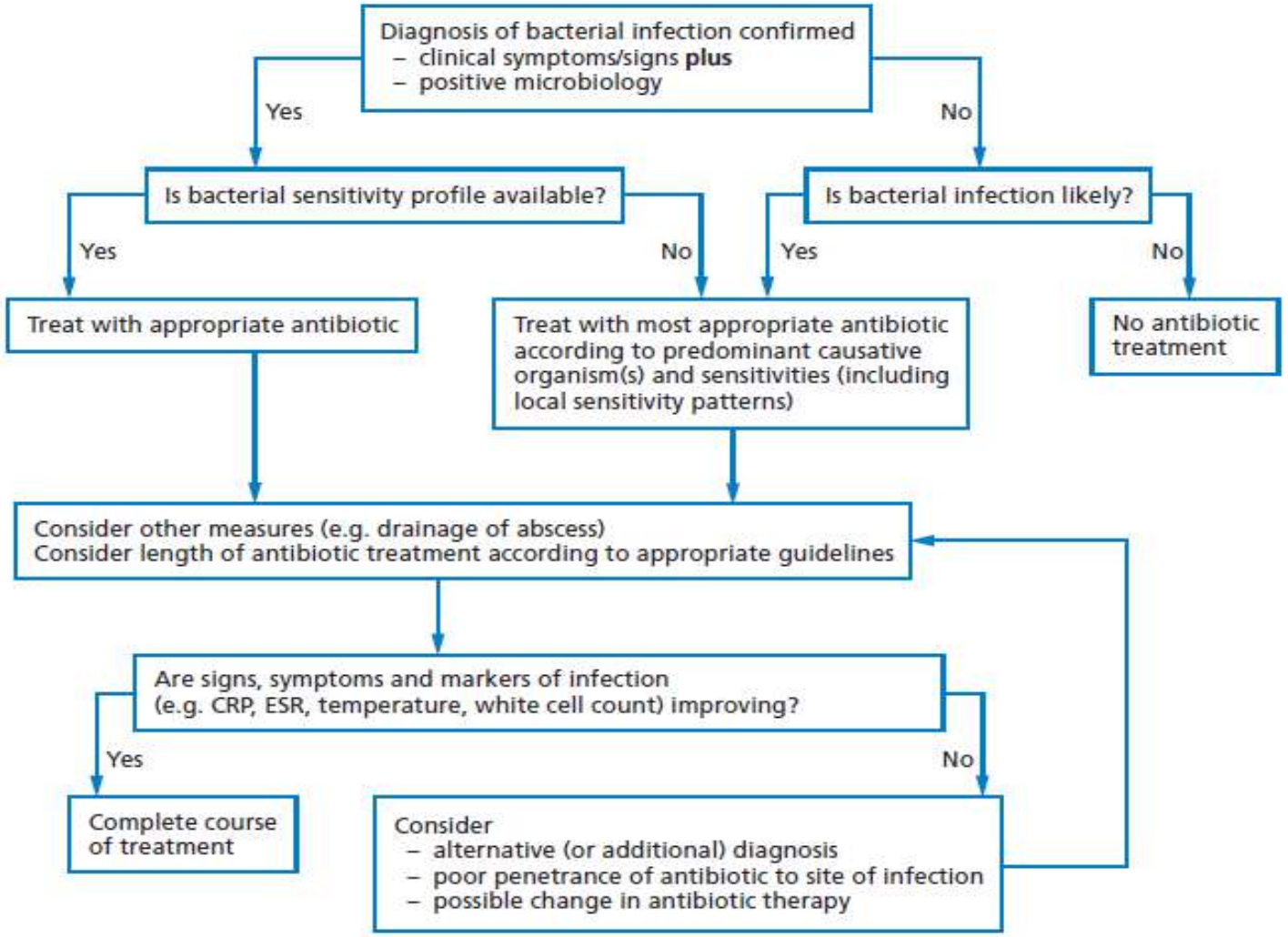
Bactericidal	Bacteriostatic
Penicillins	Erythromycin
Cephalosporins	Tetracyclines
Aminoglycosides	Chloramphenicol
Co-trimoxazole	Sulphonamides
	Trimethoprim

Mechanism of action	Antibacterial agent
Inhibition of cell wall synthesis	Penicillins
	Cephalosporins
	Monobactams
	Vancomycin
Inhibition of DNA gyrase	Quinolones
Inhibition of RNA polymerase	Rifampicin
Inhibition of protein synthesis	Aminoglycosides
	Tetracyclines
	Erythromycin
	Chloramphenicol
Inhibition of folic acid metabolism	Trimethoprim
	Sulphonamides

Principle of antibacterial chemotherapy

- In addition, the **dose** may be guided by plasma concentration measurements of drugs with a narrow therapeutic index (e.g. aminoglycosides). The duration of therapy depends on the nature of the infection and response to treatment.
- The *British National Formulary* provides a good guide to initial treatments for common bacterial infections. In view of regional variations in patterns of bacterial resistance, these may be modified according to local guidelines.
- Close **liaison** with the local microbiology laboratory provides information on local **prevalence** of organisms and **sensitivities.** The minimum inhibitory concentration **(MIC)** is often quoted by laboratories and in promotional literature. It is the minimal concentration of a particular agent below which bacterial growth is not prevented. Although the MIC provides useful information for comparing the susceptibility of organisms to antibacterial drugs, it is an ***in vitro*** test in a **homogenous** culture system, whilst *in vivo* the concentration at the site of infection may be considerably lower than the plasma concentration which one might predict to be **bactericidal** (e.g. drug penetration and concentration in an abscess cavity are very low).

General algorithm in the treatment of bacterial infection



Bacterial Resistance

- The resistance of bacterial populations to antimicrobial agents is constantly changing and can become a serious clinical problem, rendering previously useful drugs inactive. Overuse of antibiotics will lead to a future where infectious disease has the same impact as in in the pre-antibiotic **era**. Although most **multiresistant** bacteria have developed in **hospitalized patients**, the majority of antimicrobial prescribing in the UK takes place in primary care. Current guidelines therefore emphasize the following points:
- 1. No prescribing of antibiotics for coughs and colds or viral sore throats.
- 2. limit prescribing for uncomplicated cystitis to three days for otherwise fit women.
- 3. limit prescribing of antibiotics over the telephone to exceptional cases.

- Antimicrobial resistance is particularly common in intensive care units and transplant units, where the use of antimicrobial agents is frequent and the patients may be immunocompromised.

Bacterial Resistance

- **The evolution of drug resistance involves:**

1. Selection of naturally resistant strains (which have arisen by spontaneous mutation) that exist within the bacterial population by elimination of the sensitive strain by therapy. Thus the incidence of drug resistance is related to the prescription of that drug. The hospital environment with intensive and widespread use of broad-spectrum antibacterials is particularly likely to promote the selection of resistant organisms.

1. Transfer of resistance between organisms can occur by transfer of naked DNA (transformation), by conjugation with direct cell-to-cell transfer of extrachromosomal DNA (plasmids), or by passage of the information by bacteriophage (transduction). In this way, transfer of genetic information concerning drug resistance (frequently to a group of several antibiotics simultaneously) may occur between species.

Bacterial Resistance

- **Mechanism of drug resistance can be broadly divided into three groups:**

1. inactivation of the antimicrobial agent either by disruption of its chemical structure (e.g. penicillinase) or by addition of a modifying group that inactivates the drug (e.g. chloramphenicol, inactivated by acetylation).
2. restriction of entry of the drug into the bacterium by altered permeability or efflux pump (e.g. sulphonamides, tetracycline).
3. modification of the bacterial target – this may take the form of an enzyme with reduced affinity for an inhibitor, or an altered organelle with reduced drug-binding properties (e.g. erythromycin and bacterial ribosomes).

Drug combination

- **Most infections can be treated with a single agent. However, there are situations in which more than one antibacterial drug is prescribed concurrently:**

1. to achieve broad antimicrobial activity in critically ill patients with an undefined infection.
2. to treat mixed bacterial infections in cases where no single agent would affect all of the bacteria present.
3. to prevent the emergence of resistance.
4. to achieve an additive or synergistic effect.

Prophylactic use of antibacterial drug

- On a few occasions it is appropriate to use antibacterial drugs prophylactically. Wherever possible a suitably specific narrow spectrum drug should be used.

Prophylactic preoperative antibiotics

- **GENERAL PRINCIPLES**

1. Prophylaxis should be restricted to cases where the procedure commonly leads to infection, or where infection, although rare, would have devastating results.

2. The antimicrobial agent should preferably be bactericidal and directed against the likely pathogen.

3. The aim is to provide high plasma and tissue concentrations of an appropriate drug at the time of bacterial contamination. Intramuscular injections can usually be given with the premedication or intravenous injections at the time of induction. Drug administration should seldom exceed 48 hours. Local hospital drug and therapeutics committees can help considerably by instituting sensible guidelines on the duration of prophylactic antibiotics.

4. If continued administration is necessary, change to oral therapy post-operatively wherever possible.

Commonly prescribed antibacterial drug

β-lactam antibiotics

- These drugs each contain a β-lactam ring. This can be broken down by β-lactamase enzymes produced by bacteria, notably by many strains of *Staphylococcus and Haemophilus influenzae,* which are thereby resistant. β-Lactam antibiotics kill bacteria by inhibiting bacterial cell wall synthesis. Penicillins are excreted in the urine. **Probenecid blocks the renal tubular secretion** of **penicillin. This interaction may be used therapeutically to** produce higher and more prolonged blood concentrations of **penicillin. Antibiotics in this group include the penicillins,** monobactams, carbapenems and cephalosporins.