Antibiotic

Summary

This update reviews the principles underlying the choice of an antibiotic and its use in prophylaxis and urinary tract infections. Some new antibacterial antiviral and antifungal agents are discussed briefly.

There must be few of us who can conceive of practising medicine without the availability of the antimicrobial drugs.

While it is true that countless lives have been saved by these 'wonder drugs', on the other hand, deaths from infection have not decreased, despite newer and better antibiotics.

The world population is growing and people are living longer but we have altered the microbiological ecology to our cost.

The spectrum of organisms causing infection has changed with resistant strains developing. Opportunistic infections are rampant in an ever-increasing hoard of immunologically bankrupt patients.

The Immune-Comprised host

Typical causes are:

- Defect in white cells - congenital, acquired.
- Defect in immunoglobulin production -congenital, acquired.
- Malignancies
- Malnutrition
- Diabetes mellitus (uncontrolled)
- Alcoholism
- Asplenia
- Iatrogenic - antibiotics; corticosteroids; immunosuppressives; cytotoxics.

Let us not forget that antibiotics may have dangerous side-effects.

Dangers of antibiotic usage

These may be life-threatening for example:

- Anaphylaxis - penicillin;
- Blood dyscrasia - chloramphenicol;
- Supra-infection - bacterial or fungal.

Also resistance may become a problem, in the individual or the community.

Resistance has occurred with the staphylococcus, meningococcus, gonococcus, pneumococcus and salmonella typhi, to mention but a few, and disasters have occurred world-wide as a result.

The old adage "to know an organism is to know its sensitivity" no longer applies.

Four questions

Before prescribing an antibiotic, there are four questions to be answered:

(1) Is infection present? (Pyrexia is not only caused by infection)
(2) What is the most likely organism?
(3) What is the appropriate treatment?
(4) Is the treatment more dangerous than the disease?

We should aim at identifying the organism wherever possible. I do not wish to imply that every infection must be specifically identified and that the choice of treatment must be dependent on better laboratory tests for diagnosis.

Using our clinical judgement we can infer what organism is likely to be responsible. We should choose an effective narrow-spectrum agent and not indiscriminately use the broadest-spectrum antibiotic we can find.

Koprowsky, the pioneer virologist, has said, "If a universal antibiotic is found, immediately organise societies to prevent its use. It should be dealt with as we should have treated, and did not treat, the atomic bomb!"

Mode of action of Antibiotics

Antibiotics may act in several ways at different sites on the organism (Fig. 1): Cell wall synthesis - penicillin, cephalosporins; Membrane permeability - amphotericin B, nystatin; Metabolic processes - sulphanamides, trimethoprim; Genetic processes: DNA, RNA - rifampin, idoxuridine, adenine arabinoside; Protein synthesis: ribosomes - aminoglycosides, tetracycline, chloramphenicol, erythromycin, clindamcycin.

Resistance

Resistance may be a natural phenomenon or it may be acquired and even transferred by a genetic mutation. It may be due to lack of target site; poor permeability; production of drug-modifying enzymes.

Transfer of resistance

Resistance may be transferred via the processes of conjugation, transduction, and transformation.

This coding is employed in genetic engineering but the phenomenon has occurred in nature, particularly with gram negative organisms, resulting in the development of multiple drug resistant strains. It is conceivable that resistance may be transferred from non-pathogenic bacteria to virulent organisms whose sensitivity is thereby totally altered.

Clavulanic Acid

A recent interesting development has been the introduction of clavulanic acid which possesses minimal antibacterial activity but is a potent inhibitor of b-lactamase.

It has been combined with amoxycillin (Augmentin) to produce an enhanced spectrum of activity but it is still early days to appreciate just how effective it really is.

It does not inhibit the rarer chromosomally-coded (as opposed to plasmid-coded) b-lactamase and is ineffective against penicillin-resistant pneumococci and gonococci as well as cloxacillin-resistant staphylococci.

Lack of response

Failure of the temperature to settle or other features indicating a lack of response should not be handled simply by ringing the changes, by adding or substituting drugs. We have to consider the following issues:

- Is the diagnosis correct?
- Is the choice of drug correct?
- Is the dosage adequate?
- Is the route of administration appropriate?
- Is there a barrier preventing access of the anti-microbial agent to the organism?
- Is the organism resistant?
- Are more than one organisms responsible for the infection?
- Is there pus which requires to be drained?
- Are there associated diseases contributing to patient failure?
- Is drug fever causing the pyrexia?

Update

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The world of Cephalosporins

The last few years have been characterized by the explosion of cephalosporin derivatives. Just what is their role today?

Certain facts have emerged.

They are rarely the drug of choice. Oral administration is seldom necessary. They are expensive agents. The steep commercial competition results in more products and more confusion.

There are differences between each succeeding generation. The injections have become less painful; half-life has increased and higher blood levels are attained. The disadvantage is that they have become less effective against gram positive organisms but this is countered by increased potency against gram negative strains. Hopefully, the fourth generation cephalosporins will demonstrate more activity against pseudomonas.

A warning should be given that the cephalosporins do not cross the blood-brain barrier and should not be used to treat meningitis. The exception is Moxolactam which diffuses readily into the cerebrospinal fluid and may be the drug of choice for gram negative bacterial meningitis due to a susceptible organism. It should not be used for gram positive organisms such as in pneumococcal meningitis.

Cefotaxime (Claforan) has similar penetrative properties into the cerebrospinal fluid but has perhaps not been written about as extensively.

Its advantage over Moxolactam is that it does have considerable activity against gram positive cocci such as strep. pneumoniae and penicillinase-producing staph. aureus.

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Prophylaxis

What is the place of antibiotics in the prevention of infection?

Chemoprophylaxis is only likely to succeed if you know what organism you are trying to protect against - a single, identifiable and treatable microbe.

The prophylactic agent should be given just before the event which is liable to introduce the organism into the blood stream and need not be continued for long afterwards.

Another aspect of prophylaxis worth mentioning is the use of vaccines. We are familiar with immunisation against smallpox, yellow fever, poliomyelitis, diphtheria, tetanus, whooping cough, measles, rubella, hepatitis and others. Recently the pneumococcal vaccine has been added to the list.

Why should prophylaxis be necessary with all the antibacterial agents that are available?

In the USA more than one million cases of pneumococcal pneumonia occur annually, and the hospital mortality has not been significantly reduced - over the age of 50 years, it remains at about 30%. Most of the deaths occur in the first five days from early irreversible physiologic injury which is unaffected by antimicrobial drugs.

The mortality of pneumococcal meningitis is still 40%. Otitis media has an appreciable morbidity. Recently multidrug-resistant strains of the pneumococcus caused virulent epidemics among children.

For these reasons, a real need for pneumococcal vaccine has arisen. Significantly, the initial trials were conducted in South African mineworkers who are particularly susceptible to pneumonia. Patients in whom its use should be considered include the elderly with cardiac or pulmonary disease, patients with malignancies, the nephrotic syndrome, haemoglobinopathies, aplastic anaemia, asplenia, immunodeficiency states, immunosuppressive therapy and transplants.

A) Good Chance of Success	B) Variable Success	Not Indicated
1 Rheumatic fever	1 Chronic bronchitis	1 'Clean' surgery
2 Infective endocarditis	2 Cardiac and neurosurgery	2 Cardiac catheterisation
3 Tuberculosis	3 Burns	3 Bladder catheterisation
4 Meningococcal meningitis	4 Prolonged labour with ruptured membranes	4 Virus infections
5 Pelvic and colonic surgery		5 Coma
		6 Patient on corticosteroids

Urinary Tract Infections

Infections of the urinary tract warrant a special mention as there have recently been some changing concepts in their management. Bacteriological examination of the urine is essential to the diagnosis of urinary infection and the assessment of the efficacy of treatment.

Infections may be asymptomatic while symptoms may occur in the absence of infection. The presence of infection is particularly important in the pre-school child, in pregnancy, and in the male.

The 'urethral syndrome' or the 'frequency-burning syndrome' is common in young females. It may be related to sexual activity, is often self-limiting, is troublesome, but rarely leads to renal damage.

Infection in the various groups merit separate consideration.

Non-pregnant women

About 80% of acute infections are caused by E. Coli; Proteus mirabilis accounts for another 10% and staphylococcus saprophyticus is a recently recognized pathogen. In symptomatic sterile pyuria one should also consider the possibility of chlamydia infection.

A single organism is the culprit in the majority of acute infections.

Most of the organisms are sensitive to sulphonamides and ampicillin and a 7-10 day course is usually given. A single dose of 3G Ampicillin or a cephalosporin has resulted in cures; this may simply have been an aid to nature. At any rate, a three day course is as effective as ten days. A relapse refers to a recrudescence of infection shortly after treatment and the organism is identical.

Re-infection is due to a different organism and is managed by retreatment appropriately. Relapse implies a persistent organism with the risk of renal complications if it is not eradicated. It is not always possible to distinguish upper and lower renal tract infection. Treatment of the relapse is by a two week course of an antibiotic to which the organism is sensitive.

Supportive measures which apply to all are a good fluid intake and frequent complete micturition especially on retiring to bed when the last dose of the antibiotic should be taken. With another relapse, radiography should be performed to establish whether a remediable abnormality is present. This also applies to the patient who has frequent re-infections.

Long-term treatment

Long-term therapy has three distinct purposes; cure; suppression; prophylaxis.

A number of agents have been used - mandelamine, nitrofurantoin (as antiseptics), sulphonamides, trimethoprim and cotrimoxazole. Once control has been achieved, the dose can be reduced to nightly or alternate nightly. Toxicity and super-infection are rare.

Pregnancy

Screening is important in pregnancy. About 5% of pregnant patients may have asymptomatic bacteriuria. Of these patients, about 30% may develop clinical pyelonephritis with the risk of abortion, premature labour and still births. One must remember to avoid treating with a tetracycline. Sulphadimidine, ampicillin and nitrofurantoin may be used throughout, although sulphonamides are best avoided in the last trimester as they displace bilirubin from their protein-bound sites.

Children

The risk is of damage to the kidney with resultant scarring and chronic pyelonephritis. A search must be made for an abnormality especially cystoureteric reflux. The principles of treatment are the same as in the adult.

Adult male

If an unusual organism or a mixed infection are found or re-infection occurs in an adult male, an IVP should be performed. If no organism is found, chlamydia may be the cause and this can be treated with erythromycin or tetracycline. In some patients the source may be the prostate and trimethoprim concentrates well in this tissue and may be used alone or in combination with a sulphonamide (cotrimoxazole).

Interaction of Antimicrobials

While the effects of drug interaction with the antimicrobials do not constitute a major problem, it may be worth bearing the following in mind:

Anti-viral agents

Selective anti-viral action is a difficult objective to achieve. The organism is intracellular and the agent is likely to be toxic to both the human cell as well as the invading microbe.

Furthermore, the cell has already been damaged by the time the diagnosis of a viral infection is made and therefore therapy is not likely to be successful.

Interferon has been somewhat disappointing but **Adenine Arabinoside (Ara-A),** originally used as an anti-cancer agent, has had some success in treating disseminated herpes simplex and zoster infections, particularly in the compromised host. Acyclovir (Zovirax) shortens the course of genital heripes but does not prevent recurrences. It is available as a cream but is undergoing trials in oral and intravenous forms.

Anti-fungal drugs

Drugs for treating mycotic infections include amphotericin B, flucytosine, griseofulvin, nystatin and miconazole.

to page 20

Antimicrobial	Interacting Drug	Effect
Aminoglycoside	Ethacrynic acid)	↑ Ototoxicity
	Ethacrynic acid)	
	Muscle relaxants	Neuromuscular blockade
	Some cephalosporins	↑ Nephrotoxicity
Tetracyclines	Antacids)	↓ Absorption of tetracycline
	Ferrous sulphate)	
	Anticoagulants	↓ Prothrombin index
Sulphonamides	Oral hypoglycaemics)	↓ Blood sugar
	Anticoagulants	↓ P.I.
	Methotrexate	↑ Toxicity of methotrexate
Chloramphenicol	Oral hypoglycaemics	↓ Blood sugar
	Anticoagulants	↓ P.I.
	Phenytoin	↑ Toxicity of Phenytoin
Ampicillin	Contraceptive pill	Pregnancy
Rifampicin	Anticoagulant	↑ P.I.
	Corticosteroids	↑ Dose of corticosteroid required
	Contraceptive pill	Pregnancy
Metronidazole	Alcohol	Antabuse effect
	Anticoagulant	↓ P.I.
Amphotericin B	Digoxin	Digitalis toxicity (hypokalaemia)

↓ = decreased → = increased