Rational Antibiotic Therapy

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Antibiotics are prescribed by clinicians working in all medical disciplines. Many doctors would think twice before prescribing a hypotensive agent or a hormone, but antibiotics, like psychotropic drugs, are frequently given to patients without a thought as to whether or not they are really indicated, and the potential consequences of their prescription are often ignored.

Antibiotics differ from most other drugs in that they are normally derived from microbiological sources and act therapeutically by killing or stopping the growth of living organisms. As a result, their adverse effects are wide-ranging, affecting most organs and systems of the body, producing reactions by allergic mechanisms (penicillins), direct cell damage (aminoglycosides) and microbiologically (clindamycin). Indiscriminate use of antibiotics encourages the selection of resistant bacteria that are transmissible to other persons, while the relative complexity of their manufacture makes them expensive.

When selecting an antibiotic for the treatment of an infection the clinician should consider five factors—
1. the infection;
2. the patient;
3. the known or presumed infecting organism;
4. the environment;
5. the available agents.

The Infection

Many infections are of viral aetiology and antibiotics are not indicated for their treatment. Others, such as bacterial gastroenteritis, are self-limiting with the aid of symptomatic therapy. The site of the infection may influence the choice of antibiotic and also the duration of treatment; for example, certain antibiotics diffuse poorly or not at all into the cerebrospinal fluid and are, therefore, not indicated for the treatment of bacterial meningitis, while deep-seated infection in a heart valve or bone may require prolonged therapy. Infections associated with abscess formation will not be cured until the pus has been drained.

The Patient

The patient’s age, weight, sex, race, allergies, and renal, hepatic and immune functions must all be considered when selecting an antibiotic.

Whereas a lower than average dose may be sufficient in the elderly, neonates frequently require higher doses on a weight basis than those recommended for older children. As tetracyclines chelate with calcium and are deposited in growing bone and teeth, producing staining and sometimes disfigurement of teeth, they should not be given to children under the age of 12 years unless there is no alternative. The weight of the patient is also important and is frequently overlooked when prescribing an antibiotic; for example, a patient weighing 17 stones may be given the same dose as a seven stone woman and, as a result, treatment may fail in one while the other can suffer from dose-related adverse reactions.

Certain antibiotics are contra-indicated or best avoided in pregnancy, especially during the first trimester (Table 1); the safest antibiotics in pregnancy are the penicillins and cephalosporins. Patients suffering from glucose 6-phosphate deficiency (usually negroes and Asians) can develop haemolysis during treatment with certain chemotherapeutic agents, notably the sulphonamides (including co-trimoxazole) and nitrofurantoin.

| Table 1. Antibiotics in pregnancy. |
|-----------------------------------|
| **Best Avoided**                  |
| Tetracycline                      |
| Co-trimoxazole                    |
| Rifampicin                        |
| Metronidazole                     |
| (first trimester only)            |
| **Use with Care**                 |
| Aminoglycosides                   |
| Nitrofurantoin                    |
| Sulphonamides                     |
| (third trimester only)            |
| **Reason**                        |
| Staining of teeth                 |
| Folic acid inhibition             |
| Effect on fetus unknown           |
| Effect on fetus unknown           |
| Mutagenic in animals              |
| Fetal eighth nerve damage         |
| Nausea and vomiting in mother     |
| Displacement of fetal bilirubin   |
| from protein (kernicterus)        |

Allergy to the penicillins or cephalosporins (the beta-lactam antibiotics) is a contra-indication to their future use. Unfortunately, there is no sure way of determining whether a patient is allergic to these agents and, as a result, many are wrongly labelled as being so. When the cephalosporins were first introduced it was hoped that there might not be cross-sensitivity between these antibiotics and the penicillins. However, experience has shown that about 10 per cent of those who are penicillin-allergic are also allergic to the cephalosporins.

Before prescribing certain antibiotics the state of renal and hepatic function should be known. This is particularly important with the amino-glycoside antibiotics (Table 2), as their ototoxicity and nephrotoxicity are...
Table 2. The aminoglycoside antibiotics.

| Antibiotic      | 1977 | 1978 |
|-----------------|------|------|
| Streptomycin    | 80   | 96   |
| Neomycin        | 56 (8)| 56 (9)|
| Kanamycin       | 38   | 45   |
| Gentamicin      | 24   | 13   |
| Tobramycin      | 23   | 28   |
| Amikacin        | 13   | 9    |
| Netilmicin*     | 12   | 4    |
| Sisomicin*      | 4    | 10   |
| Pseudomonas aeruginosa | 1    | 2    |
| Meningococci    | 0    | 1    |
| Listeria monocytogenes | 0   | 3    |
| Candida albicans| 3    | 3    |
| Total           | 251  | 267  |

(Figures in parentheses = *Strep. faecalis*)

*Not available in UK.

The known or presumed infecting organism

When the causative organism has been cultured and its antibiotic sensitivity determined it is relatively simple to select an appropriate antibiotic. Frequently, however, the doctor is faced with a patient suffering from an infection requiring immediate antibiotic therapy that must be selected 'blindly'. Under these circumstances it is necessary to have a knowledge of prevalent organisms and their current antibiotic sensitivities. Table 3 lists the

Table 3. Septicaemic patients – East Birmingham Hospital.

| Enterobacteria* | 1977 | 1978 |
|-----------------|------|------|
| Enterobacteria  | 80   | 96   |
| Strep. faecalis | 56 (8)| 56 (9)|
| Staph. aureus   | 38   | 45   |
| Bacteroides spp.| 24   | 13   |
| Salmonella spp. | 23   | 28   |
| Clostridium spp.| 13   | 9    |
| H. Influenzae   | 12   | 4    |
| Pseudomonas aeg. | 4    | 10   |
| Meningococci   | 1    | 2    |
| Listeria monocy. | 0   | 1    |
| Candida albicans| 0   | 3    |
| Total           | 251  | 267  |

(bacteria causing septicaemia at East Birmingham Hospital during 1977 and 1978. Consideration of the patient's illness may allow the clinician to predict the organism causing septicaemia, e.g. *Bacteroides fragilis* in association with abdominal sepsis, or *Salmonella* species in a clinically septicaemic patient with diarrhoea and vomiting.

Certain infections are almost always caused by one organism with a predictable antibiotic sensitivity pattern; bacterial tonsillitis, for example, is almost invariably due to penicillin-sensitive haemolytic streptococci and lobar pneumonia to *Streptococcus pneumoniae*. Until recently, this latter organism was always sensitive to penicillin. However, penicillin-resistant strains, which were first detected in New Guinea and more recently in South Africa, are now appearing in Europe, illustrating the importance of keeping up to date with sensitivity trends. The increasing resistance of *Escherichia coli* to ampicillin has reduced the usefulness of this antibiotic in the treatment of urinary tract infections, particularly those developing in hospital patients. Most staphylococci are now penicillin-resistant and gentamicin resistance among Gram-negative bacilli is now being recognised in UK hospitals.

The environment

As described above, the antibiotic sensitivity of bacteria varies between different countries. Other examples of 'geographical microbiology' include chloramphenicol-resistant *Salmonella typhi* originating in Central and South America and penicillin-resistant gonococci in South-East Asia and the Pacific islands. Within a hospital some infections are commoner in certain units; for example, pseudomonas infections are common in burns units and intensive therapy units, and fungal infections in wards treating immunosuppressed patients. In certain circumstances, for example an outbreak of infection caused by an antibiotic-resistant organism, it may be necessary to impose an antibiotic policy within a unit, or even a whole hospital, to restrict the use of some antibiotics and thus limit the clinician's choice.

The available agents

After consideration of the preceding four factors the clinician's choice will usually have been reduced to two or three antibiotics. His final selection will depend on the properties of these agents, including antibacterial spectrum, pharmacology, adverse effects, interactions with other drugs, and cost. When making the final selection the dose and duration of therapy must also be considered.

In general, 'narrow-spectrum' antibiotics are preferable to 'broad spectrum' agents such as the cephalosporins which, by ablating commensal bacteria, may encourage super-infection with resistant organisms, especially fungi such as *Candida albicans*.

The pharmacology of an antibiotic may influence whether or not it is indicated for a particular infection. Nitrofurantoin should not be used for the treatment of urinary tract infections if there is a possibility of associated septicaemia, as serum levels are inadequate for the treatment of blood stream infections. Further, it cannot...
be given to patients who are vomiting as there is no available injectable preparation. Phenoxymethylpenicillin (penicillin V) is unpredictably absorbed from the gut and should never be used to treat patients who are acutely ill, at least in the initial stage of therapy.

Because of the possibility of causing serious, and sometimes fatal, adverse reactions the indications for a number of antibiotics are strictly limited. Examples include chloramphenicol (bone marrow aplasia) which should be reserved for typhoid fever and life-threatening infections caused by *Haemophilus influenzae*, and clindamycin (pseudomembranous colitis) whose use should be restricted to staphylococcal bone and joint infection and intra-abdominal sepsis (in combination with an aminoglycoside).

Antibiotics can interact with other drugs to produce unwanted effects (Table 4). Although combinations of two, or occasionally three, antibiotics are sometimes necessary their use should be restricted to a small number of indications. These include tuberculosis, certain types of endocarditis, intra-abdominal sepsis, and life-threatening infections of undetermined cause. The use of more than one agent is very seldom indicated for other infections, including bacterial meningitis in which benzylpenicillin is sufficient for meningococcal and pneumococcal infections, and chloramphenicol for those caused by *H. influenzae*.

Having finally selected an antibiotic, the clinician must determine the therapeutic, and also safe, dose before writing the prescription. A good example of the importance of careful dosage is that of the aminoglycoside antibiotics where the margin between the optimum therapeutic dose and that producing adverse effects is narrow. It is essential that the dose should be calculated by using a formula that takes into account the patient's weight and renal function: if renal function is normal the formula for gentamicin is 5 mg/kg body weight every 24 hours given in divided dosage every 8 hours. Decrease in renal function necessitates increase in the time between doses and if there is severe kidney damage, also reduction in the individual dose.

### Table 4. Some interactions with antibiotics.

| Antibiotics  | Other Drugs | Interaction       |
|--------------|-------------|------------------|
| Aminoglycosides | Frusemide  | Ototoxicity       |
|              | Ethacrynic acid |                 |
| Sulphonamides | Sulphonylureas | Displacement from plasma protein binding sites |
| (includes co-trimoxazole) | Warfarin  |                 |
|              | Phenytin    |                 |
|              | Methotrexate |                 |
| Tetracyclines | Calcium     | Chelation forming insoluble complexes |
|              | Iron        |                 |
| Metronidazole| Alcohol     | 'Antabuse' effect |
| Rifampicin   | Oral contraceptives | Risk of pregnancy |

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### Table 5. Cost of drugs — East Birmingham Hospital — 1978/79.

| Antibiotics | £     |
|-------------|-------|
| Antibiotics | 116,500 |
| CNS preparations | 56,266 |
| Anticoagulants | 35,626 |
| Cytotoxic drugs | 28,852 |
| CVS and diuretics | 22,144 |
| Anti-rheumatics | 20,288 |
| Other preparations | 261,730 |
| Total | £541,406 |

### Table 6. Cost of E.C. 10 prescriptions — England and Wales — 1976.

|                          | Millions (£) | %   | Unit cost |
|--------------------------|--------------|-----|-----------|
| CVS and diuretics        | 84.00        | 20.2| 1.956     |
| CNS preparations         | 71.02        | 17.0| 0.805     |
| Antibiotics              | 52.18        | 12.5| 1.157     |
| Anti-rheumatics          | 35.65        | 8.6 | 2.424     |
| Hormones                 | 30.70        | 7.4 | 1.935     |
| GI preparations          | 23.80        | 5.7 | 0.909     |
| Other preparations       | 114.91       | 28.6|           |
| Total                    | 412.26       | 100|           |

Antibiotics are expensive agents that figure prominently in the national drug bill. Their cost in hospital (Table 5) is proportionately higher than in general practice (Table 6) as a result of greater use of expensive new agents and also much more prescribing of injectable preparations that are several times more costly than oral formulations. Whenever possible, therefore, well-tried agents are preferable to new drugs, injection therapy should be changed to oral treatment as soon as clinically indicated, and courses of treatment should not be prolonged unnecessarily.

This article is based on a paper read at the College Regional Conference in Birmingham in September 1979.