Today's Treatment

Use of antibiotics

Infection in the compromised host

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Hospital practice is increasingly concerned with treating patients whose disease was previously considered incurable. In many of them the body's natural protective mechanisms are seriously impaired either by the disease, drug treatment, or both. This results in increased susceptibility to infection. If the benefits of major surgery and complex drug regimens are to be realised the recognition and correct management of complicating infection is of vital importance. Despite advances in antibiotic treatment and supportive care, infection remains the major cause of death in many groups of these "compromised" patients. The frequency of infection depends on the disease being treated, the age of the patient, and the number of invasive procedures, but the most important factor is granulocytopenia—the frequency of infection being inversely related to the circulating neutrophil count.¹

Diagnosis of infection is difficult owing to the frequent lack of clinical signs and the many causes of fever (in addition to microbial pathogens), such as drugs, blood transfusion, or the underlying disease. The rapid deterioration and the high mortality in compromised, infected patients demand that antimicrobial treatment should be started at once, often without knowing the nature or site of infection, although this is no excuse for failing to examine the patient carefully or undertake all relevant investigations. The choice of antimicrobial treatment is, of course, critical, and in the absence of culture results it is conventional practice to prescribe on the basis of informed knowledge of likely pathogens. At first sight this is a problem, since there are numerous reports of obscure and exotic organisms causing infection in these patients.

The nature of the underlying disease determines not only the frequency of infections but also, to some extent, the type of infection—for example, patients with early-stage lymphoma have a high incidence of varicella zoster infection but develop septicaemia only rarely.² The factors predisposing to infection also have predictive value: patients with granulocytopenia have a high incidence of severe invasive septicaemic illness; those with macrophage dysfunctions have lowered resistance to intracellular parasites such as *Listeria monocytogenes* and *Cryptococcus neoformans*; and there is a raised incidence of pneumococcal disease after splenectomy. These few examples illustrate

the need for appreciating the relation between microbial agents and their host, the full discussion of which is beyond the scope of this review.

In choosing antimicrobial agents for initial treatment of presumed infective episodes there are two common misconceptions. Firstly, it is assumed that the experience of one group of clinicians in one hospital and country will necessarily be relevant to the treatment of patients in a different hospital, which may be in a different continent. Some centres record a high incidence of infection with *Pseudomonas aeruginosa* in acute myeloid leukaemia³ whereas this organism is uncommon in our experience.⁴ Secondly, undue emphasis is often placed on the occurrence of exotic infections which, although worth considering, are uncommon. The commonest life-threatening infections are caused by Gram-negative bacilli and staphylococci, but other organisms such as streptococci, anaerobic bacteria, and candida also occur often enough to be important. The overriding consideration, however, should be a knowledge of local prevalence and resistance patterns, which may dramatically alter these probabilities, as evidenced by the high incidence of coccidioidomycosis in renal transplant patients in south-western USA.

Gram-negative bacteria

Aminoglycosides, broad-spectrum penicillins, cephalosporins, and the polymyxins should be considered for treating infections with Gram-negative bacilli. Aminoglycosides give the best cover.

GENTAMICIN

Gentamicin has formed the mainstay of treatment in many regimens giving reliable activity against *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, and *Ps aeruginosa*. In recent years organisms resistant to gentamicin have been recorded with increasing frequency, particularly in the USA. Apart from localised outbreaks, however, the incidence of gentamicin resistance remains low in Britain. Tobramycin shows activity similar to gentamicin, but, although two to four times more active in vitro against pseudomonas, there is little difference in clinical results. Amikacin is active against some gentamicin-resistant organisms and may be useful should this be a problem, but it has no other advantages and is considerably more expensive, and there appears to be no other reason to prefer it to gentamicin.

The aminoglycosides have two potential problems. The ototoxicity and nephrotoxicity of these agents is well recognised; the margin between the effective dose and the toxic dose is small, and treatment with the required high dosage needs careful monitoring. The second problem concerns the efficacy of gentamicin in patients with profound neutropenia, noted by

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Bodey seven years ago.⁵ He suggested that adequate numbers of circulating granulocytes are required for gentamicin to work effectively. The evidence, however, is equivocal. In Bodey's original series, as well as gentamicin, over half the patients received other antibiotics, which were equally ineffective, and the dosage of gentamicin used would be considered inadequate by today's standards. Animal studies have also failed to show that gentamicin is less efficacious than other antibiotics in the presence of neutropenia. It is well recognised, however, that infection with persistent neutropenia carries a poor prognosis and response is unlikely until the bone marrow starts to recover. Granulocyte transfusions in persistent neutropenia appear to improve the prognosis. Several new aminoglycosides are under evaluation and it is hoped that these will be less toxic while retaining their antibacterial activity.

CEPHALOSPORINS

The cephalosporins have good activity against most Gram-negative rods with the exception of *Ps aeruginosa* but are not as reliably active as the aminoglycosides. The established drugs cephalothin and cephaloridine have their disadvantages: the former has a very short serum half life and consequently has to be administered in large doses (12 g or more a day) at frequent intervals; the latter is nephrotoxic, but this appears to be less notable with the more recent cephalosporins such as cephalozolin. Two new compounds extend the usual broad spectrum of the cephalosporins—cefoxitin (strictly a cephamycin) to include anaerobes and cefuroxime to include *Haemophilus influenzae*. Both these agents are very resistant to β -lactamases.

CARBENICILLIN

Carbenicillin and the related drugs, ticarcillin and mezlocillin, are active against a wide range of Gram-negative organisms including pseudomonas but their instability to β -lactamases means that a considerable number of important organisms will be resistant. Like other penicillins they are active against streptococci and haemophili, and have some activity against bacteroides in the high doses usually given. Mezlocillin is considerably more active than carbenicillin but is not yet available.

COLISTIN

Colistin, although active against most Gram-negative organisms apart from *Proteus*, penetrates poorly into tissues and is little used now. It is also nephrotoxic.

Gram-positive cocci

Many of the drugs already considered may be used against staphylococcal infection, notably the cephalosporins and gentamicin. Streptococci, however, are resistant to the aminogly-

cosides and it is necessary to use an additional drug—such as flucloxacillin or clindamycin—both of which have the advantage of good activity against staphylococci as well as streptococci.

Carbenicillin is useful against streptococci but should not be relied on to treat staphylococci because of its β -lactamase instability.

Anaerobes

Clindamycin and metronidazole are the most dependable agents against anaerobic bacteria. Clindamycin, however, has been associated with pseudomembranous colitis more often than other antibiotics, but the true incidence of this complication remains a subject of conjecture.

Cefoxitin and mezlocillin both show useful in vitro activity against *Bacteroides fragilis*, although not as consistently as the other two drugs.

Antibiotic combinations

The need for initial treatment with antibiotics that show reliable activity against as broad a spectrum of bacteria as possible necessitates using a combination of drugs. Bactericidal agents are preferred to bacteriostatic agents because of host deficiencies. To minimise toxicity, difficulties in administration, and costs the number of drugs should be as few as possible.

Table I is a guide to the activity of the various individual antimicrobial agents, but local resistance problems and prevalence of organisms will largely dictate the choice of antibiotics. Combinations of drugs may not only broaden the range of activity but also have other properties—some desirable and others disadvantageous. Thus a combination of gentamicin and carbenicillin is more active than either drug individually against *Ps aeruginosa*, but the combination is less effective than gentamicin alone in *E coli* and klebsiella infections.

There are reservations about combinations of aminoglycosides and cephalosporins since there appears to be synergistic nephrotoxicity,⁶ although the risks are probably lower with the more recent cephalosporins. Other combinations that have been advocated include gentamicin/clindamycin; carbenicillin/cephalothin; cephalothin, gentamicin/carbenicillin; gentamicin/flucloxacillin/metronidazole; and the five-antibiotic regimen of Tattersall *et al.*⁷ The number of combinations shows that none is ideal. Most clinicians would prefer not to use aminoglycosides, given a reliable alternative, because of their toxicity, and some of the more recent antibiotic developments may make this possible. The value of a combination of, say, cefoxitin and mezlocillin would be an interesting study.

Combination antibiotic treatment is a necessity during the first period of treatment but should be reviewed within 72 hours. By then an organism may have been isolated from bacterial cultures so that the antibiotic can be changed to the most active appropriate drug, preferably a single agent with a narrow range of activity. In as many as 40% of suspected infections no organism is isolated, and in these cases clinical criteria alone must be relied on to plan further management. The original as-

A guide to the activity of the various individual antimicrobials

	Gentamicin	Cefoxitin	Cefazolin	Carbenicillin	Mezlocillin	Flucloxacillin	Clindamycin	Metronidazole	Co-trimoxazole
<i>Escherichia coli</i>	+	+	+	±	+	—	—	—	+
<i>Klebsiella</i>	+	+	+	±	+	—	—	—	±
<i>Proteus mirabilis</i>	+	+	+	±	+	—	—	—	±
<i>Pseudomonas aeruginosa</i>	+	—	—	+	++	—	—	—	—
<i>Enterobacter</i>	+	±	±	±	+	—	—	—	±
<i>Staphylococcus aureus</i>	+	+	+	—	±	+	+	—	+
<i>Streptococci</i>	—	+	+	+	++	+	+	—	+
<i>Enterococci</i>	—	±	±	±	++	—	—	—	±
<i>Bacteroides fragilis</i>	—	+	±	±	+	—	++	++	±
<i>Haemophilus influenzae</i>	±	±	±	+	++	—	±	—	+

+ + = Highly active. + = Most fully sensitive. ± = Some strains sensitive. — = Most resistant.

sumption of an infective process should be questioned, and if it appears unlikely antibiotics should be stopped. If the patient has improved on treatment then the original combination is best continued, but if the patient's condition is deteriorating other factors should be considered.

Neutropenic patients may take several days to respond even when treated with full doses of appropriate drugs. On the other hand, it is prudent to consider further possibilities, such as fungal infections or collections of pus (especially perianal abscesses), and a thorough examination of the patient and further cultures should be performed. Faced with a deteriorating patient the doctor may have to change the treatment, and either a further antibiotic such as co-trimoxazole or an antifungal agent may help. If the patient responds to treatment antibiotics should be continued for at least seven days and preferably for five days after fever has subsided, but the risks of relapse must be carefully weighed against the progressive likelihood of superinfection if antibiotics are continued.

Prophylaxis

Some clinicians advocate using oral non-absorbed antibiotics such as FRACON (framycetin, colistin, and nystatin), usually combined with protective isolation and topical antiseptic applications, to reduce the gut flora, a frequent source of endogenous infections. The results of the effectiveness of these measures (either alone or in combination) are confusing and contradictory. The cost of rigorous protective isolation for all but the most severely compromised patients is prohibitive and there are reservations about inducing resistance by using non-absorbed antibiotics. A recent report from Canada shows impressive results using prophylactic co-trimoxazole in neutropenic patients,⁸ but the long-term effects on bacterial resistance have yet to be determined.

Non-bacterial infections

FUNGAL INFECTIONS

Invasive infections are an appreciable cause of morbidity and mortality in patients whose normal resistance to infection is defective. Delay in starting effective treatment adversely affects the outcome, but amphotericin B, the most potent and until recently the only agent suitable for systemic administration, is toxic. This, coupled with complex dosage regimens and the difficulties of proving invasive infection, leads to an understandable but often regrettable reluctance to use this drug.

Amphotericin B, a polyene, is active against most pathogenic fungi including the two most commonly encountered, *Candida albicans* and *Aspergillus*. Parenteral administration is only by intravenous infusion in 5% dextrose. The daily dose is progressively increased from 1 mg initial dose to a maximum of 0.6 mg/kg/day, achieved after about two weeks. Response to treatment relates to the total amount of administered drug, and the duration of treatment is based on the severity of infection. Adverse reactions, which include nephrotoxicity, fever, rigors, vomiting, hypokalaemia, and anaemia are common and may lead to stopping treatment. Nephrotoxicity may be decreased by taking mannitol, and corticosteroids may reduce febrile reactions. The combination of amphotericin with flucytosine may allow the dose of amphotericin to be reduced with a consequent reduction in toxicity. Flucytosine may be given by mouth or intravenously and is relatively non-toxic. Nevertheless, it has

only a narrow range of activity, principally against *Candida albicans*, and natural and induced resistance occurs not uncommonly. The inhibition of flucytosine by cytosine arabinoside may also be a problem in some patients.

The imidazoles, clotrimazole and miconazole, may also be given systemically and have a wide range of activity. Their place in treating systemic mycoses is being evaluated. Gastrointestinal, hepatic, and cerebral side effects have been recorded.

A comprehensive review of antifungal agents is given in another article in this series.

VIRAL INFECTIONS

Infections with herpes viruses, especially varicella zoster and cytomegalovirus are not uncommon, and hepatitis B and the virus of non-A-non-B hepatitis from frequent blood transfusions may also be a problem. Adenine arabinoside (Ara-A) is the most promising agent in disseminated herpes virus infections. Treatment of such virus infections is still in its infancy, however, and no viricidal agent can be confidently recommended.

PNEUMOCYSTIS CARINII

Pneumocystis carinii, an unclassified infective agent that causes severe, rapidly progressive interstitial pneumonia in patients with leukaemia and lymphoma, may respond to 14 days' treatment with either pentamidine isethionate 4 mg/kg/day or co-trimoxazole trimethoprim 20 mg/kg/day and sulphamethoxazole 100 mg/kg/day. Some patients need longer treatment, and the best results are obtained by continuing the original drug rather than by changing treatment. Co-trimoxazole is less toxic than pentamidine and is to be preferred.

Summary

The care of the compromised patient requires constant vigilance for signs of infection. Once infection is suspected full dosage combination antibiotic treatment should be started promptly, with drugs chosen on the basis of local prevalence and resistance of organisms. Both the organisms and their antibiotic sensitivity may change from time to time, and joint surveillance of this problem by clinician and microbiologist is essential. The effect of antibiotics is seen not only in the patient receiving them: unnecessary antibiotics given to other patients in the hospital may lead to resistant organisms emerging, which, although of low pathogenicity by conventional standards, may produce severe infections in patients with immune deficiencies. One patient's topical gentamicin may be another's fatal pseudomonas septicaemia.

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