and nitrofurantoin. Clearly identification of these causes is important for the management of the patient—especially in Wilson's disease, in which chelating agents such as D-penicillamine are life saving. Another group of patients have chronic active hepatitis negative for hepatitis B whose disease is epidemiologically typical of non-A, non-B viral infection—that is, it occurred after transfusion of blood or blood products or in an intravenous drug abuser. Despite numerous claims for the development of specific non-A, non-B detection assays, none has withstood the rigours of testing against coded samples from well documented cases, and this diagnosis remains one of exclusion. Until such assays become available which can confidently identify patients with chronic non-A, non-B hepatitis the clinical course of the disease and the appropriate treatment will remain uncertain.

In general, the prognosis of chronic active hepatitis associated with hepatitis B virus is poorer than its counterpart negative for hepatitis B.^{4,9} Hepatitis B e antigen, DNA polymerase, and full hepatitis B virus DNA may be present in the serum and indicate continuing viral replication. In these patients treatment with corticosteroids serves only to potentiate viral replication and is of no benefit¹³; indeed, in one study it was shown to have a deleterious effect.¹⁴ Recent studies, however, have suggested that corticosteroids may benefit patients with chronic active hepatitis who are negative for hepatitis B e antigen or positive for hepatitis B e antibody—that is, when viral replication has apparently stopped and when an autoimmune process may be responsible for continuing hepatic damage.¹⁵ In recent years treatment has concentrated on the use of antiviral agents (on the basis that termination of viral replication is associated with reduction in liver inflammation¹⁶), whose value has been recently reviewed.¹⁷

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Third generation cephalosporins

The "third generation" cephalosporins may be defined as having high stability to β -lactamases, particularly those produced by coliforms, high potency against most of these coliforms, and moderate to good activity against *Pseudomonas aeruginosa*.¹ Any review of the merits of this large and expanding group would, unfortunately, have to rely mainly on the vast amount of in vitro and pharmacological data that have been accumulated.^{2,4} There have been no good clinical trials comparing these antibiotics—presumably because such trials require large numbers of patients and would be difficult to assess in view of the similar properties of these compounds.

What can probably be decided is their place, as a group, in the treatment and prevention of serious sepsis. Clinical experience has been largely with cefotaxime, ceftazidime, and latamoxef, all of which are marketed as broad spectrum replacements for the aminoglycosides. Other members of the group are ceftizoxime, which has been available for about a year, and ceftriaxone and cefotetan, both likely to be available soon.

The spectrum of activity of these agents is very wide, but it does contain important gaps. Their increased activity against the common Gram negative organisms does not adequately cover rarer causes of hospital infections such as *Acinetobacter* spp and the less common *Pseudomonas* spp. All are less active against Gram positive bacteria and inactive against enterococci and listeria. Furthermore, they have only modest activity against staphylococci, and, in the case of latamoxef, pneumococci. Their activity against anaerobic bacteria is only moderately increased compared with earlier cephalosporins, and none could be considered superior to cefoxitin. Many anaerobic cocci, bacteroides, and some clostridia are relatively resistant.^{5,6}

With these gaps in their antibacterial spectrum the new cephalosporins cannot be relied on as single drug antibiotic treatment for serious undefined sepsis where organisms other than Gram negative rods are likely pathogens. What, then, is their place? Their activity against the Enterobacteriaceae and their stability to most of the clinically relevant β -lactamases makes these new compounds useful for serious sepsis acquired in hospital and caused by Gram negative bacilli resistant to older agents. They are proving to be useful in neonatal meningitis, where their penetration of the central nervous system and intrinsic activity are superior to those of the earlier cephalosporins.^{6,7} They should certainly not be used in circumstances in which the first and second generation cephalosporins are used successfully—for example, cefuroxime for its activity against penicillinase producing neisseria and haemophilus, cephalozin as a prophylactic agent for biliary surgery, and cephalothin (although little used in Britain) for Gram positive infections.

Before they may be considered as replacements for the aminoglycosides, however, several questions need to be answered about the development of resistance, interactions with other antibiotics, toxicity, and the promotion of superinfection. Some cephalosporins appear active in routine laboratory tests of sensitivity but may induce resistance both to themselves and to other β lactams clinically; this has resulted in therapeutic failures when treating infections with some of the Enterobacteriaceae.⁸

The mechanisms of this resistance are complex and not fully understood but there may be reversible induction of a β -lactamase that hydrolyses the antibiotic or possibly binds to it, preventing its action on the appropriate target site.^{9,10} Irreversible resistance due to mutation has also led to failures of treatment and may even be associated with resistance to aminoglycosides.¹¹⁻¹³ Experience suggests cause for concern, but further laboratory work is required together with careful clinical observations to assess the importance of these various mechanisms.

Antibiotics are often used in combination, and if their interaction is synergistic the effect is probably beneficial, particularly in immunosuppressed patients.^{14,15} In the past aminoglycosides and β lactams have been given together in the hope that useful synergy will occur. Evidence from laboratory and animal studies suggests, however, that two β lactams combined may be antagonistic, something very rarely found with combinations of β lactams with aminoglycosides.^{14,16} Such combinations are cephalosporins together with a broad spectrum penicillin such as azlocillin, mezlocillin, or piperacillin.¹⁶ Both the induction of β -lactamase and competition for penicillin target sites may be behind this antagonism.^{9,16} At present the problem seems related to only a few of the new cephalosporins,¹⁶ and the results of clinical trials of β lactam combinations have been encouraging,¹⁴ but further study is needed. In the mean time we would advise caution in the use of such combinations in neutropenic patients, in whom antagonism might be serious.

Toxicity is rarely a problem with cephalosporins. Certainly none of the new ones show any signs of being seriously nephrotoxic, and the large therapeutic index suggests that serum concentrations will rarely need to be monitored. Worrying reports have appeared of coagulation problems with those cephalosporins (such as cephamandole and latamoxef) that contain the *N*-methyl-thiotetrazole side chain, which has been implicated in the inhibition of vitamin K dependent synthesis of prothrombin and in the production of a "disulfiram" effect.¹⁷ Sporadic reports have also appeared of neutropenia probably due to immunological mechanisms.¹⁸ The broad spectrum of these agents has led to fears of fungal superinfection, but the risk is probably no worse than with other broad spectrum agents; indeed, superinfection with enterococci may be a greater problem.⁶

The conclusion must, therefore, be that we need much more evaluation—particularly clinical—of these new agents. Ideally, large multicentre trials should be set up to compare them alone and in various combinations, but this is perhaps asking too much. In the mean time their cost and the need to limit spread of resistance should limit their routine use. They should not be used for infections that can be treated with cheaper, well tried penicillins and cephalosporins. We suggest that they might be considered in the following groups of patients: (a) non-neutropenic patients with serious undefined sepsis, where they can probably be combined safely with most other antibiotics as necessary—for example, metronidazole if abdominal sepsis is suspected; (b) non-neutropenic patients with serious proved Gram negative sepsis, when they can usually be used as sole antibiotics; (c) Gram negative bacillary meningitis; (d) neutropenic patients with Gram negative sepsis, when they

should be combined with an aminoglycoside; and (e) patients with chronic relapsing infections such as those caused by *Ps aeruginosa* in cystic fibrosis, where repeated courses of broad spectrum antibiotics may be necessary and toxic compounds, such as the aminoglycosides, may be better avoided.

The cephalosporins have been described as agents in search of diseases¹⁹; indeed, the whole development of such powerful agents as the third generation cephalosporins has been questioned.¹² They have, nevertheless, arrived as genuine contenders for first line antibiotic treatment. Just which agent to use in which setting should become more apparent in the future. In the mean time the choice will have to depend on consideration of the spectrum of activity, pharmacokinetics, toxicity, and cost.

Future research is likely to be concerned with developing compounds capable of providing monotherapy for all infections—the holy grail of the pharmaceutical companies. Such an agent will require more predictable activity against a wider range of pathogens than offered by currently available drugs. In particular, better activity against staphylococci and *Bacteroides* spp is important.

The pharmaceutical industry may need to be reminded, however, that, despite the impressive in vitro data—ratio of peak serum concentrations to minimal inhibitory concentrations of 100-500 are common¹²—the clinical data on these new agents do not suggest great advantages over more conventional treatment. Perhaps more effort should be put into studying the methods of bacterial killing, development of resistance, host immune system interaction, and immune modulation.

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