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3. **Findell CM, Sherris JC.** Susceptibility of enterobacter to cefamandole: evidence for a high mutation rate to resistance. Antimicrob Agents Chemother 1976;9:970–4.
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Commentary 2

Hospital formulary committees are increasingly being pressured from two sides. Hospital administrators, feeling the crunch of prospective reimbursement, are pressuring departments in their institutions to cut costs. Thus, the pressure on formulary committees is to trim, restrict and control whenever possible. On the other side, pharmaceutical manufacturers are spewing out an array of clinically attractive, but expensive new drugs. Some of the most prevalent and pervasive of these are antimicrobial agents, particularly cephalosporins. Hence, the pressure is on formulary committees to review and adopt new agents if they are even marginally superior to older, less costly products.

An important marketing tool in today's health care environment is the buzzword "cost-effective." Attaching this label to any new drug adds to the pressure on formulary committees to add this agent to the hospital's drug list. Restriction policies to limit drug use aside, this simple act of approving a new drug for use in a hospital, particularly a teaching institution whose policies influence other local hospitals, is analogous to the Good Housekeeping Seal of Approval. Therefore, it is absolutely imperative that members of formulary committees clearly understand that "cost-effective" does not only mean that the drug is less expensive to administer. A long half-life and prolonged dosing intervals do not equate with cost-effectiveness. The drug must be *clinically* effective at the prescribed dosing regimens before the cost-effective label is relevant.

The dilemma of cefonicid is that the drug is priced such that its once daily dosing regimen makes the total cost less than first generation cephalosporins that are traditionally given three to four times a day. However, the cefonicid clinical trials have yet to be published and therefore cannot be closely scrutinized. The preliminary reports appear to be very promising with the exception of the failures in staphylococcal endocarditis. A supplement to the *Reviews of Infectious Diseases* to be published in late 1984 will contain the bulk of the clinical experience with cefonicid. Until that time and until more experience is gained to ascertain and document the clinical effectiveness of the drug, formulary committees should be cautious in adopting cefonicid. If this experience is positive, there is no question that the drug will be truly cost-effective.

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Commentary 3

Cefonicid is another new cephalosporin in search of its appropriate place in our formularies. Its antimicrobial spectrum is nearly equivalent to that of cefamandole, which it closely resembles. Its major difference is a markedly prolonged half-life, which permits its promotion as a drug that can be given only once a day.

In evaluating cefonicid, problems arise which are by no means unique for this drug, but which are difficult for the clinician to interpret. In vitro, its efficacy is markedly decreased by testing in serum, rather than in broth, and such testing is also influenced by inoculum size. In vivo, its high degree of protein-binding may account for its strikingly high blood levels, but this attribute also strikingly shrinks its volume of distribution. Such reservations may be ignored, but they add up to giving us pause when we learn that plasma concentrations are above many reasonable MICs at 12 hours, but only "detectable" (projected to 1 μg/ml) at 24 hours, a level above the MIC for only a few organisms.[1] Even for those who support peak-trough dosing, one might wonder how long would serum levels fall below the MIC in this second 12 hours. This may, of course, account for the difficulty in being sure of the role of this drug in staphylococcal infections, and even of the possibility of paradoxic benefit in osteomyelitis, but perhaps not in soft-tissue infection. This requires further clarification.

The prolonged half-life and once-daily dose leads to two kinds of savings — one of cost and one of efficiency or convenience — and these must be examined separately. In considering cost alone, the cost of cefonicid should be compared with its most likely competitor: cefamandole. Courses of 2 g every 24 hours of cefonicid are more expensive than 1 g every 6 hours of cefamandole according to the average wholesale price in Drug Topics Red Book.[2] Many of the series cited in Pontzer and Kaye's review examine courses of only 1 g every 24 hours. At this dose cefonicid is much less expensive. In institutions using any form of unit dose systems, requiring separate administration sets or tubing for each dose, the overall saving in single daily doses is immediately evident. However, until further clinical trials assure us of the safety of single daily doses, the cost question alone is not likely to predominate, especially for institutions mixing a full daily dose in a single intravenous bottle.

There may well be a number of situations, however, in which convenience or accessibility are also much better with daily regimens. Home care, particularly for long courses of antibiotics as in treatment of osteomyelitis, is certainly one such area. One should note with caution, however, that the other common infection requiring long courses of antibiotics, endocarditis, has had much more discouraging results in the trials cited by Pontzer and Kaye. The population used — *Staphylococcus aureus* endocarditis in drug addicts — is admittedly a most stringent standard.[3]

The domiciliary situations where once daily administration of a parenteral antibiotic of this spectrum may be most helpful is *not* in the acute-care hospital, where more conservative and aggressive care is more justifiable, but in chronic-care facilities, nursing homes and the like. In these settings nursing staffing or limited intravenous access might make a single daily dose of antibiotic most acceptable, particularly since its efficacy in the commonest infections found in such places seems reasonably well documented: urinary tract infections, soft-tissue infections (although with uncertainty about staphylococci) and perhaps pneumonia. Those seeking to use cefonicid in this setting should remain suspicious of the tendency to find highly-resistant gram-negative bacilli appearing in some such institutions, particularly in urinary tract infections, often in epidemic patterns.

The difficulty we currently have in evaluating the clinical place of cefonicid is that we do not yet have adequate data available to allow an impartial judgement. Many of the clinical trials, as the authors point out, are "limited to open, non-blinded, comparative trials" with inadequate numbers