A New Wave of Antibiotics Builds

New β-lactams active against resistant organisms are about to flood the market, but some physicians and hospitals may drown

The next few years "are probably going to be one of the most difficult times ever in clinical medicine in terms of evaluating new drugs," says Robert C. Moellering, Jr., of Harvard Medical School about new β-lactam antibiotics and, particularly, the third-generation cephalosporins. "I can't think of a time when we have had more drugs that really are clinically similar poised to come on the market in so short a time. The problem is that these drugs all have significant advantages in terms of spectrum of activity and lack of toxicity over what is already on the market. It's going to be very hard to separate them out one from another clinically."

It is a problem, however, that most clinicians will gladly face because the new drugs represent a significant advance in treatment of hitherto resistant microorganisms. The first of these new cephalosporins to reach the market was cefotaxime, which was approved by the U.S. Food and Drug Administration (FDA) in March and became available in May. Moxalactam was approved by FDA in October and its manufacturer is expected to announce its availability on 9 December. Cefoperazone is also expected to be approved very soon. Ceftizoxime, ceforanide, and cefsulodin have new drug applications pending, and ceftriaxone and ceftazidime are in clinical trials. This list does not include another 10 to 15 third-generation cephalosporins that are in earlier stages of development, as well as other β-lactam antibiotics and β-lactamase inhibitors. "These drugs," says Calvin M. Kunin of the Ohio State University College of Medicine, "are magnificent examples of good scientific thinking and good chemistry on the part of the pharmaceutical manufacturers."

The interest in the drugs on the part of physicians has been very strong. Most of the manufacturers have sponsored one or more well-attended symposia on clinical results obtained with their products, and such clinical reports have been the highlight of many other medical meetings. A substantial fraction of the papers at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Chicago in November also were on the new cephalosporins. Virtually all of these reports have emphasized the effectiveness of these new agents against various recalcitrant microorganisms, as well as the remarkable safety of the drugs. The overwhelming numbers of such reports make any kind of comprehensive reporting of results nearly impossible. Perhaps more important, they will also make it exceptionally difficult for physicians to choose among the drugs as they come into regular use. Harold C. Neu of the Columbia University College of Physicians and Surgeons speculates that it may be the better part of a decade before completely rational choices can be made.

The key structural feature of these current and potential antibiotics is the presence of a β-lactam, a four-membered ring in which a carbonyl and a nitrogen are joined in an amide linkage. The penicillins, originally isolated from the fungus *Penicillium notatum*, were the first generation of β-lactam antibiotics. In the penicillins, the amide nitrogen and an adjacent carbon are fused to a five-membered thiazolidine ring containing a sulfur atom. The penicillins are now in their fourth generation—each new generation showing an increased spectrum of activity or other therapeutic advantage.

The second generation of β-lactams are the cephalosporins, first isolated from the fungus *Cephalosporium acremonium*. In these, the amide nitrogen and the carbon are fused to a six-membered dihydrothiazine ring containing a sulfur atom and a double bond. The various penicillins and cephalosporins differ in the identity of the side chains attached to the fourth atom of the β-lactam ring and to carbon-3 of the fused ring. All the cephalosporins are produced by chemical modification of naturally occurring side chains—except moxalactam, which is totally synthetic.

The key therapeutic feature of these agents is also the β-lactam ring. Held in a strained configuration by the fused ring system, the β-lactam and adjacent atoms have a spatial configuration similar to that of a peptidoglycan used in the synthesis of the bacteria cell wall. The antibiotics substitute for this peptidoglycan and inhibit enzymes important to cell wall synthesis. The β-lactams are thus effective only against actively growing bacteria. Since mammalian cells have a much different membrane, the β-lactams are highly specific for bacteria and have remarkably few side effects.

For many years, it was believed that the fused ring system was necessary to maintain the β-lactam in the proper configuration. Recently, however, scientists at the Squibb Institute for Medical Research in Princeton started clinical trials with one of a family of compounds, called monobactams, in which the fused ring is replaced by a sulfate moiety attached to the amide nitrogen. The monobactams are third-generation β-lactams (*Science*, 11 September, p. 1238).

The first β-lactams suffered from two main shortcomings. First, they had a limited spectrum of activity. They were effective primarily against aerobic bacteria and Gram-positive bacteria, which can be stained purple by certain reagents. Gram-negative bacteria, which have a more complicated cell wall structure and are not stained, and anaerobic bacteria are generally insensitive to penicillins and the first- and second-generation cephalosporins.

When the penicillins were first introduced, the most important disease-producing agents were Gram-positive, aerobic, or both. But in recent years, says Jay Sanford of the Uniformed Services University of the Health Sciences, "the source of most serious infections has shifted from the home to the hospital," where Gram-negative organisms predominate. The most common Gram-negative infectious agents are *Escherichia coli*, which causes respiratory and urinary tract infections and meningitis; *Klebsiella*, which causes urinary tract infections, pneumonia, and meningitis; and *Proteus mirabilis*, which causes pneumonia and other infections. All three also cause intra-abdominal infections such as peritonitis. Anaerobic microorganisms such as *Peptostreptococcus*, *Bacteroides fragilis*, and *Clostridium* are common sources of infection that require surgical management. Two others that are particularly difficult to combat are *Pseudomonas aeruginosa* and *Haemophilus influenzae*.

The second problem is the presence in certain bacteria, both Gram-negative and Gram-positive, of enzymes known variously as penicillinases or β-lactamases.

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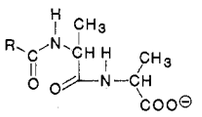
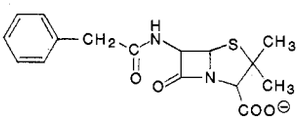
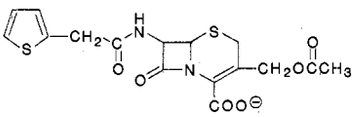
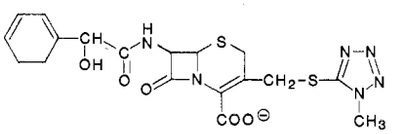
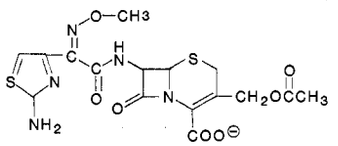
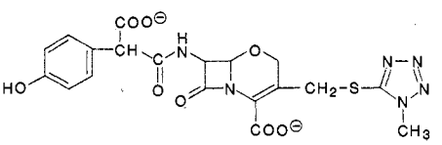
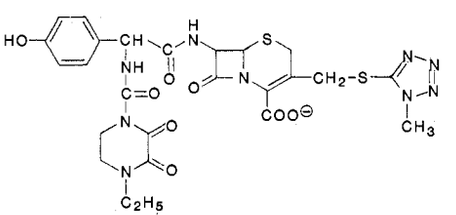
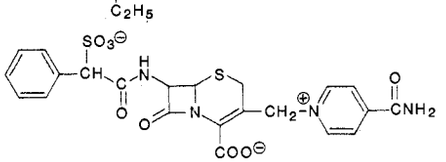
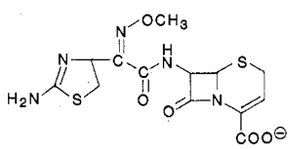
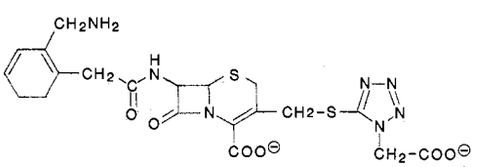
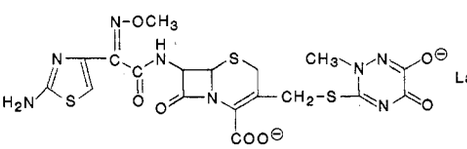
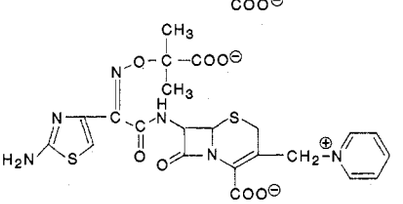
Name		Manufacturer	Market status
Growing d-alanyl-d-alanine peptidoglycan			
Penicillin G		Several	Approved
Cephalothin (Keflin) first generation		Eli Lilly & Company	Approved
Cefamandole (Mandol) second generation		Lilly	Approved
Cefotaxime (Claforan)		Hoechst-Roussel Pharmaceuticals Inc.	Approved U.S. West Germany France Switzerland
Moxalactam		Lilly	Approved
Cefoperazone (Cefobid)		Roerig div. of Pfizer Inc.	Pending
Cefsulodin		Takeda-Abbott Products	Pending in U.S. Approved by Japan Switzerland
Ceftizoxime (Cefizox)		Fujisawa SmithKline Corporation	Pending
Ceforanide		Bristol Laboratories	Pending
Ceftriaxone		Roche Laboratories	Pending
Ceftazidime		Glaxo Inc.	Pending

These enzymes hydrolyze the amide linkage of the β-lactam, rendering the drugs impotent. Unfortunately, the genes that control the production of these enzymes can be transferred from antibiotic-resistant to nonresistant microorganisms with relative ease.

Penicillin-resistant strains of infectious agents began to appear soon after penicillins were introduced into medical practice and have proliferated since. One of the most worrisome such organisms is *Neisseria gonorrhoeae*; a penicillin-resistant strain of this agent, which causes gonorrhea, has proved very difficult to treat. Many investigators argue that widespread, unnecessary use of antibiotics is a prime cause for the emergence of this and other β-lactam-resistant infectious agents; such use wipes out susceptible organisms and allows resistant ones to flourish. Some microorganisms have also developed resistance by altering the permeability of their cell walls.

Both problems have been attacked by treating resistant infections with more potent—and more toxic—drugs, including the tetracyclines, chloramphenicol, and the aminoglycosides. The last, which include tobramycin, amikacin, and gentamicin, are effective against many nosocomial (hospital-acquired) infections. They have a great potential for producing kidney damage and hearing loss, however, and should not be used until it has been shown that the infectious agent is resistant to other drugs.

The other approach to this problem has been to synthesize newer and better β-lactams. These have included second- and third-generation penicillins and first- and second-generation cephalosporins. The cephalosporins, in particular, have an inherently broader spectrum of activity than the penicillins and an intrinsically greater resistance to β-lactamases. They have become a major component of drug therapy and now account for roughly 35 percent of all antibiotic use, with world sales annually of about $1 billion. They are largely ineffective against nosocomial infections, however.

The third-generation cephalosporins give what Neu terms "a tremendous increase in effectiveness." These drugs can be grouped into three major categories, he says. In the first group are the aminothiazyl cephalosporins, which include cefotaxime, ceftizoxime, ceftriaxone, and ceftazidime. The acyl side chains of these are all very similar, but there are differences in substitution at position 3 of the dihydrothiazine ring. These changes alter the pharmacology and, to a lesser extent, the antimicrobial activity of the compounds. "These com-

Cephalosporins Are Not the Only Answer

The third-generation cephalosporins are but one of several approaches to improving the efficacy of β-lactam antibiotics. Another approach is to combine an existing β-lactam antibiotic with a specific inhibitor of the β-lactamases. Two such compounds are clavulanic acid, developed by Beecham Pharmaceuticals of Betchworth, England, and Sulbactam (penicillanic acid sulfone), developed by Pfizer Inc. of Groton, Connecticut. These chemicals—termed "fascinating" by Clyde Thornsberry of the Centers for Disease Control—have a very limited antibiotic activity in themselves, but they inhibit microbial β-lactamases irreversibly so that more potent antibiotics are not destroyed. Clavulanic acid is undergoing clinical trials in combination with amoxicillin; the combination is known as Augmentin. Sulbactam is also in clinical trials.

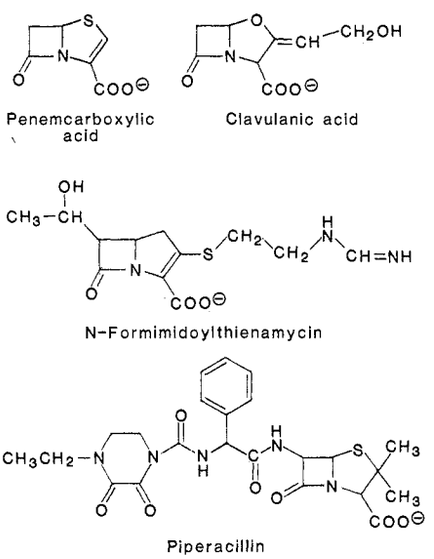
Much clinical data has been presented about the β-lactamase inhibitors. It is perhaps typified by a report by A. Watson of Beecham at the recent Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). In a study of 553 patients with severe infectious diseases, who were treated with Augmentin, Watson and his colleagues found that the cure rate for amoxicillin-resistant organisms was virtually identical to that for amoxicillin-sensitive pathogens. Other investigators reported similar findings for both Augmentin and Sulbactam.

Thornsberry says that he would particularly like to see clinical trials of the β-lactamase inhibitors on the strain of *Neisseria gonorrhoeae* that is resistant to penicillin. Robert C. Moellering, Jr., of the Harvard University School of Medicine calls the β-lactamase inhibitors "conceptually interesting," but he cautions that many of their features are incorporated in the third-generation cephalosporins. Clinical use of the inhibitors might well be limited, he says, if the new cephalosporins prove to be highly successful.

Piperacillin is a fourth-generation penicillin developed by Lederle Laboratories of Pearl River, New York. Piperacillin has a broad spectrum of activity but, most important, it is three to six times as effective against *Pseudomonas* species as existing penicillins. According to Harold C. Neu of the Columbia University College of Physicians and Surgeons, piperacillin's spectrum of activity is broadened substantially when it is used in conjunction with clavulanic acid or Sulbactam, so that it is effective against many Gram-negative organisms. Lederle has a new drug application pending at the U.S. Food and Drug Administration.

"One of the most exciting drugs to come along in a long time," according to Moellering, is thienamycin. Thienamycins, developed by Burton G. Christenson and his colleagues at Merck Sharp & Dohme Research Laboratories Division in Rahway, New Jersey, are analogs of penicillin in which the sulfur atom in the thiazolidine ring is replaced by a carbon atom. The first members of this family showed activity against a wide spectrum of microorganisms, as well as resistance to β-lactamases, but they were chemically unstable, being degraded through an intramolecular catalytic reaction involving an amine on the side chain. This problem was eventually overcome by making the *N*-formimidoyl derivative of thienamycin.

Rial D. Wolfe of the Wadsworth Veterans Administration Hospital in Los Angeles and his colleagues reported at the ICAAC meeting that *N*-formimidoylthienamycin "showed impressive in vitro activity against anaerobic bacteria," much better than the third-generation cephalosporins against which it was compared. But this compound also presents problems: It is degraded rapidly in the human kidney by an enzyme known as dehydropeptidase-1. Investigators at Merck have thus developed another compound, sodium (*Z*)-7-[[(2*R*)-(2-amino-2-carboxyethyl)thio]-2-[(1*S*)-(2,2-dimethyl cyclopropylcarboxamido)]-2-heptenoate, that is administered with the thienamycin to block the peptidase activity. Several investigators reported on successful safety trials with the combination at the ICAAC meeting, and clinical trials have recently been initiated. Physicians are anxiously awaiting the results from those trials because thienamycin's spectrum of activity is exceptionally broad.



Another group of β-lactams, called penems, were originally synthesized by a team headed by the late Robert B. Woodward at the Woodward Research Institute in Basel, Switzerland. The penems are penicillin analogs that incorporate the double bond present in the dihydrothiazine ring of cephalosporin; unlike other natural and semisynthetic penicillins, the penems also have no substituents attached to carbon six. Until the discovery of the monobactams, the penems were the simplest known active β-lactams.

The penems are related to thienamycins, in which the penem sulfur is replaced by a carbon. In vitro studies so far indicate that the penems have a somewhat narrower spectrum of activity than thienamycin and are somewhat less resistant to β-lactamases. This is partially counterbalanced, however, by their greatly increased chemical stability. Preliminary studies in animals also show that the simplest penems are excreted too rapidly to be clinically useful, perhaps because they are so small. Several pharmaceutical companies are believed to be working with variations of the penem structure, but none seem prepared to talk about their work at this point.—T.H.M.

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pounds are very effective and they are very similar, with only minor differences in terms of activity, β-lactamase stability, ability to pass through a complex Gram-negative cell wall, or to bind to a receptor." The second class includes principally cefoperazone, which is a piperazine derivative of the basic cephalosporin nucleus with a methyltetrazole moiety in position 3. "It is less stable to β-lactamases than the first category," says Neu, "but it is more effective against *Pseudomonas* than the other drugs are. It has a longer half-life, so it stays around in the body longer than the other drugs."

The third-generation cephalosporins give "a tremendous increase in effectiveness."

The third category is moxalactam, in which the sulfur in position 1 of the dihydrothiazine ring has been replaced with oxygen, so that it is no longer technically a cephalosporin; several changes in the side chains were also made. "Given all those modifications," says Neu, "you have tremendous resistance to β-lactamases and tremendous activity against many Gram-negative organisms, but you lose some Gram-positive activity. . . . Again, it stays in the body a long time, so it might be able to be given every 8 to 12 hours."

Some other differences can be picked out, says Moellering, particularly among cefotaxime, moxalactam, and cefoperazone, for which there is a tremendous amount of clinical data obtained both here and abroad. "Cefotaxime probably has the best activity against Gram-positive organisms, and therefore might be a better choice if you are going to use it as a first-line drug against [bacterial] meningitis. Moxalactam gets in cerebrospinal fluid better, and is probably therefore the drug of choice for Gram-negative meningitis," particularly meningitis of childhood and adolescence. Moxalactam is slightly better against anaerobic bacteria, adds Clyde Thornsberry of the Centers for Disease Control, and might be better for intra-abdominal infections and for surgical prophylaxis. Cefotaxime has better activity against enteric bacteria.

Cefsulodin is a narrow-spectrum drug that is particularly potent against *P. aeruginosa* and *Staphylococcus*. Ceforanide has a long half-life and remains in the blood in high concentrations, so it too might be useful for prophylaxis. Ceftazidime also has good activity against *P. aeruginosa*, while ceftizoxime has high activity against most Gram-negative organisms. Ceftriaxone appears to be especially effective against *H. influenzae*, *N. gonorrhoeae*, and *P. aeruginosa*.

Nonetheless, says Thornsberry, the evidence so far is that all the drugs are similar. "My guess," says Moellering, "is that, if you subjected all of these to randomized clinical trials, you couldn't get enough cases to show any significant clinical differences." Unfortunately, adds Sanford, the way that drugs are tested in this country precludes any such head-to-head trials for quite some time.

The side chains of all the new cephalosporins are readily degraded by digestive enzymes, so the new drugs must be given parenterally, either by intramuscular injection or infusion into the bloodstream. All have few side effects: the most common are rash, itching, and a vitamin K deficiency caused by the eradication of intestinal flora. Some also produce an occasional Antabuse-like reaction when a patient receiving them ingests alcohol. But these side effects are so mild, says Neu, and the spectrum of activity is so broad that the new antibiotics open the potential for blind therapy—the "treatment for an unknown organism in an unknown location, in a very sick hospitalized patient." Since they have such low toxicity, says Thornsberry, they can also be used for home treatment of patients who cannot be hospitalized.

Because there are so few apparent differences among the drugs, adds Moellering, "what we are going to be left with is a situation where a large number of drug companies have spent millions of dollars developing these things and all—reasonably—want to recoup their investments. There is going to be just tremendous competition to market the drugs, both here in the United States and worldwide. The clinician is going to be bewildered. The infectious disease experts aren't going to be much help because they aren't going to be able to say much. . . . I think we're going to be in for a very tough time in terms of tremendous competition and, whenever that happens, there's going to be a big tendency for overutilization."

That sentiment is echoed by others. The third-generation cephalosporins, says Kunin, are a response to the needs of tertiary-care hospitals, with large burn, cancer, and surgical wards. About 5 percent of the patients in such hospitals, he says, have antibiotic-resistant Gram-negative infections that are very difficult to clear up. The new drugs do precisely that, "but there is no money to be made in this area, so they will be marketed for everything. That's going to be very bad for several reasons." One problem is that widespread, indiscriminate use of the new agents could promote resistance to them. Already, Neu and Moellering have observed resistant strains of *P. aeruginosa* and Enterobacteriaceae when the new drugs were used alone and in too small a dosage.

Furthermore, says Kunin, most infections are still caused by Gram-positive organisms, against which the new drugs are only weakly potent. Physicians will thus use large doses to control the infections, often as much as 12 grams per day. Such use will contribute to the development of resistance but, more important, it will lead to "an explosion in costs," since the drugs sell for more than $10 per gram. (Conventional cephalosporins cost a maximum of about $40 per day.) A 10-day course of therapy—the normal time for clearing an infection—could cost well over $1000 for antibiotics alone. Such costs, he says, "will break the backs of hospitals."

Some of these problems may be overcome as more experience is gained with the drugs. It may be possible, says Neu, to use smaller doses and shorter periods of therapy in many cases. While a 10-day course of therapy may be required for strep throat, he notes, cystitis can be cured in one dose. For surgical prophylaxis, 24 hours may be sufficient compared to the usual 2 or 3 days. And despite their high cost, argues H. Harlan Stone of Emory University, the new drugs could still cut hospital costs by reducing infections and side effects among hospitalized patients. Above all, adds Sanford, costs can be contained by reserving the "unique capabilities" of the drugs for those cases where they are really needed.

The third-generation cephalosporins "are not the be-all and end-all," concludes Moellering. There are still several clinical areas that need new drugs. "The biggest gap is an antifungal therapy," where there are few effective drugs. The enterococci, he adds, are "surprisingly resistant" to existing drugs, and none of the new agents is "the ultimate antipseudomonal." Nonfermenting organisms are another problem area. In short, the pharmaceutical chemists have enough problems to keep them busy for a long time.—THOMAS H. MAUGH II