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An Overview of the Newer Antibiotics

Ramon del Busto
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The introduction of a large number of new antibiotics has made selecting the one most appropriate for treatment a confusing task for the practicing physician. One problem is that the differences in pharmacokinetics, in vitro activity, and clinical indications between some of these agents may be relatively minor; this is especially true of the new cephalosporins. Another problem is that the generic names of the cephalosporins are so similar that it is impractical, even for the infectious diseases specialist, to be familiar with all of them. This review attempts to summarize the most important characteristics of these new antibiotics and emphasizes their indications in clinical practice.

A list of the new parenteral antibiotics appears in Table I. Among the so-called second-generation cephalosporins, cefuroxime and cefonicid have been recently introduced for clinical use in the United States. The third-generation cephalosporins that are available commercially include cefotaxime, moxalactam, cefoperazone, and ceftizoxime. The fourth-generation penicillins include the ureidopenicillins, mezlocillin, and azlocillin as well as a piperazine-derivative, piperacillin. Among the aminoglycosides, the newest agent available is netilmicin, a derivative of sisomicin.

### TABLE I

**Newer Parenteral Antibiotics**

<table>
<thead>
<tr>
<th>Cephalosporins</th>
</tr>
</thead>
</table>
| **Second-Generation**| Cefuroxime (Zinacef)
|                      | Cefonicid (Monocid)
| **Third-Generation** | Cefotaxime (Claforan)
|                      | Moxalactam (Moxam)
|                      | Cefoperazone (Cefobid)
|                      | Ceftizoxime (Cefizox)
| **Fourth-Generation Penicillins** | Mezlocillin (Mezlin)
|                      | Azlocillin (Azlin)
|                      | Piperacillin (Pipracil)
| Aminoglycosides      | Netilmicin (Netromycin)

Newer Cephalosporins

All the cephalosporins consist of a dihydrothiazine ring, which is a six-sided nucleus attached to a four-sided, beta-lactam ring (Fig. 1). They all have a sulfur atom at position 1, except for moxalactam which has an oxygen atom and is therefore not considered a true cephalosporin but an oxa-beta-lactam antibiotic. In the search for cephalosporins with greater antibacterial activity and better pharmacological properties, innumerable substitutions and modifications have been made at virtually all positions on the cephalosporin molecule. The most important changes have been made at positions 3 and 7. In general, substitutions at position 3 of the dihydrothiazine ring usually affect pharmacokinetic properties, and modifications to the acyl chain at position 7 of the beta-lactam ring mostly affect the microbiological activity of the cephalosporin (1-3). In addition, the presence of a methylthiotetrazole ring at position 3 is associated with some side effects of these agents.

Currently, 12 parenteral and four oral cephalosporins are available commercially. As if these were not enough, many more cephalosporins and cephalosporin

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derivatives are currently being investigated and will soon be available for clinical use (Table II).

**TABLE II**
Classification of Parenteral Cephalosporins

<table>
<thead>
<tr>
<th>First-Generation</th>
<th>Second-Generation</th>
<th>Third-Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalothin (Keflin)</td>
<td>Cefamandole</td>
<td>Cefotaxime (Claforan)</td>
</tr>
<tr>
<td>Cefazolin (Ancef, Kefzol)</td>
<td>Cefoxitin* (Mefoxin)</td>
<td>Moxalactam* (Moxam)</td>
</tr>
<tr>
<td>Cepapirin (Cefadyl)</td>
<td>Cefuroxime (Zinacef)</td>
<td>Cefoperazone (Cefobid)</td>
</tr>
<tr>
<td>Cephradine (Velosef)</td>
<td>Cefonicid (Monocid)</td>
<td>Cefitoxime (Cefizox)</td>
</tr>
<tr>
<td>Ceforanide**</td>
<td></td>
<td>Cefazidime**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefmenoxime**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftriaxone**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cefsulodin**</td>
</tr>
</tbody>
</table>

* Not a true cephalosporin
** Investigational

**In vitro activity**

Third-generation cephalosporins have a wider spectrum of activity against aerobic gram-negative bacilli compared to the older agents, but they are less active against gram-positive organisms. Table III compares the in vitro activity of the cephalosporins against gram-positive organisms. All the cephalosporins are active against most gram-positive bacteria, except for Streptococcus faecalis, methicillin-resistant Staphylococcus aureus, and Listeria monocytogenes. However, the first-generation cephalosporins, as represented by cefazolin or cephalothin, are more active than the later ones, especially in comparison with moxalactam, a third-generation cephalosporin with the weakest activity against gram-positive organisms (4).

Table IV compares the in vitro activity of the cephalosporins against gram-negative organisms. The first-generation cephalosporins are active only against these few gram-negative organisms: E. coli, Klebsiella, and Proteus mirabilis. Even some of these organisms are now resistant to the first-generation cephalosporins, as evidenced by their high MIC90s. The first-generation cephalosporins are not active against many other gram-negative organisms, such as Enterobacter, Serratia, Morganella, Providencia, or Pseudomonas, which are frequently seen in hospital-acquired infections. Nor are they active against H. influenzae or Bacteroides fragilis.

The second-generation cephalosporins have a somewhat wider anti-gram-negative spectrum. Cefamandole, cefuroxime, and cefonicid are active against Enterobacter and H. influenzae. Cefoxitin has some limited activity against indole-positive proteus and Serratia but is particularly active against Bacteroides fragilis.

The third-generation cephalosporins have an even wider anti-gram-negative spectrum. Except for Acinetobacter, they are fairly active against most of the gram-negative organisms, including some weak anti-pseudomonas activity. Apart from minor differences,

**TABLE III**
Comparative In-vitro Activity of the Cephalosporins against Gram-positive Organisms* (MIC90)**

<table>
<thead>
<tr>
<th>Streptococcus Group A</th>
<th>Cefazolin</th>
<th>Cefotaxime</th>
<th>Moxalactam</th>
<th>Cefoperazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus Group B</td>
<td>0.05</td>
<td>0.12</td>
<td>4</td>
<td>0.12</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>0.1</td>
<td>0.12</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>Streptococcus (alpha, non-hemolytic, non-group D)</td>
<td>0.25 (Cephalothin)</td>
<td>0.25</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>Streptococcus faecalis</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.5</td>
<td>2</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>

* Neu, H. (4)
**MIC90 = minimal concentration of antibiotic in micrograms/ml required to inhibit 90% of isolates
cefotaxime and ceftizoxime have very similar in vitro activity. Cefoperazone is less active than the other third-generation cephalosporins against most gram-negatives, except for Pseudomonas aeruginosa. Moxalactam is most active against Bacteroides fragilis, and its activity against this organism is comparable to that of cefoxitin.

**Pharmacokinetics (Table V)**

The new cephalosporins have a more prolonged half-life than the older agents, except for cefazolin, which has a half-life of 1.4 hours. Cefuroxime, a second-generation cephalosporin, has in vitro activity similar to...
Clinical Indications

In general, the third-generation cephalosporins are rarely indicated, especially when older, less expensive antibiotics can be used. They are indicated, however, to treat infections resulting from organisms resistant to older cephalosporins, infections that may require prolonged therapy with aminoglycosides (i.e., osteomyelitis due to Enterobacteriaceae), and certain types of gram-negative bacillary meningitis.

Urinary tract infections. Third-generation cephalosporins are indicated in those urinary tract infections that are caused by organisms resistant to older cephalosporins, penicillins, or aminoglycosides. These organisms are usually seen in complicated, hospital-acquired urinary tract infections. In these instances, the cure rates are comparable to those of the older cephalosporins or the aminoglycosides. However, in urinary tract infections caused by Pseudomonas aeruginosa the cure rate has been only 50-70% (4).

Soft tissue and skeletal infections. In skin and soft tissue infections, the newer cephalosporins should be used only in those infections caused by enterobacteriaceae resistant to older agents (5). The older cephalosporins are preferred to treat Staphylococcus aureus and susceptible gram-negative organisms. In bone and joint infections caused by Staphylococcus aureus, nafcillin or a first-generation cephalosporin is preferred because both offer greater activity at lower cost. The newer cephalosporins may also replace the aminoglycosides to treat osteomyelitis or septic arthritis resulting from enterobacteriaceae that are resistant to the older cephalosporins, although the number of patients treated is relatively small (6,7). Since therapy in these cases lasts four or more weeks, the new cephalosporins offer a clear advantage over the more toxic aminoglycosides. However, these cephalosporins should not be used to treat Pseudomonas osteomyelitis, since many failures have been reported (4).

Lower respiratory infections. The third-generation cephalosporins are not indicated in the treatment of pneumococcal or staphylococcal pneumonia, as older antibiotics are less expensive and more effective. It is not known if the newer cephalosporins are better than ampicillin or trimethoprim sulfamethoxazole in treating Haemophilus influenzae pneumonia, but they may be useful against ampicillin-resistant Haemophilus. In community-acquired aspiration pneumonia, which is generally caused by anaerobic organisms, penicillin or clindamycin is the drug of choice. Third-generation cephalosporins have been successfully used as single agents to treat nosocomial pneumonias caused by gram-negative bacilli; however, they should not be used alone to treat Pseudomonas pneumonia (4).

Meningitis. The new cephalosporins are clearly superior to chloramphenicol, and to intrathecal and parenteral aminoglycosides to treat certain types of gram-negative meningitis (8-10). Cefotaxime or moxalactam is the drug of choice for meningitis caused by such gram-negative bacilli as E. coli, Klebsiella, or Proteus. The new cephalosporins may also be used instead of chloramphenicol for patients who have meningitis caused by H. influenzae resistant to ampicillin. Cefuroxime (11) and ceftriaxone (12) have been shown to be as effective as ampicillin and chloramphenicol to treat meningitis caused by H. influenzae, N. meningitidis, and S. pneumoniae. Cefotaxime also appears to be an excellent antibiotic to treat bacterial meningitis that results from susceptible organisms, but clinical experience is still limited (13). Cefoperazone may penetrate less well into the cerebrospinal fluid than other new cephalosporins (14).

The newer cephalosporins are not indicated in the following types of meningitis: 1) as single therapy for purulent meningitis in the neonate before the causative organism has been identified; they are not active against Listeria monocytogenes, which is a relatively frequent pathogen in this age group; 2) in Pseudomonas meningitis, where an aminoglycoside (intrathecal or intraventricular) and an anti-pseudomonal penicillin should be used; 3) in meningitis beyond the neonatal period and before an organism is identified, moxalactam should be avoided since it is insufficiently active against S. pneumoniae; 4) in meningococcal and pneumococcal meningitis, where penicillin remains the drug of choice.
Bacteremia and endocarditis. The third-generation cephalosporins have been used with good results in patients who have bacteremia caused by organisms which are resistant to the older cephalosporins and aminoglycosides. However, some failures have been reported with Pseudomonas, Enterobacter, Serratia, and Acinetobacter (4). They can be used as initial therapy in suspected bacteremia as long as the patient is not neutropenic and Pseudomonas is not a likely organism. In patients who are febrile and neutropenic, most authors agree that the initial therapy should consist of two antibiotics, generally a combination of an aminoglycoside with an anti-pseudomonas penicillin. Preliminary studies suggest that ceftazidime, a new cephalosporin with a broad spectrum of activity that includes Pseudomonas, may be a successful single agent for the initial therapy of febrile granulocytopenic patients (15). The new cephalosporins, particularly moxalactam, have been used in combination with an aminoglycoside or with ticarcillin, but further studies are needed to determine if these combinations are superior to currently used programs. The new cephalosporins are not useful in the treatment of endocarditis, as older agents are more active against the gram-positive organisms associated with this disease; in addition, failures have been reported in cases of Serratia and Pseudomonas endocarditis (4).

Abdominal and gynecologic infections. Some studies have found cefotaxime, moxalactam, and ceftizoxime, when used as single therapies for intra-abdominal and gynecologic infections, to be as effective as a combination of clindamycin and gentamicin (16-19). However, their use is still controversial, and many infectious diseases specialists prefer to use the standard combination therapy. Two problems with the usage of the third-generation cephalosporins to treat intra-abdominal infections have been the appearance of resistant organisms, usually Pseudomonas and Enterobacter, and superinfection with Enterococci.

Sexually transmitted diseases. The newer cephalosporins are very active against the gonococcus, but they should be used only in the treatment of penicillinase-producing Neisseria gonorrhoeae. Cefotaxime (single dose of 1 gm) and ceftriaxone (single dose of 250 mg IM) have been effective against penicillinase-producing Neisseria gonorrhoeae (4,20). These agents are not effective against Chlamydia or Ureaplasma organisms associated with non-gonococcal urethritis.

Surgical prophylaxis. The new cephalosporins are not indicated for surgical prophylaxis; they are no more effective than older, less expensive agents such as cefazolin. Two recent studies have shown no difference between cefotaxime and cefazolin in the prevention of infection after genitourinary or gynecological surgery (21,22).

Adverse reactions
In general, the newer cephalosporins are very safe drugs. Their adverse effects are similar to those seen with the older cephalosporins, except for two reactions: serious bleeding and a disulfiram-like reaction after alcohol ingestion. Bleeding has been associated mostly with moxalactam, which has an incidence rate of approximately 2.5%, usually a result of hypoprothrombinemia and, less frequently, platelet dysfunction. The manufacturers of moxalactam now recommend giving prophylactic vitamin K, 10 mg/week, to all patients using the drug, limiting the dose to 4 gm/day whenever possible, and monitoring the bleeding time if higher doses are given (23).

A disulfiram-like reaction after ingestion of alcohol has been reported with moxalactam, cefoperazone, and cefamandole. This reaction, like hypoprothrombinemia, appears to be related to the presence of a methylthiotetrazole group in position 3 of the dihydrothiazine ring of the three cephalosporins. The pathogenesis of the disulfiram reaction seems to be inhibition of the enzyme acetaldehyde dehydrogenase by the cephalosporin, resulting in the accumulation of toxic acetaldehyde (24).

Cost
One fact that limits the usefulness of the newer cephalosporins is their high cost. Table VI identifies the cost of the cephalosporins to the Henry Ford Hospital pharmacy. The daily cost for the maximum dose of cefazolin is only $19, as compared with $66-81 for second-
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Newer Penicillins

In vitro activity and pharmacology

The so-called fourth-generation penicillins include piperacillin, mezlocillin, and azlocillin (25). They have the advantage of being more active in vitro than ticarcillin and carbenicillin against many gram-negative organisms. They are frequently active against such ticarcillin-resistant bacteria as Klebsiella, Serratia and Citrobacter. Table VII compares the in vitro activity of the newer penicillins with that of ticarcillin (26,27). Piperacillin and azlocillin are four times more active than ticarcillin and mezlocillin against Pseudomonas aeruginosa. Piperacillin and mezlocillin have similar activity against most of the Enterobacteriaceae and are more active than ticarcillin, with azlocillin having intermediate activity. Unlike the cephalosporins, all the new penicillins are active against the Enterococci. They are also fairly active against Bacteroides fragilis, although high concentrations may be required to inhibit some strains. The new penicillins are also active against ampicillin-susceptible Haemophilus influenzae and gram-positive cocci, except for Staphylococcus aureus.

The pharmacology of the newer penicillins (Table VIII) is fairly similar to that of ticarcillin, with the advantage of a sodium content that is less than half that of ticarcillin.

Clinical indications

These newer agents are indicated in the treatment of infections caused by ticarcillin-resistant organisms. There is no evidence that they are superior to ticarcillin against infections due to ticarcillin-susceptible organisms. Because the newer penicillins are not bactericidal except at high concentrations, and because resistance is a definite potentiality during therapy, they should not be used alone but in combination with an aminoglycoside (25). These drugs, like ticarcillin and the third-generation cephalosporins, are not the drugs of choice for any gram-positive coccal infection.

Adverse reactions

The side effects of the new penicillins are similar to those reported with older, broad-spectrum penicillins and include allergic reactions, phlebitis, neutropenia, elevation of liver enzymes, and prolongation of bleeding time. Studies of a few volunteers have shown that mezlocillin and piperacillin have a less profound effect on bleeding time than ticarcillin or carbenicillin (28-30); however, the clinical importance of these results has not been established. The risk of fluid overload and hypokalemia may also be lower with these new penicillins, because their sodium content is less than that of ticarcillin. The clinical significance of this difference has not been determined either (31).

Cost

Although the difference in cost between the newer and older penicillins is not as much as that seen between the...
older and newer cephalosporins, the newer penicillins are still more expensive than ticarcillin (Table IX).

### TABLE IX
Cost of the New Penicillins at Henry Ford Hospital

<table>
<thead>
<tr>
<th></th>
<th>Cost per gm</th>
<th>gm/day</th>
<th>Daily Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticarcillin (Ticar)**</td>
<td>$2.27</td>
<td>18</td>
<td>$40.86</td>
</tr>
<tr>
<td>Mezlocillin (Mezlin)</td>
<td>3.15</td>
<td>18</td>
<td>56.70</td>
</tr>
<tr>
<td>Azlocillin (Azlin)</td>
<td>3.94</td>
<td>18</td>
<td>70.92</td>
</tr>
<tr>
<td>Piperacillin (Pipracil)</td>
<td>3.47</td>
<td>18</td>
<td>62.40</td>
</tr>
</tbody>
</table>

*Cost to Pharmacist
**HFH Formulary Agent

Netilmicin

A new aminoglycoside, netilmicin, is now available for clinical use in the United States. Netilmicin is the 1-ethyl derivative of sisomicin, an aminoglycoside related to gentamicin 1A. The ethyl group at the 1-amino position appears to protect netilmicin against the most common of the aminoglycoside inactivating enzymes, the 2'' adenyl transferase (Fig. 2). As a result, some gram-negative bacilli that are resistant to gentamicin and tobramycin may be susceptible to netilmicin. However, they are more likely to be susceptible to amikacin, which remains the aminoglycoside of choice when resistant organisms are common.

**Pharmacokinetics**

The pharmacokinetics of netilmicin are similar to that of gentamicin. The serum half-life in the adult with normal renal function is about 2.5 hours, with 80% eliminated unchanged in the urine. As with other aminoglycosides, the cerebrospinal fluid penetration is poor. The dosage of netilmicin is 4-6.5 mg/kg/day, slightly higher than that of gentamicin and tobramycin. Desirable peak and trough serum levels are 6-10 and 0.5-2 mcg/ml, respectively. As with all the aminoglycosides, the dose has to be adjusted in patients with decreased renal function.

**Clinical experience and toxicity**

Netilmicin appears to be as effective as tobramycin. In a recent collaborative study, netilmicin in combination with ticarcillin was as effective as tobramycin and ticarcillin in the treatment of 164 patients (32). Netilmicin has been found to be less ototoxic and nephrotoxic in animals than gentamicin and tobramycin, and the collaborative study (32) showed that there was significantly less ototoxicity in humans treated with netilmicin than with tobramycin. In this same study, nephrotoxicity was also less common with netilmicin, but the difference was not statistically significant. We are currently participating in a collaborative study to verify these results.

**Cost**

The cost of aminoglycosides is shown in Table X. At Henry Ford Hospital, generic gentamicin is about five to eight times less expensive than the other aminoglycosides.

### TABLE X
Cost of Aminoglycosides at Henry Ford Hospital

<table>
<thead>
<tr>
<th></th>
<th>Cost To Pharmacist</th>
<th>Usual Daily Dosage</th>
<th>Daily Cost for Maximum Dosage for 70 Kg/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin*</td>
<td>$0.87/80mg</td>
<td>3-5mg/kg</td>
<td>$3.80</td>
</tr>
<tr>
<td>Tobramycin*</td>
<td>5.42/80mg</td>
<td>3-5mg/kg</td>
<td>23.71</td>
</tr>
<tr>
<td>Amikacin*</td>
<td>15.17/500mg</td>
<td>15mg/kg</td>
<td>31.85</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>6.05/150mg</td>
<td>4-6.5mg/kg</td>
<td>18.35</td>
</tr>
</tbody>
</table>

*HFH Formulary Agent

**Investigational Antibiotics**

In addition to the newer antibiotics available commercially, there are a large number of agents under clinical investigation. Some of the investigational cephalosporins include: ceftriaxone, ceforanide, ceftazidime, and cefsulodin (4). Ceftriaxone is the cephalosporin with the most prolonged half-life (8 hours).
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permitting every 12- or even 24-hour doses. It has been used successfully in meningitis caused by H. influenzae, S. pneumoniae, and N. meningitidis. Ceforanide is a first-generation cephalosporin with a prolonged half-life of three hours, but its spectrum of activity is narrower than that of ceftriaxone. Ceftazidime has the best activity against Pseudomonas aeruginosa, and cefsulodin is active against pseudomonas and only moderately so against Staphylococcus aureus.

In addition to the cephalosporins, other investigational beta-lactam compounds include thienamycin (primaxin), the monobactams, and clavulanic acid. Thienamycin is a very promising antibiotic. It has the widest in vitro spectrum of all the antimicrobials, as that of the third-generation cephalosporins, and in addition, it is active against Streptococcus faecalis, methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter. In contrast to the penicillins and cephalosporins, the monobactams (eg, azthreonam) have a structural formula consisting of only one ring, the beta-lactam ring. They are active only against aerobic gram-negative bacilli. A new concept of antimicrobial combination is clavulanic acid with amoxicillin or ticarcillin. Although clavulanic acid is a beta-lactam compound with poor intrinsic activity, it permits the antibacterial action of amoxicillin or ticarcillin by inhibiting the beta-lactamase.

There are of course many other investigational antimicrobials, but a complete review of them is beyond the scope of this paper. Some of the new drugs will be a welcome replacement to less active antibiotics and more toxic aminoglycosides. However, their appearance on the market will make the selection of antibiotics even more difficult for the practicing physician and, unless used judiciously, may cause greater expense.

Addendum
Since this manuscript was submitted for publication, ceforanide (Precef) and the combination of clavulanic acid and amoxicillin (Augmentin) have been introduced on the market in the United States.

References


