Piperacillin/Tazobactam: A Critical Review of the Evolving Clinical Literature

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Piperacillin/tazobactam is the most recently approved combination of a β-lactam agent with an inhibitor of bacterial β-lactamases. It has a broader spectrum than do preceding inhibitor-drug combinations, and it is generally more potent. In terms of clinical and microbiological outcomes, comparative studies have shown that piperacillin/tazobactam was comparable to imipenem (1.0 g q8h) and to clindamycin plus gentamicin for intraabdominal infections, to clindamycin plus gentamicin for infections of the skin and skin structures and pelvic tissues in women, and to ticarcillin/clavulanate for skin and soft-tissue infections. Piperacillin/tazobactam was statistically superior to imipenem (0.5 g q8h) for intraabdominal infections, to ticarcillin/clavulanate for community-acquired lower respiratory tract infections, and to ceftazidime for nosocomial lower respiratory tract infections and febrile episodes in neutropenic patients. Adverse effects with piperacillin/tazobactam were generally of only mild-to-moderate severity. Piperacillin/tazobactam may be especially useful for the treatment of infections that are likely to be polymicrobial or to be due to any one of an array of aerobic or anaerobic bacteria; this agent may also be useful in situations where organisms with plasmid-mediated β-lactamases have become problematic.

Overview of the Antimicrobial Properties and Pharmacology of Piperacillin/Tazobactam

A number of factors influence the spectrum and potency of combinations containing a β-lactam antibiotic and a β-lactamase inhibitor [1]. One important factor is the potency of the β-lactam antibiotic in the combination; in general, when the antibiotic has greater potency, less protection from a β-lactamase inhibitor is needed for the antibiotic [2] because fewer drug molecules are needed for optimal activity. Overall, piperacillin is a more potent β-lactam antibiotic than are the carboxypenicillins, and it has a broader antimicrobial spectrum than do the aminopenicillins [3, 4]. A second factor influencing spectrum and potency of inhibitor-drug combinations is the potency of the inhibitor. In general, tazobactam and clavulanic acid are more potent inhibitors of plasmid-mediated β-lactamases than is sulbactam, while tazobactam and sulbactam are more potent inhibitors of chromosomally-mediated β-lactamases than is clavulanic acid [5–10]. However, it should be noted that studies of the in vitro potency of an inhibitor of isolated β-lactamases often do not correctly predict the potency of inhibitor-drug combinations because the relative concentrations of enzyme and inhibitor in such studies may not be similar to those encountered in situ (i.e., in the intact, viable bacterial cell). Furthermore, other factors such as the potency of the β-lactam drug itself and the pharmacokinetics of each component have a greater impact on the potency of the inhibitor-drug combination.

On the basis of these factors, it is not surprising that piperacillin/tazobactam possesses a broader spectrum of activity than do older combinations of a β-lactam agent with a β-lactamase...
inhibitor and that this combination is also as potent or more potent than its predecessors [1, 8, 11-13]. Piperacillin/tazobactam is highly active against gram-positive bacteria, including strains that produce \( \beta \)-lactamase. Its spectrum of activity against these organisms is comparable to that of ampicillin/subactam and is broader than that of ticarcillin/clavulanate, especially against staphylococci and enterococci. None of these agents is active against methicillin-resistant staphylococci. Piperacillin/tazobactam inhibits a wide spectrum of both fastidious and nonfastidious gram-negative bacilli, including *Pseudomonas aeruginosa*. It inhibits significantly more strains of these organisms than does ticarcillin/clavulanate or ampicillin/subactam, which is inactive against *Pseudomonas* species. That the activity of piperacillin/tazobactam is broader than that of ticarcillin/clavulanate against gram-negative isolates relates not only to piperacillin’s intrinsic potency, which is greater than that of ticarcillin, but also to the fact that tazobactam does not induce the Bush group 1 \( \beta \)-lactamase, whereas clavulanic acid has the potential to induce this enzyme [1, 14, 15]. Piperacillin/tazobactam inhibits a broader spectrum of anaerobes than does ampicillin/subactam or ticarcillin/clavulanate [8, 13].

Potency of activity has been evaluated for strains susceptible to each of the parenteral \( \beta \)-lactam/\( \beta \)-lactamase inhibitor combinations. In general, piperacillin/tazobactam is more potent than ticarcillin/clavulanate and is equivalent in potency to ampicillin/subactam against gram-positive isolates [8, 11, 12]. It is frequently more potent (and rarely less potent) than either of the older combinations against facultative gram-negative bacilli and obligate anaerobes [8, 11–13].

The pharmacokinetics of piperacillin and tazobactam, alone and in combination, have been studied extensively by investigators in the United States and abroad. The numerous publications have been reviewed recently by Sorgel and Kinzig [16, 17] and by Bryson and Brogden [18]. The reader is referred to these reviews for more detail and citations of the original literature. In general, the pharmacokinetics of piperacillin and tazobactam are similar; both drugs behave nearly identically alone or in combination. The pharmacokinetics of tazobactam are characteristic of a \( \beta \)-lactam compound, with typical tissue penetration and distribution primarily into extracellular spaces. The protein binding of both molecules is \( \sim 20\%\)–30\%. Both are excreted by renal mechanisms. The tubular secretion of tazobactam is inhibited somewhat by piperacillin, but this is of little consequence clinically.

Renal failure compromises the elimination of both molecules; therefore, the dosage of the combination (rather than the individual components) should be adjusted, even though the elimination of tazobactam is impaired to a greater extent than is that of piperacillin. It has been suggested that the dosing interval be extended by 2 hours for creatinine clearances that range between 20 mL/min and 40 mL/min and by 4 hours for creatinine clearances of <20 mL/min [16]. The manufacturer (Lederle Laboratories, Pearl River, NY) recommends that the dosage be reduced by one-third for patients with moderate renal impairment and by one-half, with an increase in the dosing interval of 2 hours, for those with severe impairment. Renal clearance of this combination is diminished by \( \sim 25\%\) in the elderly; however, in the absence of renal disease, dosage adjustment is seldom necessary. Hepatic disease has little effect on the elimination of piperacillin/tazobactam.

The amount of inhibitor that can be delivered to the site of infection is an important determinant of the activity of \( \beta \)-lactamase inhibitor/\( \beta \)-lactam drug combinations. The importance of this factor in determining overall activity can be illustrated in a direct comparison of ticarcillin/clavulanate with piperacillin/tazobactam. The usual dose of ticarcillin/clavulanate is 3.1 g (3 g of ticarcillin and 0.1 g of clavulanate) administered every 4–6 hours [19]. The usual dose of piperacillin/tazobactam is 3.375 g (3 g of piperacillin and 0.375 g of tazobactam) administered every 6 hours [20]. These dosage regimens result in higher levels of tazobactam than clavulanic acid over the dosing interval (figure 1). These differences are taken into account when routine susceptibility tests are performed: ticarcillin/clavulanate is tested with the inhibitor at a constant concentration of 2 \( \mu \)g/mL, while piperacillin/tazobactam is tested with the inhibitor at a constant concentration of 4 \( \mu \)g/mL [19–22].

When susceptibility tests are performed in a manner that takes into account the differences in pharmacokinetics between the two \( \beta \)-lactamase inhibitor/\( \beta \)-lactam drug combinations, great differences in activity are observed [11, 23–27]. These differences in activity are most apparent when data collected on strains resistant to the \( \beta \)-lactam drug alone are considered. As shown in figure 2, when differences in pharmacokinetics were factored into the method used for susceptibility testing of piperacillin-resistant Enterobacteriaceae, the activity of pip-

![Figure 1. Pharmacokinetics of tazobactam and clavulanic acid. Serum levels of clavulanic acid (solid line) in adults after a 30-minute intravenous infusion of 3.1 g of ticarcillin/clavulanate (0.1 g of clavulanate). Plasma levels of tazobactam (dashed line) in adults after a 30-minute intravenous infusion of 3.375 g of piperacillin/tazobactam (0.375 g of tazobactam). Data are from [19] and [20].](image-url)
eracillin/tazobactam exceeded that of ticarcillin/clavulanate by fourfold or more against 121 (80%) of 152 strains [27]. In addition, 42 (28%) of the strains were resistant to ticarcillin/clavulanate but susceptible to piperacillin/tazobactam. Data are from [27].

Methods Used in Clinical Studies

Nearly all of the studies on piperacillin/tazobactam that have been published to date were performed for purposes of licensing and registration. Most closely followed the guidelines of the U.S. Food and Drug Administration (FDA) and International Boards of Health for clinical trials. In a comparative study of two regimens, it was required that infecting microorganisms be susceptible to both regimens. This requirement potentially impedes demonstration of an advantage of a new agent, such as piperacillin/tazobactam, when it is active against organisms that are resistant to the most nearly comparable older agents. In spite of this requirement, a number of significant differences have emerged in comparative clinical trials.

Criteria for diagnoses and exclusions were relatively uniform and consistent with FDA guidelines. For example, the diagnosis of pneumonia almost always required documentation by chest roentgenography in association with typical signs and symptoms such as fever, purulent sputum, and abnormal WBC counts. Many studies, but not all, required gram staining or other stains of sputum to validate the appropriateness of the specimen for culture. Cultures and susceptibility testing were done routinely. Many studies of lower respiratory tract infection included patients with purulent bronchitis, which was defined by presence of acute symptoms, a pyogenic response in sputum, and minimal or no changes on the chest roentgenogram. Cultures were performed for nearly all of these patients. Data on pneumonia and bronchitis were usually analyzed separately as well as collectively. Patients with intraabdominal infections usually had appendicitis with the accumulation of cloudy fluid locally and a positive culture, peritonitis (confirmed by culture), or intraabdominal abscesses.

Skin and soft-tissue diseases included in these trials were cellulitis, abscesses, infections of posttraumatic and postsurgical wounds, decubiti, and diabetic foot ulcers. Cultures were required, but the nature of the specimen obtained was not always clearly stated. In some studies, but not all, surgical debridement was performed, and data were analyzed to include this as a confounding variable. Gynecologic studies usually included otherwise healthy women with vaginal cuff cellulitis, tubo-ovarian abscesses, and pelvic soft-tissue infections. Cultures were obtained, but identification of a presumptive pathogen was not always required for inclusion or evaluability. For studies of urinary tract infections, typical signs and symptoms plus a positive culture that yielded significant numbers of organisms (appropriate for the collection method used) were required.

Exclusion criteria were consistent from study to study and included, among other factors, tuberculosis, AIDS, severe granulocytopenia or other profoundly immunocompromising states, terminal illnesses, profound hepatic or renal disease, advanced malignancies, recent antimicrobial therapy, and recent participation in a clinical trial. Criteria for outcomes (cure, clinical improvement, and treatment failure) were almost always consistent with FDA guidelines. Marked deviations from usual definitions and criteria will be indicated in the descriptions of the trials that follow.

Intervals of follow-up varied from study to study, as did the criteria for an end-point determination of outcome. The majority of investigators specified times for early, late, and end-point determinations; some separately analyzed outcomes at each interval, while others focused on one interval, excluding the remainder. In the analysis that follows, endpoint determinations are considered wherever possible; otherwise, data from the last follow-up examination are used. Also, the terms “successful” or “favorable”, as applied to clinical outcomes, refer to the sum of “cure” and “improved” results.

The greatest variability between studies was found in analysis of therapeutic failures and adverse events. Definitions and terminology differed in descriptions of apparent failure to permanently eradicate the presumed pathogen (such failure was often referred to as frank therapeutic failure, relapse, persistence, colonization, or reinfection). Definitions of relapse, superinfection, or new infection also varied or overlapped. In the setting of persistence or apparent reappearance of the pre-
sumed pathogen, there was seldom an attempt to determine if the sequentially isolated strains were genetically or antigenically identical or if resistance had emerged in subsequent isolates. Some authors simply listed the numbers and percentages of therapeutic failures without providing analysis of the probable causes.

There was also great variability in presentation of data on adverse experiences. Some investigators described adverse experiences by organ system involved; others specifically identified almost every abnormality, while others described only those reactions that occurred in excess of 1% of patients or that differed statistically from those observed for the comparative agent. Finally, a minority of reports clearly defined the presumed relationship of therapy to an adverse experience (e.g., "remotely," "possibly," "probably," or "definitely related"), and even fewer specified the degree of relationship required for inclusion in the analysis actually presented. Despite these inconsistencies and the limitations of some of the diagnostic criteria, a relatively clear profile of the clinical utility of piperacillin/tazobactam is emerging. The clinical and microbiological outcomes in various clinical trials are presented in table 1.

**Clinical and Bacteriological Efficacy of Piperacillin/Tazobactam**

*Lower respiratory tract infections.* The efficacy of piperacillin/tazobactam has been evaluated by four groups of investigators (table 1). Mouton and associates [42] performed an open, noncomparative study of monotherapy with this combination at 36 sites in six countries. Patients with severe respiratory disease and infection due to *P. aeruginosa*, as well as those who met the usual exclusionary criteria, were not enrolled. Approximately one-half of infections were community acquired. The most common diagnosis was pneumonia, followed by bronchitis and bronchopneumonia. Patients with lower respiratory symptoms and normal findings on chest roentgenograms were included and categorized as having "bronchitis." Two hundred-thirty patients were enrolled to receive iv piperacillin/tazobactam (4/0.5 g q8h). Of these patients, 133 (58%) were evaluable for clinical response and 106 (46%) were evaluable for bacteriologic outcome.

Clinical cure or improvement was noted for 96% of patients, and bacteriologic eradication was noted for 93%. Outcomes did not differ significantly for the patients with bronchitis and those with pneumonia. Of 142 presumed pathogens isolated, 15 were resistant to piperacillin but susceptible to piperacillin/tazobactam, and all of these 15 were eradicated early in the course of therapy. One instance of late reappearance of *Staphylococcus aureus*, apparently without evidence of clinical relapse, was recorded. This study contributed results for relatively large numbers of patients to the database on efficacy and safety. The limitations of this study included the lack of comparative data, the relatively large numbers of patients deemed nonevaluable—especially because of inadequate or supplemented regimens and missed visits—the lack of a combination therapy arm, and prudent exclusion of infection due to *P. aeruginosa* as well as advanced infections in critically ill patients.

Smith [43] described an open, prospective trial of piperacillin/tazobactam plus amikacin performed in 22 hospitals in France. Seventy-one patients receiving intensive care for severe lower respiratory tract infections were enrolled. Diagnostic criteria included fever, leukocytosis, pulmonary infiltrates, arterial oxygen desaturation, and the need for ventilatory assistance. Patients were given iv piperacillin/tazobactam (4/0.5 g q6h) plus iv amikacin (7.5 mg/kg q12h), with dosage adjustment based on drug serum levels. Therapy with amikacin was discontinued promptly if the infecting organism was resistant or was identified as belonging to a genus other than *Enterobacter* or *Serratia*. Treatment was given for a minimum of 5 days and for 48 hours after resolution of signs and symptoms of infection. Clinical failure was defined as lack of response in the first 3 days of treatment.

At the end point, 48% of patients were evaluable clinically and 38% were evaluable microbiologically. Clinical cure was observed for 74% of patients; microbiological eradication occurred in 70%. Analysis of outcome by presumed pathogen (44 isolates from 27 patients) revealed eradication rates of 92% for all organisms and 78% for *P. aeruginosa*, which constituted 34% of total isolates. The results of this study indicated the potential usefulness of piperacillin/tazobactam plus an aminoglycoside for serious lower respiratory tract infections, including those due to *Pseudomonas* species. Potential limitations of the trial were its noncomparative design, the lack of clearly described criteria for an etiologic diagnosis, and overlapping or inconsistent clinical diagnoses.

Shlaes and co-workers [40] described a double-blinded, comparative trial in patients with community-acquired pneumonia which was performed at 15 centers in the United States and 4 centers in Canada (table 1). Patients were randomized in a 3:2 ratio to receive iv piperacillin/tazobactam (3/0.375 g q6h) or iv ticarcillin/clavulanate (3/0.1 g q6h) for a minimum of 5 days. Diagnostic and exclusionary criteria were as described above. It was required that findings in a gram stain of an appropriate specimen be consistent with a bacterial etiology. A total of 299 patients with pneumonia or acute purulent bronchitis were enrolled. Demographics, diagnoses, and the nature of comorbid diseases were similar for the two treatment groups. A favorable clinical outcome at the end point was observed for 84% of evaluable patients in the piperacillin/tazobactam group and 64% of evaluable patients in the ticarcillin/clavulanate group (*P < .01*). Intent-to-treat analysis confirmed the significant difference in clinical outcome at endpoint. Bacteriologic response rates (eradication documented or presumed) were identical to clinical response rates (84% for piperacillin/tazobactam and 64% for ticarcillin/clavulanate [*P = .02*]).

Shlaes et al. analyzed their data retrospectively in an attempt to explain the greater success with piperacillin/tazobactam. No apparent specific differences in patient characteristics, etiologic agents, or disease severity were found. All isolates were ini-
tially susceptible to both regimens. Analysis of responses by pathogen revealed no differences in outcome when the infecting organism was *Haemophilus influenzae* or *Streptococcus pneumoniae*; however, response rates for infections due to other pathogens were 84% with piperacillin/tazobactam and 57% with ticarcillin/clavulanate (*P* = .06). Differences in response rates were pronounced with *Moraxella catarrhalis* and gram-negative bacilli (primarily the Enterobacteriaceae), but statistical significance was reached only when all organisms were considered collectively. It is of interest that neither combination was especially effective for infections due to *S. aureus*, despite in vitro susceptibility of the organism. The authors contend that this relatively poor response is frequently seen “regardless of the antimicrobial agent used.”

Joshi and co-workers [41] reported the results of a randomized, multicenter trial that compared iv piperacillin/tazobactam (3/0.375 g q4h) with iv ceftazidime (2 g q8h) in patients with hospital-acquired lower respiratory tract infections. All patients also received iv tobramycin (5 mg/ [kg · d]) in three divided doses to provide coverage for possible *P. aeruginosa* infection. The aminoglycoside was switched to iv amikacin (15 mg/ [kg · d]) if the *Pseudomonas* isolate was resistant to tobramycin. Tobramycin therapy was discontinued if no *Pseudomonas* species was isolated. Treatment was continued for at least 5 days, and preferably, until 48 hours after resolution of signs and symptoms of infection.

Patients with acute purulent bronchitis or acute bacterial pneumonia were eligible for this study. The usual exclusionary criteria, including initial resistance to either of the comparative regimens, were applied. Three hundred patients were enrolled, of which 40%–50% were evaluable (i.e., for varying outcomes: microbiological, clinical, or for adverse events). Demographics were comparable in the two groups. A significantly larger number of patients in the ceftazidime group had bronchitis (*P* ≤ .01), which might have introduced a bias in favor of the ceftazidime regimen because the illness was less severe and rapid response to antimicrobial therapy was expected. However, this was not the case; clinical outcome was significantly better for the patients treated with piperacillin/tazobactam at early, late, and end-point analyses. Favorable outcome at the end point was observed for 74% and 50% of patients treated with piperacillin/tazobactam and ceftazidime, respectively (*P* = .< .01).

Similar differences were observed for bacteriologic outcomes: 66% and 38% of the patients had presumed or documented eradication, respectively, at the end point. Analysis of outcomes by pathogen suggested that piperacillin/tazobactam was more effective than ceftazidime in eradicating *H. influenzae* (100% of infections vs. 50%, respectively), *S. aureus* (69% vs. 34%), and *P. aeruginosa* (66% vs. 30%). However, only the difference observed for *H. influenzae* was statistically significant (*P* ≤ .01). The differences in initial diagnosis (bronchitis vs. pneumonia) appeared to have had no positive or negative impact on outcome of therapy with either regimen.

**Intraabdominal infections.** Three groups of investigators have reported the outcome of comparative trials in patients with intraabdominal infections, and one group has reported the results of a noncomparative trial in such patients (table 1). Vestweber and Grundel [32] described results of a noncomparative trial conducted at 21 centers throughout Europe. One hundred fifty-five patients were treated with iv piperacillin/tazobactam (4/0.5 g q8h for 5–10 days) in addition to surgery (usually drainage), as appropriate. Major diagnoses were peritonitis, abscess, complicated appendicitis, and cholecystitis. Cultures yielded mixed bacterial flora in nearly all cases. Approximately two-thirds of patients were evaluable. Favorable clinical and bacteriologic outcomes were observed for 87% and 90% of patients, respectively. This study clearly documented the efficacy of piperacillin/tazobactam, although few details were given regarding therapeutic failures or adverse events. The relative paucity of anaerobic isolates was not explained.

Ekblund and colleagues [28] and Brismar et al. [29] have reported the results of an open trial of piperacillin/tazobactam vs. imipenem/cilastatin for severe intraabdominal infections that was conducted at six centers in Sweden. One hundred thirty-four patients were enrolled, of which 75%–89% were evaluable in terms of outcome. Patients were randomized to receive iv piperacillin/tazobactam (4/0.5 g q8h) or iv imipenem/cilastatin (0.5 g of each drug q8h) for at least 3 (not to exceed 14) days. Culture specimens were obtained at laparotomy or by puncture of an abscess before therapy was initiated. Approximately one-half of the patients had complicated appendicitis, one-third had peritonitis, and the balance had intraabdominal abscesses.

Piperacillin/tazobactam was found to be superior to imipenem/cilastatin on the basis of every analysis of outcome performed. Clinical cure or improvement was observed for 93% of patients treated with piperacillin/tazobactam and 69% of those treated with imipenem/cilastatin (*P* = .001). Relapse or treatment failures were noted for only four patients who received piperacillin/tazobactam, while relapse or treatment failures were noted for 18 who received imipenem/cilastatin (*P* = .005). Results of analysis of microbiological cure or improvement were similar. Eradication rates were 93% in the piperacillin/tazobactam group and 76% in the imipenem/cilastatin group (*P* = .029), and superinfections, reinfections, and bacterial persistence were noted more frequently in the imipenem/cilastatin group than in the piperacillin/tazobactam group (25% vs. 7%, respectively; *P* = .036). No emergence of resistance was observed.

This study was performed with care: rates of evaluability were high, and the results were interpreted cautiously. Although concern has been expressed by some investigators with regard to the lower dose of imipenem/cilastatin used in this study, this dose is usual in Sweden [28, 29] and is commonly used in the United States (see discussion below).

Niinikoski and associates [30] reported results of a five-center, open label, parallel group comparative trial conducted in Finland. Patients were randomized to receive iv piperacillin/tazobactam (4/0.5 g q8h) or a higher dose of imipenem/cilastatin than that reported above (1 g of imipenem and 1 g of
Table 1. Clinical and bacteriologic outcomes in trials of piperacillin/tazobactam.

<table>
<thead>
<tr>
<th>Site or type of infection, study design [reference]</th>
<th>Regimens</th>
<th>No. of patients enrolled</th>
<th>Clinical outcome</th>
<th>Bacteriologic outcome</th>
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<tr>
<td></td>
<td></td>
<td>No. evaluable (%)</td>
<td>Percent favorable (%)</td>
<td>Percent unfavorable (%)</td>
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<tr>
<td>Intraabdominal</td>
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<tr>
<td>Comparative</td>
<td>[28]</td>
<td>Pip/Taz (4/0.5 g q8h); 69</td>
<td>55 (80)</td>
<td>93</td>
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<td></td>
<td>[29]</td>
<td>Imi (0.5 g q8h); 65</td>
<td>58 (89)</td>
<td>69</td>
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<td></td>
<td>[30]</td>
<td>Pip/Taz (4/0.5 g q8h); 47</td>
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<td>77</td>
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<td></td>
<td>[31]</td>
<td>Pip/Taz (3/0.375 g q6h); 39</td>
<td>29 (74)</td>
<td>73</td>
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<tr>
<td>Noncomparative</td>
<td>[32]</td>
<td>Pip/Taz (4/0.5 g q8h) 155</td>
<td>106 (68)</td>
<td>87</td>
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<td>Skin and skin structure</td>
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<td>Comparative</td>
<td>[33]</td>
<td>Pip/Taz (3/0.375 g q6h); Tic/CA (3/0.100 g q6h) 153</td>
<td>67 (44)</td>
<td>76</td>
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<tr>
<td>Noncomparative</td>
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<td>Pip/Taz (4/0.5 g q8h) 136</td>
<td>120 (88)§</td>
<td>93</td>
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<td></td>
<td>[35]</td>
<td>Pip/Taz (4/0.5 g q8h [severe] or 2/0.25 g q8h [moderately severe]) 132</td>
<td>129 (98)§</td>
<td>95</td>
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<td>Pelvic infection in women</td>
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<td>Comparative</td>
<td>[37]</td>
<td>Pip/Taz (3/0.375 g q6h); Cm (0.9 g q8h) + Gm (2.5 mg/ [kg·d], divided) 196</td>
<td>86 (44)</td>
<td>78</td>
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<tr>
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<td>Pip/Taz (4/0.5 g q8h) 25</td>
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<td>[39]</td>
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<td>84</td>
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<td></td>
<td>[41]</td>
<td>Pip/Taz (3/0.375 g q4h) + Tm (5.0 mg/ [kg·d] divided q8h) or Amik (15 mg/ [kg·d] divided q8h) if resistant to Tm; Czid (2 g q8h) plus Tm (5.0 mg/[kg·d] divided q8h) or Amik (15 mg/ [kg·d]) 155</td>
<td>78 (50)</td>
<td>74</td>
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<tr>
<td>Noncomparative</td>
<td>[42]</td>
<td>Pip/Taz (4/0.5 g q8h) 230</td>
<td>133 (58)</td>
<td>96</td>
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<td></td>
<td>[43]</td>
<td>Pip/Taz (4/0.5 g q6h) + Amik (7.5 mg/kg q12h) 71</td>
<td>34 (48)</td>
<td>74</td>
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A North American multicenter trial compared piperacillin/tazobactam to clindamycin plus gentamicin among 331 patients with a representative spectrum of intraabdominal infections [31, 47]. Patients were randomized in a 2:1 ratio either to receive IV piperacillin/tazobactam (3/0.375 g q6h) or IV clindamycin (0.6 g q6h) plus IV gentamicin (2–5 mg/[kg·d]) in divided doses that were adjusted initially on the basis of renal function and then according to serum drug levels. Thirty-eight percent of patients in the clindamycin/gentamicin group and 48% in the piperacillin/tazobactam group were evaluable. The commonest cause for nonevaluability was failure to isolate a pathogen at baseline. There were more exclusions because of initial pathogen resistance in the clindamycin/gentamicin group. The majority of resistant isolates were enterococci. Clinical response rates at the end point were 88% and 77% for the piperacillin/tazobactam and clindamycin/gentamicin groups, respectively, and microbiological eradication rates were 86% and 75%, respectively. The rates were similar at early and late follow-up. Eradication rates for specific genera paralleled those for all organisms considered collectively. None of these differences were statistically significant. Polymicrobial and monomicrobial infections responded equally well. Therapeutic success was documented for 10 of 11 patients infected with organisms that were resistant to piperacillin but susceptible to piperacillin/

cilastatin q8h) for at least 3 days and, preferably, for 48 hours after resolution of signs and symptoms. Eighty-six patients with characteristic intraabdominal infections were enrolled (~50% had peritonitis, 40% had appendicitis or cholecystitis, and 4%–10% had abscesses). Of these, 64%–67% were evaluable clinically and 21% to 23% were evaluable microbiologically. Approximately 20% of patients were excluded because of initial resistance of their bacterial isolates; these patients were distributed equally between the two treatment groups. The demographics were similar in the two groups, except that patients in the imipenem/cilastatin group were older and weighed more.

Satisfactory clinical outcomes were noted for 87% of patients treated with piperacillin/tazobactam and 73% of patients treated with imipenem/cilastatin; satisfactory microbiological outcomes were noted for 100% and 89% of the patients, respectively. Eradication rates for the pathogens, considered individually and collectively, were similar for the two regimens. None of the differences observed at early and late follow-up or at endpoint were statistically significant. The authors provided a thoughtful, detailed analysis of outcomes and treatment failures. The limitations of the trial were the relatively small numbers of patients included, the low rate of bacteriologic evalability, and exclusion of the most severely ill (septic, hypoxemic) patients.

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Site or type of infection, study design [reference]</th>
<th>Regimens</th>
<th>No. of patients enrolled</th>
<th>No. evaluable (%)</th>
<th>Percent favorable</th>
<th>Percent unfavorable</th>
<th>Clinical outcome</th>
<th>No. evaluable (%)</th>
<th>Percent cured</th>
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<tr>
<td>Urinary tract</td>
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<tr>
<td>Noncomparative [44]</td>
<td>Pip/Taz (4/0.5 g q8h) 217</td>
<td>134 (62)</td>
<td>86</td>
<td>14</td>
<td>...</td>
<td>112 (52)</td>
<td>73</td>
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<td>Bacteremia</td>
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<tr>
<td>Noncomparative [45]</td>
<td>Pip/Taz (4/0.5 g q6–8h [severe] or 2/0.5 g q8h [less severe]) ± an aminoglycoside 142</td>
<td>73 (51)</td>
<td>91</td>
<td>8</td>
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<td>55 (39)</td>
<td>91</td>
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<td>Osteomyelitis</td>
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<tr>
<td>Noncomparative [35]</td>
<td>Pip/Taz (4/0.5 g q8h) 34</td>
<td>32 (94)</td>
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<td>0</td>
<td>...</td>
<td>27 (79)</td>
<td>89</td>
<td>11</td>
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<td>Mixed (ICU-acquired)</td>
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<tr>
<td>Noncomparative [46]</td>
<td>Pip/Taz (4/0.5 g q8h) ± Amik (7.5 mg/kg q2h) ND 21</td>
<td>95</td>
<td>5</td>
<td>...</td>
<td>21</td>
<td>86</td>
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NOTE. Amik = amikacin; Cm = clindamycin; Czid = ceftazidime; Gm = gentamicin; ICU = intensive care unit; Imi = imipenem; Pip/Taz = piperacillin/tazobactam; Tic/CA = ticarcillin/clavulanate; Tm = tobramycin; ND = not done; NS = not significant; ± = with or without agent.

* χ² test.
† Wilcoxon rank sum test.
‡ Fisher’s exact test.
§ Patients infected with *S. aureus* only.
|| Early follow-up.
** Late follow-up.

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CID 1996;22 (January)  
Piperacillin/Tazobactam  
113
tazobactam. The authors of this study were especially thorough in their analysis of outcomes, treatment failures, and costs.

Skin and soft-tissue infections. There have been four reports of therapeutic trials in patients with infections of skin and contiguous structures; three were noncomparative and one was comparative. Tassler et al. [34] described an open, multicenter trial of iv piperacillin/tazobactam (4 g of piperacillin and 0.5 g of tazobactam q8h) conducted in four European countries. One hundred thirty-six patients were enrolled, of which 120 were evaluable. Diagnoses included wound infections (58 patients), cellulitis (36), cutaneous abscesses (16), infections of ischemic and diabetic ulcers (11) and others. Forty-three percent of patients were infected by more than one organism. The drug was administered for a mean of 8 days. Approximately 58% of patients underwent concomitant surgery, usually debridement. Patients were evaluated 1–3 and 10–14 days after therapy was discontinued. Clinical cure or improvement was observed for 93% of patients at both early and late follow-up, and bacteriologic eradication was achieved for 85% and 95% of patients at early and late follow-up, respectively. Cure rates tended to be higher among patients who had undergone surgery and had received antimicrobial therapy early in the course of the infection. The authors commented that their results were comparable to those obtained with other broad spectrum β-lactam agents. The results of this study were analyzed thoroughly; however, a possible limitation was the decline in the number of patients who were evaluable between early and late follow-up.

Tassler [35] then reported the results of a cooperative, multicenter, open study conducted in Germany. One hundred thirty-two patients were enrolled. Diagnoses included cellulitis (63 patients), wound infection (62), perirectal abscess (14), diabetic foot infection (9), erysipelas (5), and others (14). Many of the infections were serious and potentially life-threatening; over one-half were polymicrobial. Patients with infections judged to be moderately severe were given iv piperacillin/tazobactam (2/0.5 g q6h) and those with more-severe illnesses were given a higher dose (4/0.5 g q8h). Treatment was continued for a mean duration of 1 week. Evaluations were performed 1–3 days and 10–14 days after treatment was discontinued. Clinical success rates were 95% and 92% at early and late follow-up, respectively, and microbiological success rates were 79% and 89% at early and late follow-up, respectively. The strengths of this study were inclusion of a large number of seriously ill patients with polymicrobial infections and the fact that an extensive bacteriologic analysis was performed. There was no breakdown of results according to severity of illness or by the two dosage regimens. However, given the high success rates, it is unlikely that important differences would have emerged.

Gould and associates [36] treated 25 consecutive cases of cellulitis (five were associated with abscesses) in patients in Aberdeen, Scotland. Fourteen of the 25 patients had failed to respond to previous oral antimicrobial therapy. Enrollees were given iv piperacillin/tazobactam (4/0.5 g q8h) for a mean duration of 1 week. The abscesses were drained surgically. Clinical success was achieved in two-thirds to three-quarters of the cases, depending on evaluable criteria used [34, 36]. Analysis of bacteriologic outcomes was not presented, and treatment failures were analyzed on a case-by-case basis (see below).

Tan and associates [33] reported the outcome of a double-blind comparative study performed in 20 centers in the United States. Two hundred fifty-one patients were hospitalized for complicated skin and soft-tissue infections. Approximately one-half of the infections were considered to be severe by blinded investigators and over three-quarters required adjunctive surgery. Patients with severe underlying disease or infection elsewhere in the body were excluded. Enrollees were randomized in a 3:2 ratio to receive either iv piperacillin/tazobactam (3/0.375 g q6h) or iv ticarcillin/clavulanate (3/0.1 g q6h) for a minimum of 5 days and at least 48 hours after resolution of all signs and symptoms of illness. Less than one-half of cases were evaluable; this circumstance was primarily due to the inability to isolate a pathogen, especially in a large number of cases of cellulitis in which there was no drainage or obvious fluid collection.

Clinical success was noted for 76% of patients treated with piperacillin/tazobactam and 77% of patients treated with ticarcillin/clavulanate, respectively. Rates were highest (>90%) for patients with abscesses, intermediate for patients with cellulitis, and lowest (59%–67%) for patients with infected feet. Cases in which bacteriologic success (eradication) was achieved were presented only for those patients infected with S. aureus (table 1). Bacteriologic success rates were presented by specific organism; collective eradication rates were 76% and 83% for piperacillin/tazobactam and ticarcillin/clavulanate, respectively. None of the differences in clinical or microbiologic outcomes were statistically significant. For purposes of registration, it was required that amputation (even after abatement or resolution of infection) and changes in antimicrobial regimen (even to oral therapy to facilitate early discharge from the hospital) be equated with clinical failure. This led the investigators to assess outcomes subjectively rather than on the basis of these arbitrary definitions of failure and to present a revised outcomes analysis. This revised analysis yielded clinical success rates of 84% and 86% for piperacillin/tazobactam and ticarcillin/clavulanate, respectively, and comparable increases in the microbiological success rates were noted.

Intent-to-treat analysis confirmed the findings of the analysis for registration and demonstrated that the investigators’ evaluability criteria imposed no bias on the interpretation of clinical outcome. Strengths of this study were the large number of patients included with relatively severe illnesses (such as diabetic foot infections) and the thorough analysis of data. It is unfortunate that a pathogen could not be identified in many of the cases of cellulitis, but this is often the situation in clinical practice and therefore does not diminish the value of the study.

Pelvic infections in women. Tapp et al. [38] described an open, noncomparative trial conducted in several hospitals in Surrey, England. Of 25 patients enrolled, eight had endometritis, eight had vaginal cuff cellulitis, six had pelvic inflammatory disease, two had abscesses, and one had pelvic soft-tissue
infection. Twenty (80%) were evaluable. Exclusion criteria included severe illness and major comorbid conditions. Patients were given iv piperacillin/tazobactam (4/0.5 g q8h) until 48 hours after resolution of signs and symptoms; the mean duration of therapy was ~5 days. Clinical success was recorded for 95% and 85% of patients at early and late follow-up, respectively. Bacteriologic eradication was achieved in 86% of patients. Although the outcomes in this study appear relatively good, too few patients were studied to permit meaningful conclusions.

Sanders [39] briefly reviewed the results of an open, multicenter noncomparative trial performed at medical centers in France, the United Kingdom, and Germany. One hundred-three patients were enrolled. Diagnoses included salpingitis (50 patients), endometritis (25), tubo-ovarian abscesses (16), vaginal cuff infection (10), and pelvic soft-tissue infection (2). Patients were given iv piperacillin/tazobactam (4/0.5 g q8h) for a mean of five days. Eighty-nine (86%) of the patients completed the study; 66% were evaluable clinically, and 29% were evaluable microbiologically. Results were analyzed at early and late follow-up intervals and at the end point. Favorable clinical outcomes were observed for 90% of patients at the end point. Bacteriologic eradication was achieved in 90% of patients (97% of isolates were eradicated in the same time frame). This trial contributed results for a significant number of patients to the efficacy and safety database; however, it was limited by the open-label design and the relatively low number of bacteriologically evaluable patients.

Results of a larger multicenter, open-label, comparative trial have been analyzed by Sweet et al. [37]. Two hundred ninety-nine patients with upper genital tract infection were enrolled at 14 centers in the United States and Canada. Diagnoses were primarily endometritis (50% of patients) and pelvic inflammatory disease (~40% of patients). Over one-half of the infections were polymicrobial. Most infections (88%) were considered severe, but patients with significant comorbid conditions were excluded. Patients were randomized in a 2:1 ratio to receive iv piperacillin/tazobactam (3/0.375 g q6h) or iv clindamycin/gentamicin (clindamycin, 900 mg and gentamicin, 2.5–5.0 mg/[kg·d] in divided doses given q8h) for at least 3 days in the hospital. The mean duration of therapy was ~5 days. Nearly 80% of patients completed the full course of therapy. The demographics of the treatment groups were comparable. Clinical results were analyzed on the basis of the total number of individuals enrolled. Clinical success was observed for 85% and 87% of patients treated with piperacillin/tazobactam and clindamycin/gentamicin, respectively; favorable microbiological outcomes were recorded for 78% and 82% of patients, respectively. None of the differences in outcome were statistically significant. The strengths of this study were its size, the relatively high rate of evaluable, and the statistical analyses of outcomes and adverse events. Retrospective analysis of 399 pretreatment isolates revealed that only five (1.2%) were resistant to piperacillin/tazobactam while 29 (7.3%) were resistant to clindamycin/gentamicin.

Other infections. The efficacy and safety of piperacillin/tazobactam has also been assessed in patients with urinary tract infections, bacteremia, osteomyelitis, and infections acquired in an intensive care unit. Nowé [44] described a multicenter (Belgium, Mexico, the United Kingdom, France, and Germany), open label, noncomparative trial of iv piperacillin/tazobactam (4/0.5 g q8h) in 217 patients with severe, complicated urinary tract infections. Of these patients, 62% were clinically evaluable, and 52% were bacteriologically evaluable. Approximately one-half of the patients had pyelonephritis. Thirty-six blood isolates were recovered. Favorable clinical and microbiological outcomes were observed for 86% of the clinically evaluable patients and 73% of the microbiologically evaluable patients. Eradication rates, by organism, were as follows: E. coli, 80% of 47 isolates; P. aeruginosa, 88% of 13; and enterococci, 100%. This study clearly documented the efficacy of piperacillin/tazobactam in urinary tract infections that are characteristically difficult to treat. Its limitation was the lack of comparative data.

Wise [45] described outcomes of treatment of bacteremia with piperacillin/tazobactam. The cases of 1,110 patients enrolled in phase 1 and 3 studies of piperacillin/tazobactam that were conducted at 182 centers in nine countries were reviewed. One hundred forty-two bacteriologically proven instances of bacteremia were identified. Patients had been given varying doses of piperacillin/tazobactam depending upon the site and severity of infection and the study protocol into which they had been enrolled. Approximately one-third had been given an aminoglycoside concurrently (especially those in studies of severe respiratory tract infections or febrile neutropenia). Of all patients with bacteremia who were treated, 73 (51%) were evaluable for clinical outcome, while 55 (39%) had follow-up cultures and were therefore bacteriologically evaluable. Most patients considered nonevaluable had received other antimicrobial agents not included in the protocol. Clinical and bacteriologic cures each were documented for 91% of evaluable patients. In this retrospective analysis it was not possible to analyze outcome in terms of severity of illness. However, the author noted that a significant percentage of patients (27%) were neutropenic or had other underlying noninfectious diseases.

Tassler [35] reviewed the results of treatment of 34 patients with osteomyelitis at several centers in Germany. The patients were adults (mean age, 42 years). Approximately two-thirds had acute osteomyelitis. Most infections were severe; approximately one-half were polymicrobial. Debridement and reconstructive surgery (but not amputation) were performed as indicated and were not considered exclusion criteria. Patients were given iv piperacillin/tazobactam (4/0.5 g q8h) for a mean duration of ~2 weeks. Patients were evaluated 1–3 days and 6 months after therapy was discontinued; 94% and 68% were evaluable at early and late follow-up, respectively. Clinical cure was noted for 100% of evaluable patients at both follow-up visits. Bacteriologic eradication was documented or presumed for 89% and 100% of patients at early and late follow-
up examinations, respectively. The results of this study suggest that piperacillin/tazobactam is effective for severe osteomyelitis that requires extensive surgical intervention. The limitations of the study were its noncomparative nature, the absence of criteria for the diagnosis of osteomyelitis, the lack of a method of culturing, and the lack of analysis by specific pathogen or pathogen group.

Offenstadt and associates [46] treated 21 patients with serious infections in an intensive care unit in Paris. Most patients were elderly and had severe underlying diseases; 10 required mechanical ventilation. Piperacillin/tazobactam (4/0.5 g q8h) was given iv. Amikacin (7.5 mg/kg) was given iv every 12 hours to three of the patients with advanced lower respiratory tract infections. Favorable clinical and bacteriologic outcomes were observed in 95% and 86% of patients, respectively. This study was limited by its small size and noncomparative nature. However, a useful analysis of treatment failures and adverse effects was performed.

**Empirical use of piperacillin/tazobactam for fever during neutropenia.** Several studies have been performed to evaluate the empirical use of piperacillin/tazobactam during febrile episodes in neutropenic patients. The results of early studies and those available only as abstracts have been reviewed by Bryson and Brogden [18]. Miccozzi and associates [48] performed a prospective randomized trial to compare the efficacy of piperacillin/amikacin/teicoplanin (58 patients) to that of iv piperacillin/tazobactam (4/0.5 g q6h) plus amikacin (56 patients). In the event that fever persisted, teicoplanin was added empirically to the latter regimen on day 4, and amphotericin B was given to patients in both groups on day 6. Consecutive neutropenic patients over 15 years of age were enrolled. Absolute neutrophil counts were <500/mm³ on enrollment or within 48 hours. Patients were stratified by the presence of central venous catheters, underlying diseases, and marrow transplantation status. Demographics were comparable in the two groups. All were given oral ciprofloxacin (500 mg twice daily) for prophylaxis.

Treatment was initiated for 126 febrile episodes, of which 114 were evaluable. The response of fever by day 4 was equivalent in the two treatment groups (57%). The overall success rate—without modification of therapy—was 60% with piperacillin/amikacin/teicoplanin and 41% with piperacillin/tazobactam plus amikacin. However, the rates for the latter group improved significantly with addition of teicoplanin. The necessity of adding amphotericin B was equivalent in the two groups.

In approximately 60% of episodes, no etiologic agent was identified. Approximately 30% of episodes were the result of sepsis, which in the majority of cases was due to gram-positive organisms. Many of the staphylococcal isolates (both coagulase negative and coagulase positive) were resistant to methicillin. The relatively high frequency of sepsis due to gram-positive organisms could be attributable to the use of ciprofloxacin prophylaxis and indwelling central venous catheters. Three cases of "breakthrough sepsis" due to gram-negative bacilli occurred in the group of patients who received piperacillin/amikacin/teicoplanin. The authors concluded that piperacillin/tazobactam plus amikacin is a potentially useful regimen, when appropriately modified (usually with a glycopeptide), in the event of persistent fever. It appeared to the authors that use of piperacillin/tazobactam in the regimen may have prevented breakthrough bacteremia due to amikacin-resistant organisms. Since the numbers were small, this assertion will require evaluation in future trials.

Kelsey and associates [49] described a trial of iv piperacillin/tazobactam (4/0.5 g q6h) plus gentamicin (the dose was adjusted based on serum level determinations) in 44 febrile neutropenic patients with underlying hematologic malignancy. All patients had been given colistin and co-trimoxazole for bowel decontamination. Forty-three (98%) of 44 patients were evaluable clinically. A favorable outcome (complete resolution in 51% and significant improvement in 16%) was noted for 67% of patients. Twenty-seven bacterial pathogens (predominantly gram-positive cocci) were isolated from 23 patients with microbiologically documented infections. Seventy-eight percent of pathogens were eradicated, 4% persisted, and the outcome was indeterminate for 17%; clinical resolution paralleled these eradication rates. The authors concluded that piperacillin/tazobactam plus gentamicin is an "effective combination for empirical therapy in febrile neutropenic patients, even in a unit with a predominance of gram-positive infections." They also concluded that this regimen may be an "effective alternative to the use of glycopeptide antibiotics" in this setting. The authors provided a thorough and useful evaluation of treatment failures. Unfortunately, the study was not comparative.

Cometta and associates, in collaboration with the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC), compared the efficacy of their standard regimen of iv ceftazidime (2 g q8h for adults) plus amikacin (20 mg/[kg·d]) to iv piperacillin/tazobactam (4/0.5 g q6h for adults) plus amikacin (20 mg/[kg·d]) as empirical therapy for fever in granulocytopenic patients with cancer [50]. A total of 858 episodes in adults and children were studied, of which 706 were evaluable for efficacy. Successful outcome was observed significantly more often in the piperacillin/tazobactam/amikacin group (210 [61%] of 342 episodes) than in the ceftazidime/amikacin group (196 [54%] of 364 episodes) (P = .05). Time to defervescence was significantly shorter (P = .01), and time to treatment failure was significantly longer (P = .02) with the piperacillin/tazobactam/amikacin regimen.

The piperacillin-containing regimen was also significantly more successful (40 [50%] of 80 patients) than was the ceftazidime/amikacin regimen (35 [35%] of 101 patients) in the treatment of bacteremic infections (P = .05). Multivariate analysis demonstrated that the probability of therapeutic failure was significantly greater (P = .02) with ceftazidime/amikacin than with piperacillin/tazobactam/amikacin. An intent-to-treat analysis also showed superiority of the piperacillin-containing regimen and confirmed the results of the previous multivariate analyses. The authors of this study provided a thorough analysis
of therapeutic failures and adverse reactions. They attributed the differences in efficacy to the greater activity of the piperacillin-containing regimen against many gram-positive organisms.

Analysis of Therapeutic Failures

Non-neutropenic patients. Investigators in most therapeutic trials categorized an unsatisfactory clinical outcome as "relapse" or "failure." A few simply reported the rate for the two outcomes collectively. Overall, these two outcomes tended to occur with similar frequency with few striking disparities between and within studies. A few investigators offered tentative explanations for the clinical failures observed in their trials: most identified host factors and the timing of therapeutic interventions as important considerations, in addition to intrinsic activity of the antimicrobial agent administered. Tassler and associates [34] noted a correlation of success in treatment of soft-tissue infections with early antimicrobial therapy (piperacillin/tazobactam) and surgical intervention; delays clearly resulted in less satisfactory outcomes.

In terms of lower rates of response to piperacillin/tazobactam and ticarcillin/clavulanate, Tan and co-workers [33] identified ischemia and diabetic foot infections as opposed to cellulitis, abscesses, or other wound infections, as important factors. In the outcome analysis of the treatment of bacteremia with piperacillin/tazobactam, Wise [45] identified delay either in surgical drainage or removal of foreign bodies as potentially important factors in drug failure.

Microbiological failures were analyzed in detail in approximately one-half of the published therapeutic trials. In the analyses, failures were usually categorized as persistence, superinfection, or reinfection. Occasionally, persistence was identified as "documented" (microbiologically confirmed) or "presumed" (lack of clinical response without microbiological confirmation or another obvious explanation). In instances designated as persistence or reinfection, pretreatment isolates and subsequent isolates were identified only at the species level; no attempt was made to determine strain identity by antigenic or genetic analysis. Furthermore, antimicrobial susceptibility testing was seldom performed on the persisting or reinfecting isolates; hence, determination of rates of emergence of resistance was not possible.

Overall, persistence of the infecting organism accounted for the majority of microbiological failures. The rates of bacterial persistence tended to correlate closely with unfavorable clinical outcomes. Rates of superinfection and reinfection were generally low (0–4%). The highest rates of superinfection occurred in the most severely ill patients (≤10%).

Relatively few publications specifically identified the organisms responsible for microbiological failures, and none addressed the issue of emergence of resistance during therapy. When identified, the organisms associated with failure tended to vary widely. Gram-positive organisms (both staphylococci and streptococci) tended to predominate when treatment failures occurred in patients with skin and soft-tissue infections. Several investigators indicated that staphylococci, especially strains of S. aureus, historically are among the most difficult pathogens to eradiate with antimicrobial therapy alone. However, Tan and associates [33] attributed the failures with staphylococci more to host factors, such as ischemia or underlying diabetes, than to the intrinsic virulence of the organism itself. Organisms associated with therapeutic failures in intraabdominal infections also varied and included gram-positive organisms, enteric bacilli, and anaerobes. Gram-positive organisms tended to predominate when failure was observed with imipenem cilastatin, as opposed to piperacillin/tazobactam; however, the numbers of these isolates were too small to subject this observation to statistical analysis.

Organisms associated with therapeutic failure tended to differ in the comparative trials for lower respiratory tract infections. In one comparison, clinical and microbiological failures occurred significantly more often with ticarcillin/clavulanate than with piperacillin/tazobactam, and these failures were attributed to organisms other than H. influenzae or S. pneumoniae [40]. Although M. catarrhalis and gram-negative bacilli individually were prominent among these organisms, the difference between treatment groups was significant only when they were considered collectively (failures, 10 [38%] of 26 patients vs. 4 [16%] of 25, respectively). In a second comparison, failures were encountered significantly more often with ceftazidime than piperacillin/tazobactam [41]. In comparing piperacillin/tazobactam with ceftazidime, differences in therapeutic failure were most striking when infections were due to H. influenzae (0 [0] of 22 patients vs. 5 [50%] of 10), S. aureus (31% vs. 66%), and P. aeruginosa (34% vs. 70%), respectively. However, only the difference with H. influenzae was statistically significant.

Neutropenic patients. The nature of the clinical and microbiological failures was examined in each of the trials for episodes of fever in neutropenic patients [48–50]. In the studies by Micozzi and associates [48] and Kelsey and co-workers [49], fungal infection (either documented or presumed) played a significant role in failures, regardless of the antibacterial regimen administered. Bacteriologic failures in both of these trials were due predominantly to gram-positive organisms, often methicillin-resistant strains of S. aureus or Staphylococcus epidermidis. Infection by these strains appeared to have been favored by prior oral chemoprophylaxis and extensive use of indwelling intravenous devices.

The presence of gram-positive organisms appears to have played significant roles in outcomes when piperacillin/tazobactam/amikacin and ceftazidime/amikacin were compared [50]. First, therapy with piperacillin/tazobactam/amikacin was stopped because resistance to the allocated β-lactam was documented in 23 (25%) of 93 episodes, and therapy with ceftazidime/amikacin was stopped because resistance was documented in 39 (35%) of 112 episodes (P = .15). The majority of the resistant organisms were gram positive; coagulase-negative staphylococci accounted for 18 episodes in the group receiving
the piperacillin-containing regimen and for 26 episodes in the group receiving the ceftazidime/amikacin regimen.

Second, it was necessary to add a glycopeptide antibiotic significantly more often ($P = .002$) when episodes were treated with ceftazidime/amikacin (128 [35%] of 364 episodes) than when they were treated with piperacillin/tazobactam/amikacin (83 [24%] of 342); however, there was no difference in the need for empirical antifungal therapy (17% in both groups). Finally, bacteremic infections subsequent to the initial infection developed more frequently ($P = .02$) in patients treated with ceftazidime/amikacin (19 [5%] of 364) than in those treated with piperacillin/tazobactam/amikacin (6 [1.8%] of 342). Of the 19 subsequent bacteremic infections in the ceftazidime/amikacin group, 12 were due to a single gram-positive organism, and five were polymicrobial; of the total number of isolates, 15 were resistant to ceftazidime. Of the six subsequent bacteremias that occurred in the piperacillin/tazobactam/amikacin group, three were due to gram-positive organisms, and of the total number of isolates, only one was resistant to piperacillin/tazobactam.

Adverse Experiences with Piperacillin/Tazobactam

The safety profile of piperacillin/tazobactam in phase 1 and phase 3 clinical studies has been extensively reviewed by Kuye et al. [51]. Piperacillin/tazobactam was administered alone or in combination with an aminoglycoside to 1,111 patients in clinical trials. Forty-six (4.9%) of 944 patients given piperacillin/tazobactam alone died during or within 30 days of treatment. None of the fatalities were considered definitely drug related, 42 were unrelated, and four did not have a degree of relatedness (other than the absence of a definite relationship) specified. Twenty-six (15.6%) of 167 patients given piperacillin/tazobactam plus an aminoglycoside died. Only one of these fatalities was assigned a relationship to the drug regimen. This possibly drug-related death involved a 79-year-old male with hypoxemia and extensive pneumonia due to P. aeruginosa. Nearly all of the deaths observed were related to preexisting or underlying conditions.

Therapy with piperacillin/tazobactam was terminated prematurely due to an adverse event in 27 (2.9%) of 944 patients given the combination alone and in 11 (6.6%) of 167 patients given an aminoglycoside concurrently. The commonest causes of discontinuation were presumed allergy with skin manifestations (2.1% of patients) and gastrointestinal disturbances (0.8%).

Among 1,111 patients enrolled in phase 3 trials of piperacillin/tazobactam, 174 (16%) had one or more adverse experiences. A similar rate (19%) was observed among the 90 patients treated comparatively with imipenem/cilastatin. Approximately 70%–80% of all recorded adverse experiences were considered related to administration of piperacillin/tazobactam. Drug-related gastrointestinal disturbances were most common, occurring in 4.6% of patients given piperacillin/tazobactam alone and in 13.2% given an aminoglycoside concurrently. Diarrhea accounted for most gastrointestinal complaints, exceeding others by threefold to 10-fold. Reactions involving skin and appendages occurred in 2.3% of patients given piperacillin/tazobactam alone and in 7.8% of patients who received the combination with an aminoglycoside. All other adverse experiences occurred in ~2% of patients who received the drugs with or without addition of an aminoglycoside. The majority of reactions were severe and rarely interfered with continuation of therapy. Rates of reactions were comparable to those reported in the literature for piperacillin alone [52], ticarcillin/clavulanate [53], ampicillin/sulbactam [54], and imipenem/cilastatin [55].

In general, analysis of adverse experiences in the clinical trials described herein revealed similar rates of reactions. However, exceptions were noted. The overall rates of adverse experiences varied widely, ranging from 0 in a trial for serious infections to 55% in a study of lower respiratory tract infections. Unfortunately, those investigators who reported the highest rates of adverse experiences (over 40% for both piperacillin/tazobactam and ticarcillin/clavulanate) did not provide an assessment of relatedness of the events to the drug administered. It may be reasonable to assume that the bulk of these high rates were unrelated to the drug regimen because rates of discontinuation (3%–5%, when reported) for these patients were similar to those reported in other studies where the rates of adverse experiences were lower overall (0–22%).

Nearly all investigators reported deaths that occurred during therapy or in the follow-up interval (usually 30 days). No deaths were considered definitely related to administration of piperacillin/tazobactam, five were remotely related, and three were possibly related. One patient whose death was considered possibly related died with a pulmonary embolus on the first day of therapy; the second died on the third day as a result of the acute lower respiratory tract infection under treatment; and the third died with overwhelming pneumonia and hypoxemia. The latter two instances more likely represented therapeutic failures than adverse effects [42]. Several deaths occurred during therapy with comparative agents, two of which were considered remotely related.

Gastrointestinal disturbances were the most commonly recorded adverse experiences among patients receiving piperacillin/tazobactam; the rate ranged from 0 to 32% among those enrolled. Most patients complained of diarrhea. Cutaneous reactions were the next most commonly encountered adverse events, with a rate of 0–8%. Allergy was reported in 0–4% of patients; however, in one study [36] 3 (12%) of 25 patients (one of whom had eosinophilia) developed cutaneous manifestations that were suggestive of an allergic rash and were accompanied by elevated IgE levels.

Rates of the more common reactions were reported in most comparative trials. Only minor differences were observed between piperacillin/tazobactam and ticarcillin/clavulanate. When imipenem/cilastatin was compared with piperacillin/tazobactam in two studies [28, 29], no differences in the rates of reactions were observed in one study; however, gastrointestinal disturbances occurred significantly more often with piperacillin-
lin/tazobactam in the other study [47]. In a study of two comparisons of piperacillin/tazobactam with clindamycin/gentamicin [31], no differences were reported; in another study [37], gastrointestinal disturbances and diarrhea occurred significantly more frequently in the piperacillin/tazobactam group, and rash was noted significantly more often with the clindamycin/gentamicin regimen. In a comparative study of patients with nosocomial pneumonia [41], cutaneous reactions occurred significantly more often with piperacillin/tazobactam, while tachycardia and depression of respiration were noted more often among ceftazidime-treated patients.

There was no significant difference between piperacillin/tazobactam/amikacin and ceftazidime/amikacin in terms of overall side effects in the trial in patients with febrile neutropenia [50]. However, rash or urticaria was noted more frequently (P = .02) with the piperacillin-containing regimen (2.8% of patients) than with the ceftazidime/amikacin regimen (0.7%). The authors concluded that “this unwanted effect was relatively mild and its incidence was comparable to that of other penicillin compounds.” In general, other investigators also concluded that piperacillin/tazobactam was a relatively safe agent whose adverse event profile is characteristic of that observed for β-lactam drugs as a group.

### Laboratory Abnormalities

Abnormalities in laboratory tests noted during phase 1 and phase 3 trials have been reviewed in detail by Kuye et al. [51]. The most common abnormalities observed with piperacillin/tazobactam were related to hepatic function; 1.1% of patients had increased total bilirubin levels, and 5.6% had increased alanine aminotransferase levels. These rates increased slightly among patients given an aminoglycoside concurrently. In comparative studies, the rates of abnormalities during administration of imipenem/cilastatin were two- to threefold higher than those noted with piperacillin/tazobactam. Abnormalities in tests that reflect renal function were infrequent. Elevation of serum creatinine was noted in 0.4% of patients given piperacillin/tazobactam alone and in 4.2% of patients given the combination plus an aminoglycoside. Abnormalities in prothrombin and partial thromboplastin times occurred in <1% of patients. Abnormalities in formed elements of the blood occurred occasionally but were rarely, if ever, clinically significant.

Laboratory test profiles observed in published clinical trials tended to parallel those described in the composite analysis by Kuye et al. [51]. Rates of abnormalities in tests of hepatic function occasionally exceeded 10% among patients given piperacillin/tazobactam [42, 45, 46]. However, these higher rates were seen almost exclusively among the more seriously ill patients, including those who were bacteremic. Wise [45] described mild and transient hypokalemia among patients given piperacillin/tazobactam alone or in combination with another agent for bacteremia. He ascribed the potassium loss, akin to that noted previously with piperacillin [56] and ticarcillin [57], to the relatively high doses of drug used in these patients.

Only one significant difference in rates of laboratory test abnormalities was noted in the comparative trials. Elevations of blood urea nitrogen occurred significantly more often with ceftazidime (10% of patients) than with piperacillin/tazobactam (3%) during treatment of nosocomial pneumonia [41]. In other trials, rates of abnormalities in tests of renal function were seldom in excess of 1% when piperacillin/tazobactam was given alone. Investigators have almost uniformly concluded that in general, laboratory abnormalities are relatively infrequent, transient, and of little clinical consequence during administration of piperacillin/tazobactam.

### Discussion

**Efficacy and safety of piperacillin/tazobactam.** Collectively, the published trials attest to the safety and efficacy of this combination. Microbiological, pharmacodynamic, and pharmacokinetic studies predicted utility in clinical situations that (1) potentially involve pathogens from among a broad spectrum of organisms (gram-positive and gram-negative as well as aerobic and anaerobic), (2) are frequently polymicrobial, or (3) result from strains that produce one or more of a vast array of plasmid-mediated β-lactamases. The data provided to date from clinical trials confirm these predictions. At present, the FDA has approved piperacillin/tazobactam for treatment of intraabdominal infections, skin and skin-structure infections, postpartum endometritis or pelvic inflammatory disease, and community-acquired pneumonia. Evidence is accumulating that this agent may also be useful in other clinical situations that require relatively broad-spectrum antibacterial coverage such as nosocomial pneumonia, complicated urinary tract infections, osteomyelitis, bacteremia, and febrile episodes in neutropenic patients. Piperacillin/tazobactam, like other β-lactam agents, alone or in combination with a β-lactamase inhibitor, does not provide coverage for methicillin-resistant staphylococci, strains of enterococci that are resistant to both β-lactams and aminoglycosides, and gram-negative bacilli that produce high levels of chromosomally mediated β-lactamases.

There has been some uncertainty regarding the potential role of piperacillin/tazobactam in infections due to *P. aeruginosa*. Suboptimal outcomes were observed in an early trial when iv piperacillin/tazobactam was used at a relatively low dose (3/0.375 g q6h) as monotherapy. This experience underscored the critical importance of total doses of the piperacillin component in terms of the outcome of infections with these organisms. Subsequently, the use of higher doses of iv piperacillin/tazobactam (4/0.5 g q6h or 3/0.375 g q4h) in combination with an aminoglycoside produced satisfactory responses [41, 50]. As a result, it appears that these larger doses should always be used for empirical therapy when a *Pseudomonas* species may be present. In documented pseudomonas infection, addition of the inhibitor will seldom add to the activity of piperacillin alone. This results from the fact that most β-lactamase-mediated resistance in *Pseudomonas* species is due to the production of chromosomally-mediated, inhibitor-insusceptible enzymes.
Except in relatively innocuous pseudomonas infections, it may be prudent, at least initially, to add a second unrelated agent (such as an aminoglycoside) both for empirical and definitive therapy.

Analysis of adverse experiences and laboratory tests performed during the clinical trials revealed no unusual or unanticipated toxicity. Piperacillin/tazobactam possesses a safety profile characteristic of β-lactam agents. It is relatively free of adverse effects in a variety of dosages and clinical settings. Clearance of piperacillin/tazobactam may be impaired in patients with advanced renal disease, but compensatory dosage adjustment is uncomplicated. Diarrhea is the most common side effect experienced by patients, but often it does not impede completion of therapy. Allergy may be a limiting factor, but it appears to occur no more commonly with this agent than with other β-lactam agents. Disturbances in liver function tests are the most frequently encountered laboratory abnormality, but these have almost always been transient and of little clinical consequence. Theoretically, it should be relatively safe to administer piperacillin/tazobactam during pregnancy, but this has not been confirmed clinically. The compound has not been studied extensively in children.

**Comparative trials.** Many clinicians and members of institutional pharmacy and therapeutics committees are wrestling with the question of the proper place of piperacillin/tazobactam in the therapeutic armamentarium. The published comparative trials assist in providing perspective on this issue. Piperacillin/tazobactam was compared to ticarcillin/clavulanate for the treatment of skin and soft-tissue infections and for community-acquired pneumonia. No differences were observed in outcome in the trial for skin and soft-tissue infections. However, most of these infections were due to staphylococci or streptococci, and relatively few were due to organisms such as gram-negative bacilli, enterococci, or anaerobes, against which piperacillin/tazobactam possesses a potential advantage on the basis of results of in vitro studies.

The comparative trial in patients with community-acquired pneumonia provided a perspective on this theoretical advantage [40]. Analysis of the results showed that piperacillin/tazobactam was significantly more effective than ticarcillin/clavulanate in terms of both clinical and microbiological outcomes. Furthermore, the agent’s superiority was statistically associated with more effective elimination of pathogens other than *H. influenzae* and *S. pneumoniae*. The group of organisms that responded more readily to piperacillin/tazobactam (despite in vitro susceptibility to both comparative agents) largely comprised *M. catarrhalis* isolates and gram-negative bacilli.

The superiority of piperacillin/tazobactam to ticarcillin/clavulanate probably resulted from one of at least five microbiological and pharmacodynamic factors (or a combination thereof): (1) the activity of piperacillin/tazobactam is greater than that of ticarcillin/clavulanate against many susceptible organisms, especially gram-negative bacilli [1, 8, 11–13]; (2) clavulanic acid (unlike tazobactam) may induce production of chromosomally mediated β-lactamases and diminish the activity of ticarcillin [1, 14, 15]; (3) laboratory susceptibility tests performed with use of the disk diffusion procedure may falsely identify resistant isolates of *E. coli* and *Klebsiella* species as being susceptible to ticarcillin/clavulanate but not to piperacillin/tazobactam [58–60]; (4) the combination of a less active agent (ticarcillin) with a lower concentration of inhibitor (clavulanate) may lead to a lower ratio of area under the curve for serum concentrations to MICs, a finding predictive of a relatively less favorable outcome in episodes of bacteremia and pneumonia [40, 61, 62]; or (5) serum levels of tazobactam may remain higher than do those of clavulanate over a longer period during the dosing interval (figure 1).

The preceding factors may be operative when clinical isolates appear susceptible both to piperacillin/tazobactam and ticarcillin/clavulanate (as required for protocol registration purposes). However, in practice, a greater percentage of potential pathogens will be susceptible to piperacillin/tazobactam than to ticarcillin/clavulanate [1, 8, 11–13] (figure 2). The proven and theoretical advantages of piperacillin/tazobactam in comparison with those of ticarcillin/clavulanate appear to more than offset the modest difference in cost between the two compounds (see below).

Clinical and microbiological outcomes both indicated that piperacillin/tazobactam was superior to ceftazidime for the treatment of nosocomial lower respiratory tract infections. Analysis of outcomes by etiologic agent indicated more favorable outcomes with *H. influenzae*, *S. aureus*, and *P. aeruginosa*. The difference with *H. influenzae* was statistically significant (*P* < .01). The greater efficacy of piperacillin/tazobactam was perhaps predictable given the relative lack of activity of ceftazidime against gram-positive cocci and anaerobes [63] as well as its propensity (unlike that of piperacillin) to select mutants from initially susceptible populations of *Enterobacter* species, *P. aeruginosa*, and related organisms that constitutively produce high levels of chromosomal β-lactamases [64, 65].

The differential activity of the β-lactam agents against gram-positive organisms also appears to have played a major role in determining the outcome of the comparison between piperacillin/tazobactam/amikacin and ceftazidime/amikacin for febrile episodes in neutropenic patients [50]. The authors attributed the superiority of the piperacillin/tazobactam/amikacin regimen to (1) a lower incidence of emergence of resistance; (2) the better clinical response of many patients with gram-positive infections; (3) the greater clinical response in episodes of pneumonia; (4) a lower incidence of subsequent bacteremic infections; (5) possibly, a longer time above the MIC for most organisms; and (6) a differential synergism with the companion aminoglycoside.

Piperacillin/tazobactam was twice compared to imipenem/cilastatin for the treatment of intraabdominal infections. In the first study, performed in Sweden, 8-hourly doses of piperacillin/tazobactam (4/0.5 g) were compared with 8-hourly doses of imipenem/cilastatin (0.5 g). Piperacillin/tazobactam was statistically superior to imipenem/cilastatin both in clinical and bacteriological outcome [28, 29]. Treatment failures with imipenem were especially prominent in cases of complicated ap-
pendicitis. The authors speculated that the low pH of periappendicular abscesses may have inhibited the activity of imipenem [29]. In addition, they acknowledged that the dosage of imipenem/cilastatin used was lower than that used by some surgeons although it was the standard dosage administered in Sweden at the time of the study.

The second trial for intraabdominal infections [30] compared 8-hourly doses of piperacillin/tazobactam (4/0.5 g) with 1.0 g of imipenem/cilastatin. No significant differences in outcome were detected; however, relatively few patients (86) were enrolled, and even fewer were evaluable clinically (two-thirds) or microbiologically (one-fifth). Thus, the issue of relative efficacies of piperacillin/tazobactam and imipenem/cilastatin is unresolved. Selection of one of the two regimens may be guided by the prevalence of resistant organisms, the drug safety profile, and costs of acquisition and administration.

Outcomes of therapy with piperacillin/tazobactam and clindamycin/gentamicin were compared for patients with intraabdominal infections [31] and pelvic infections [37]. No significant differences were identified in terms of clinical and microbiological results. Both groups of investigators expressed concern about the increasing prevalence of organisms (especially enterococci and gram-negative bacilli) that are resistant to the combination of clindamycin and gentamicin. Other concerns included the potential for aminoglycoside toxicity, the necessity for monitoring drug serum levels, and the associated costs. These investigators concluded that, although for years clindamycin/gentamicin met the criteria for a "gold standard" agent, presently available monotherapy or combination therapy that is equally effective, safer, and less costly is now clearly more appropriate.

Costs of acquisition and administration have become increasingly important factors in making a selection from among relatively similar antimicrobial regimens. According to one report [66], the cost of piperacillin/tazobactam (given in a representative course) is roughly equivalent to or slightly more than that of ticarcillin/clavulanate, comparable to or less than that of many expanded-spectrum cephalosporins, less than that of cefazidime or imipenem, comparable to that of clindamycin/gentamicin, and more than that of co-trimoxazole.

Polk and associates [31] calculated that hospital charges for a 7-day regimen of piperacillin/tazobactam would be $1,647.03 vs. $1,843.35 for a similar course of clindamycin/gentamicin at the University of Louisville Medical Center (Louisville, KY). Davey and associates [67] have analyzed the economic benefits of monotherapy (including β-lactam/β-lactamase inhibitor combinations) over regimens that include two or more antimicrobial agents. They concluded that piperacillin/tazobactam is an attractive alternative from the perspective of efficacy and economic impact. Unfortunately, many studies fail to analyze the economic impact of factors including therapeutic failures, need for retreatment, adverse experiences, and emergence of resistance in individuals and in the environment. Such an analysis would be quite useful if it was applied to one or more of the comparative studies involving piperacillin/tazobactam.

Critique of published trials of piperacillin/tazobactam. We have described the strengths and weaknesses of individual trials in the reviews of efficacy and analyses of treatment failures above. In general, authors presented clinical and microbiological outcomes in detail and interpreted the results conservatively. The lack of statistical analysis in some studies was disconcerting, but more often than not, sufficient data were provided to permit the reader to perform an appropriate analysis, if desired. The presentations of adverse experiences and laboratory abnormalities were less consistent. There was variability in the amount of data provided and in the frequency with which statistical analyses were applied. Relatively few investigators provided complete assessments of the degree of relatedness of adverse experiences to drug administration. This relationship may not have a major impact on interpretation of data for relatively safe compounds, such as the β-lactam agents, but it might have a profound impact on consideration of compounds with unique structures or mechanisms of action. Several groups of investigators were careful to consider the impact of potentially confounding factors such as rapidity of initiation of therapy, surgical interventions, and the role of host factors (e.g., ischemia) in determining outcome. Consideration of these factors should become the standard for future studies and publications.

Perhaps the most disappointing aspect with regard to several of the reports was the absence of (or sketchy) analysis of therapeutic failures. This problem is by no means unique to studies of piperacillin/tazobactam. However, given the present worldwide concern over emerging resistance to antimicrobial agents, it is a problem that demands immediate attention. In many instances, the identity of persisting or reinfecting strains has not been stated, and when the identity has been stated, seldom have tests for antimicrobial susceptibility been performed. Determination of relatedness of sequential isolates by antigenic or genetic analysis has almost always been omitted. As a result, differentiation between persistence and superinfection is impeded and calculation of rates of emergence of resistance is impossible.

The comparative study of piperacillin/tazobactam versus ceftazidime in patients with nosocomial pneumonia provides a case in point [41]. A priori, one might expect a significantly higher frequency of emergence of resistance with ceftazidime therapy because of the drug’s greater propensity to select mutants among certain organisms that produce high levels of chromosomal β-lactamase [64, 65]. Given the higher rate of therapeutic failures observed with ceftazidime, it is possible that the selection of mutants contributed to the drug’s lack of efficacy. Future comparative studies should address this issue. Additional studies might also compare piperacillin/tazobactam with ampicillin/sulbactam or other agents, such as quinolones plus metronidazole, that have a similar spectrum of activity.

Evidence is mounting that piperacillin/tazobactam is an important addition to our therapeutic armamentarium. It is appropriate that investigators at all levels of government, industry, and the scientific community who are involved with the devel-
opment of this drug demand even greater rigor in its continuing evaluation in order to provide a model for study of future generations of antiinfective agents.

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