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Piperacillin Pharmacokinetics in Pediatric Patients

CHRISTOPHER B. WILSON,[1]* JEFFREY R. KOUP,[3] KENT E. OPHEIM,[2] LEE A. ADELMAN,[1] JACK LEVY,[1] TERRENCE L. STULL,[1] CARLA CLAUSEN,[2] AND ARNOLD L. SMITH[1]

Division of Infectious Diseases, Department of Pediatrics,[1] the Department of Laboratories,[2] and the Department of Pharmacy Practice,[3] Children's Orthopedic Hospital and Medical Center and University of Washington School of Medicine and School of Pharmacy, Seattle, Washington 98105

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The pharmacokinetics of piperacillin were studied in 15 pediatric patients (age range, 3.3 to 14.3 years). Piperacillin was administered in a dosage of 1.5 ± 0.4 g/m^2 (mean ± standard deviation) every 4 to 6 h. Peak serum concentrations ranged from 69 to 354 μg/ml. The mean elimination half-life was 37.0 ± 13.3 min, which is shorter than that observed in most adults with normal renal function. The mean elimination half-life in three patients with renal impairment was 60.1 ± 12.4 min, and the mean ratio of renal clearance to total clearance was 0.57. These results suggest a significant nonrenal elimination of piperacillin. Based on these data, a dosage of 1.5 g/m^2 given as a 30-min infusion every 4 h is suggested for children with normal renal function. For patients with renal impairment, the daily dosage could be calculated as follows: corrected dose = normal dose × (0.35 + [0.65 × {Cl_{Cr}/0.06}]), where Cl_{Cr} is the creatinine clearance expressed as liters per minute per square meter.

Piperacillin is a new semisynthetic, ureidopenicillin. This drug has broad-spectrum, gram-negative activity. It is more active on a weight basis against most strains of gram-negative enteric organisms than are carbenicillin, ticarcillin, and azlocillin (3, 7, 16, 18). It is particularly more active against strains of *Pseudomonas aeruginosa* than are carbenicillin, ticarcillin, or mezlocillin (3, 7, 16, 18). Piperacillin appears to be a clinically useful antibiotic in adults (13, 17), but its pharmacokinetics have not been evaluated in pediatric patients. This report describes the pharmacokinetics of piperacillin in 15 pediatric patients whom we studied.

MATERIALS AND METHODS

Patients. Patients were admitted to the study if they had documented (eight patients) or suspected (three patients) infections due to piperacillin-susceptible, gram-negative bacilli or if they were neutropenic (<500 granulocytes per μl) and febrile (eight patients). Informed consent was obtained from a parent or legal guardian for all patients.

Drug therapy. Piperacillin sodium was supplied by Lederle Laboratories. The drug was dissolved in sterile water and diluted in a portion of parenteral fluid being administered to the patient. The drug was then administered over 30 min; for pharmacokinetic studies, the drug was infused by a research nurse using a constant infusion (Harvard) pump. These studies were completed on 17 occasions in 15 patients. Four to six blood samples were obtained during the 2- to 3-h period postinfusion (Table 1). Timed urine samples were collected on 10 occasions in nine patients. The serum was separated, and the samples were placed on ice; they were then frozen at −70°C within 1 h of the time they were collected.

Drug assay. Serum and urine concentrations of piperacillin were measured by high-performance liquid chromatography with a Waters Associates (Milford, Mass.) system which consisted of the following components: automatic sample injector (model 710A), pump (model 6000A), fixed-wavelength UV absorbance detector (254 nm; model 440) connected in series to a variable-wavelength detector (210 nm; model 450) and a dual-channel integrating record (model 730). A reverse-phase μ-Bondapak C18 column (30 by 0.4 cm) with a guard column (no. 84550) filled with Bondapak C18/Corasil (no. 27248), also from Waters Associates, was used at room temperature.

Acetonitrile was purchased from Burdick and Jackson Laboratories (Muskegon, Mich.) and was of UV quality; other reagents used were of analytical grade. The mobile phase was prepared by combining 750 ml of 20-mmol/liter potassium phosphate buffer (pH 3.5) with 230 ml of acetonitrile; the phosphate buffer was filtered through a 0.22-μm filter (type GS; Millipore Corp., Bedford, Mass.) before the addition of acetonitrile. Piperacillin (free acid; lot PC-0322-HP103; potency, 0.918 μg/ml) was obtained from Lederle Laboratories (Pearl River, N.Y.); the internal standard, *p*-nitrobenezene-sulfonamide, was purchased from Aldrich Chemical Co. (12,050-2; Milwaukee, Wis.).

A concentrated stock piperacillin standard containing 500 μg/ml was prepared in deionized water and was used for 1 month; this stock solution was stored at

TABLE 1. Serum piperacillin concentrations

Patient no.	Age (yr)	Wt (kg)	Dosage (mg/m²)	Serum piperacillin concn (μg/ml) when sample was obtained at time (min) postdosage of:						
				Predosage immediately	Immediately[a]	30	60	90	120	150
				Piperacillin alone						
1	12.7	24.6	738	5	103	ND[b]	ND	44	ND	16[c]
2	3.3	12.2	878	0	69	24	ND	6	ND	4
3	4.0	16.7	1,188	2	170	60	32	20	14	ND
4	4.6	17.3	1,265	6	170	79	57	37	ND	20
5	14.3	35.6	1,481	0	81	41	ND	14	ND	4
6	4.7	17.4	1,831	3	354	112	67	30	17	ND
				Piperacillin and tobramycin						
7	2.8	13.1	1,206	51	200	129	100	68	48	ND
8	13.8	29.9	1,389	3	171	66	29	13	9	ND
9	8.8	32.5	1,454	4	97	51	ND	ND	5	4
10	2.9	15.5	1,731	3	199	67	34	17	7	ND
11	8.8	31.5	2,020	46	326	180	111	77	59	ND
12	11.0	32.0	2,115	10	176	89	45	28	15	ND
				Piperacillin and nafcillin						
13	9.7	34.3	1,193	2	139	50	ND	11	ND	4
14	8.3	30.4	1,414	4	245	88	51	29	19	ND
15	10.5	31.3	2,083	3	260	130	59	25	12.4	ND

[a] Approximate times after the end of a 30-min infusion when samples were obtained. Precise times were recorded in each case and ranged from 1 to 12 min, 27 to 43 min, 59 to 67 min, 85 to 100 min, 112 to 130 min, 144 to 167 min, respectively.

[b] ND, Not done.

[c] This sample was obtained 205 min after the end of the infusion.

−70°C, and a thawed portion was diluted to 75 μg/ml on each day that an assay was performed. Two serum quality control specimens were prepared by supplementing calf serum (GIBCO Laboratories, Grand Island, N.Y.), containing 0.1% sodium azide as a preservative, with piperacillin (5.6 and 83 μg/ml). These controls were divided into equal portions of 100 μl and stored at −70°C; a high (83 μg/ml) and low (5.6 μg/ml) serum control were thawed and analyzed with every batch of patient specimens. A urine control was similarly made by supplementing urine from laboratory volunteers with piperacillin (1,000 μg/ml). An acetonitrile solution containing the internal standard (15 μg/ml) was prepared and stored at 4°C. Patient serum and urine specimens were stored at −70°C for up to 12 and 14 months, respectively, until analyzed; as assessed from analysis of the serum and urine control samples, these specimens were stable (<7 and <5% decrease in assayable drug, respectively) during this storage period.

Samples were prepared for analysis by combining 50 μl of patient serum, control, or standard with 50 μl of acetonitrile/internal standard solution in 500-μl polypropylene centrifuge tubes; the samples were blended in a vortex mixer for 5 s and then centrifuged for 2 min at 7,000 × *g* to pellet the precipitated serum proteins. Ten microliters of the clear supernatant was injected into the chromatographic system and eluted with the mobile phase at 1.5 ml/min. The effluent from the column was monitored at 210 nm (0.01 absorbance units full scale [AUFS]) and at 254 nm (0.01 AUFS). Under these conditions, piperacillin eluted from the column at 10 min, and the internal standard, *p*-nitrobenzene-sulfonamide, eluted at 5 min. The piperacillin concentration in urine was determined as for serum except that a 1:20 dilution with water was usually required before the addition of the acetonitrile/internal standard. Quantitation was achieved by the peak-height ratio method. The 254-nm peak-height ratio (peak height of piperacillin/peak height of internal standard) of the unknown specimen or control sample was compared with that of the standard; over the range of 0 to 200 μg/ml, the concentration of piperacillin was directly related to the peak-height ratio. Any samples with concentrations of piperacillin greater than 200 μg/ml were diluted with water and reanalyzed.

Under these conditions, the precision, assessed as the percent coefficient of variation (standard deviation/mean × 100) calculated from 21 separate assays of the 5.6- and the 83-μg/ml serum control specimens, during a 12-month period, was 12.3 and 3.9%, respectively. Accuracy was assessed as the mean percent relative recovery (amount found/amount added × 100) by assay of triplicate samples of calf serum supplemented with piperacillin; at concentrations of 25 to 200 μg/ml, the relative recovery ranged from 94 to 103%.

As an additional check of the purity of the eluted piperacillin peak, the ratio of the piperacillin peak heights at 210 to 254 nm was compared with the corresponding ratios in the standard and controls. Any significant deviation (i.e., >10%) indicates the possible presence of an interfering substance coeluting with the piperacillin. When such samples were encountered, they were reassayed with a mobile phase prepared with pH 3.7 phosphate buffer, instead of the usual pH 3.5 buffer. Less than 20% of the specimens exhibited this type of interference and required reanalysis.

We compared the results obtained by this high-performance liquid chromatographic assay with the results obtained by a bioassay (11) for piperacillin in serum and urine. The results of these assays correlated well, except that the high-performance liquid chromatographic assay was more linear at the lower and higher extremes of the concentrations observed (K. E. Opheim, unpublished observation).

Pharmacokinetic analysis. The data were analyzed by assuming a one-compartment model with first-order kinetics. The first-order elimination rate constant (K_e) was determined by performing linear regression analysis on the natural log of serum concentration (Y) versus time (X) data obtained after infusion of the study dose. The volume of distribution (V_D) was estimated by the method of Sawchuck and Zaske (12). This method accounts for the drug concentration present before the administration of the test dose and for drug eliminated during infusion of the test dose. Total body clearance (Cl_B) was calculated by multiplying K_e by V_D. Renal clearance (Cl_R) was estimated by the following: $CL_R = XU_{\Delta t}/AUC_{\Delta t}$ where $XU_{\Delta t}$ is the amount of piperacillin recovered unchanged in the urine during a timed collection interval (3.2 ± 1.6 h) and $AUC_{\Delta t}$ is the area under the serum concentration versus time curve during the same interval (estimated by the trapezoidal rule).

Calculations, statistical evaluation, and pharmacokinetic simulations were performed with an Apple II plus microcomputer (5).

RESULTS

Nineteen patients were initially enrolled in the study. Complete serum concentration data were available in 15 patients (Table 1). Six of these patients received piperacillin alone, six received piperacillin and tobramycin, and three received piperacillin and nafcillin. Two patients with documented infections and two patients who were treated because of neutropenia and fever had incomplete data and were excluded from the analysis. Two patients (5 and 12) were studied twice during the same treatment course; the parameters assessed changed little between the first and second studies in these two patients. Since creatinine clearance (Cl_{Cr}, liters per minute per square meter) is generally reported after correction for surface area, we chose to correct V_D and clearance data to the surface area. The results of pharmacokinetic calculations are shown in Table 2. Total body clearance (Cl_B) correlated significantly ($r = 0.819$, $P < 0.001$) with creatinine clearance ($Cl_B = 0.046 + 1.71 \times Cl_{Cr}$). The volume of distribution and the elimination rate constant (K_e) also correlated with creatinine clearance ($r = 0.602$, $P < 0.02$; $r = 0.534$, $P < 0.05$, respectively). The elimination rate constants (K_e) observed in this population (0.0205 ± 0.0057 min^{-1}) were relatively homogenous (coefficient of variation = 28%) when compared with the observed range of renal func-

TABLE 2. Pharmacokinetic parameters for 15 patients receiving piperacillin therapy

Patient no.	Dosage (mg/m²)	K_e (min⁻¹)	$t_{1/2}$ (min)	V_D (liters/m²)	Cl_B[a]	Cl_R (liters min⁻¹ m⁻²)[b]	Cl_{Cr}[c]	$Cl_R/Cl_B \times 100$ (%)
				Piperacillin alone				
1[d]	738	0.0098	70.7	6.1	0.060	—[e]	0.004	—
2	878	0.0263	26.3	8.3	0.218	—	0.060	—
3	1,188	0.0206	33.6	6.3	0.130	0.098	0.042	75.4
4[d]	1,265	0.0149	46.5	6.5	0.097	—	0.018	—
5[f]	1,481	0.0182	38.1	13.9	0.253	0.229	0.091	93.4
	1,481	0.0182	38.1	14.6	0.266	—	0.121	
6	1,831	0.0246	28.2	3.9	0.096	0.068	0.051	70.8
				Piperacillin and tobramycin				
7[d]	1,206	0.0110	63.0	6.1	0.067	—	0.025	—
8	1,389	0.0255	27.2	6.2	0.158	0.102	0.085	64.6
9	1,454	0.0287	24.1	7.3	0.209	0.037	0.077	17.7
10	1,731	0.0273	25.4	6.5	0.178	0.063	0.073	35.4
11	2,020	0.0140	49.5	6.1	0.085	—	0.042	—
12	2,115	0.0210	33.0	7.9	0.166	0.085	0.043	51.2
	2,115	0.0210	33.0	5.9	0.124	0.067	0.058	54.0
				Piperacillin and nafcillin				
13	1,193	0.0203	34.1	8.1	0.164	0.087	0.092	53.0
14	1,414	0.0215	32.2	5.0	0.108	0.059	0.058	54.6
15	2,083	0.0270	25.7	4.9	0.132	0.070	0.072	53.0
Mean	1,505	0.0206	37.0	7.3	0.148	0.088	0.059	56.6
SD	422	0.0057	13.3	2.9	0.062	0.050	0.030	20.0

[a] Total body clearance of the drug.
[b] Renal clearance of the drug.
[c] Creatinine clearance.
[d] Patients with decreased renal function.
[e] —, Not done.
[f] Patients 5 and 12 were studied twice during the same treatment course.

tion (Cl_{Cr} = 0.061 ± 0.031 liters/min/m², coefficient of variation = 51%). Renal clearance calculated in nine patients with normal renal function averaged 56.6% of total body clearance. This corresponds to a nonrenal clearance of 43.4%. Using the mean Cl_{Cr} (0.067 liters/min/m²) of the nine patients in whom urine samples were collected to estimate Cl_B from Fig. 1, we obtained a value of 0.160 liters/min/m². The *Y*-intercept value in the figure (0.046 liters/min/m²) represents nonrenal clearance. Thus, the average data indicate that nonrenal clearance was 28.8% of Cl_B, which is lower than the 43.4% figure observed in our nine patients.

In the evaluable patients, the clinical results were, in general, favorable. Six of the eight patients with documented infections received a complete course of therapy. Three patients with osteochondritis and one patient with a urinary tract infection due to *P. aeruginosa* and one patient with peritonitis due to *P. putida* were successfully treated with piperacillin. One patient with cystic fibrosis had a transient decrease in the sputum density of *Pseudomonas* sp. during therapy, which returned to the pretreatment density after therapy was discontinued. Of the 19 patients, 1 developed neutropenia on day 13 of piperacillin therapy; this resolved within 6 days after piperacillin therapy was discontinued. No other adverse reactions were observed.

DISCUSSION

Drug concentration versus time curves from most patients in this study were monoexponential and fit well to a one-compartment model. Others have found that data from adults receiving the drug by infusion over at least 30 min or by intramuscular injection also have fit a single-compartment model (1, 15); data from patients receiving bolus injections have been fit to two-compartment models (2, 15). The mean elimination half-life ($t_{1/2}$) observed in this study was 37.0 ± 13.3 min; this was similar to that reported in children with cystic fibrosis (37.2 min) by Prince and Neu (10) but shorter than that observed in most adults (37 to 90 min) with normal renal function (1, 2, 8, 15). $t_{1/2}$ did not increase dramatically in our patients with renal impairment (60.1 ± 12.4 min) in three patients with Cl_{Cr} < 0.030 liters/min/m². Similarly, $t_{1/2}$ in adults with chronic renal failure are approximately 3.5 h (4, 14); this is much shorter than the $t_{1/2}$ for carbenicillin and ticarcillin in patients with chronic renal failure (6, 9). The short $t_{1/2}$ found in children indicates the need for short dosing intervals

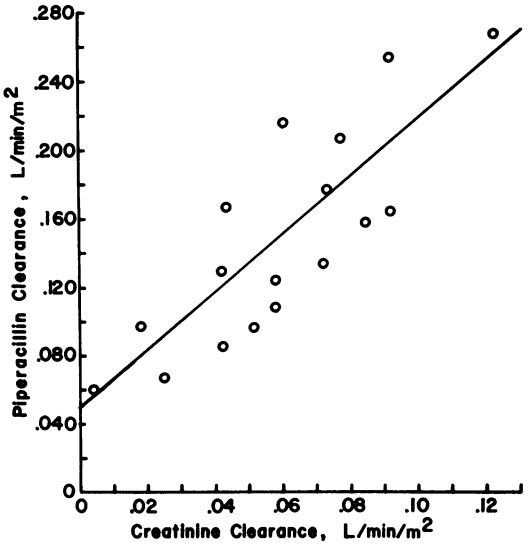

FIG. 1. Correlation of piperacillin clearance with creatinine clearance during 17 studies of 15 patients. The solid line is the least-squares regression line ($Y = 1.71X + 0.046$; $r = 0.819$, $P < 0.001$).

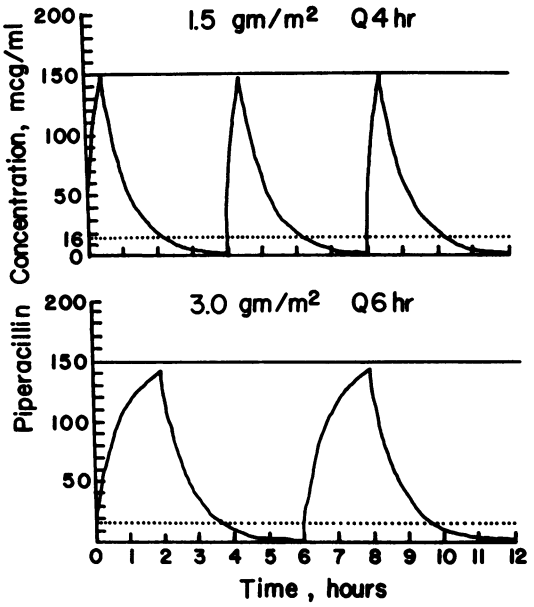

FIG. 2. Simulated piperacillin dosage regimens. Two simulated dosage regimens that would produce a serum concentration of piperacillin in the range discussed in the text in children with normal renal function are shown. The top curve indicates the serum concentration versus time curve after intravenous administration of 1.5 g/m^2 over 0.5 h every 4 h; the bottom curve is that after intravenous administration of 3.0 g/m^2 over 2 h every 6 h.

even in patients with renal impairment. These data also suggest a significant nonrenal elimination of piperacillin. This is supported by data on renal and body clearance in patients with normal renal function. The ratio of Cl_R/Cl_B in this study (0.566) was similar to that observed in studies in adults (0.41 to 0.89) (1, 8, 15). Nonrenal elimination may be due to biliary excretion (14).

Dosage recommendations. Based on the pharmacokinetic data observed in 12 patients with normal renal function ($Cl_{Cr} > 0.030$ liters/min/m^2), we simulated (5) the dosing regimens needed to obtain a therapeutic peak serum concentration (approximately 150 μg/ml) and to maintain a therapeutic level of greater than 16 μg/ml for one half of the dosing interval. A 30-min infusion of 1.5 g/m^2 given every 4 h produced the desired results in children with normal renal function (Fig. 2). If a dosing interval of 6 h was desired, both a larger dose (3.0 g/m^2) and a longer duration of infusion (2 h) would be required. With either of these regimens, serum concentration would fall below 16 μg/ml during the last 2.0 to 2.5 h of the dosing interval. An approximation of the daily dosage requirement for pediatric patients with renal impairment could be calculated as follows: corrected dose = normal dose × $(0.35 + [0.65 \times \{Cl_{Cr}/0.060\}])$ where Cl_{Cr} is the estimated creatinine clearance expressed in liters per minute per square meter. A value for the fraction eliminated by nonrenal pathways of 0.35, which is between the values found by the Cl_R/Cl_B ratio (0.43) and the regression of Cl_B versus Cl_{Cr} (0.29), was chosen for this calculation.

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LITERATURE CITED

1. **Batra, V. K., J. A. Morrison, K. C. Lasseter, and V. A. Joy.** 1979. Piperacillin kinetics. Clin. Pharmacol. Ther. 26:41–53.
2. **Evans, M. A. L., P. Wilson, T. Leung, and J. D. Williams.** 1978. Pharmacokinetics of piperacillin following intravenous administration. J. Antimicrob. Chemother. 4:255–261.
3. **Fu, K. P., and H. C. Neu.** 1978. Piperacillin, a new penicillin active against many bacteria resistant to other penicillins. Antimicrob. Agents Chemother. 13:358–367.
4. **Giron, J. A., B. R. Meyers, S. Z. Hirschman, and E. Srulevitch.** 1981. Pharmacokinetics of piperacillin in patients with moderate renal failure and in patients undergoing hemodialysis. Antimicrob. Agents Chemother. 19:279–283.
5. **Koup, J. R., and D. R. Benjamin.** 1980. Numerical integration simulation program for the microcomputer. Ther. Drug Mon. 2:243–247.
6. **Latos, D. L., C. S. Bryan, and W. J. Stone.** 1975. Carbenicillin therapy in patients with normal and impaired renal function. Clin. Pharmacol. Ther. 17:692–700.

7. **McGowan, J. E., Jr., and P. M. Terry.** 1979. Susceptibility of gram-negative aerobic bacilli resistant to carbenicillin in a general hospital to piperacillin and ticarcillin. Antimicrob. Agents Chemother. **15**:137–139.
8. **Meyers, B. R., S. Z. Hirschman, L. Strougo, and E. Srulevitch.** 1980. Comparative study of piperacillin, ticarcillin, and carbenicillin pharmacokinetics. Antimicrob. Agents Chemother. **17**:608–611.
9. **Parry, M. F., and H. C. Neu.** 1976. Pharmacokinetics of ticarcillin in patients with abnormal renal function. J. Infect. Dis. **133**:46–49.
10. **Prince, A. S., and H. C. Neu.** 1980. Use of piperacillin, a semisynthetic penicillin, in the therapy of acute exacerbations of pulmonary disease in patients with cystic fibrosis. J. Pediatr. **97**:148–151.
11. **Sabath, L. D., and J. P. Anhalt.** 1980. Assay of antimicrobics, p. 485–490. In E. H. Lennette, A. Balows, W. J. Hausler, Jr., and J. P. Truant (ed.), Manual of clinical microbiology. American Society for Microbiology, Washington, D.C.
12. **Sawchuck, R. J., and D. E. Zaske.** 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. J. Pharmacokin. Biopharm. **4**:183–195.
13. **Simon, G. L., D. R. Snydman, F. P. Tally, and S. L. Gorbach.** 1980. Clinical trial of piperacillin with acquisition of resistance by *Pseudomonas* and clinical relapse. Antimicrob. Agents Chemother. **18**:167–170.
14. **Thompson, M. I. B., M. E. Russo, J. M. Matsen, and E. Atkin-Thor.** 1981. Piperacillin pharmacokinetics in subjects with chronic renal failure. Antimicrob. Agents Chemother. **19**:450–453.
15. **Tjandramaga, T. B., A. Mullie, R. Verbesselt, P. J. De Schepper, and L. Verbist.** 1978. Piperacillin: human pharmacokinetics after intravenous and intramuscular administration. Antimicrob. Agents Chemother. **14**:829–837.
16. **Verbist, L.** 1979. Comparison of the activities of the new ureidopenicillins piperacillin, mezlocillin, azlocillin, and bay k 4999 against gram-negative organisms. Antimicrob. Agents Chemother. **16**:115–119.
17. **Winston, D. J., W. Murphy, L. S. Young, and W. L. Hewitt.** 1980. Piperacillin therapy for serious bacterial infections. Am. J. Med. **69**:255–261.
18. **Winston, D. J., D. Wang, L. S. Young, W. J. Martin, and W. L. Hewitt.** 1978. In vitro studies of piperacillin, a new semisynthetic penicillin. Antimicrob. Agents Chemother. **13**:944–950.