NEWER CEPHALOSPORINS AND "EXPANDED-SPECTRUM" PENICILLINS

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The tremendous effort of the past two decades in developing semisynthetic modifications of existing antibiotics as well as in screening for new natural agents has produced a large number of new products, which suggested some time ago that a point of diminishing returns was being approached (1). In recent years the majority of new compounds reaching clinical investigation has resulted from evolution of the technology for semisynthetic modifications of either the 6-aminopenicillanic acid (6-APA) or the 7-aminocephalosporanic acid nucleus (2–6). Chemical alterations have been designed specifically to produce more desirable properties such as the following: (*a*) improved acid stability; (*b*) broadened microbiological spectrum; (*c*) improved activity against resistant organisms (by a variety of mechanisms such as improved resistance to enzymatic degradation, inhibition of degrading enzyme production, improved intrinsic activity through better steric fit, better cell penetration, etc); (*d*) improved metabolic or pharmacologic efficiency, such as better oral absorption, slower excretion, better tissue diffusion; and (*e*) decreased allergenecity (1). Significant advances have been made toward these goals.

Major among these advances has been enhanced resistance to degradation by staphylococcal β-lactamase, accomplished with the series of semisynthetic penicillins which have seen extensive clinical application begining with methicillin and subsequently including nafcillin and the isoxazolyl series (oxacillin, cloxacillin, dicloxacillin, and most recently under evaluation, flucloxacillin). The microbiology, pharmacology, and clinical applications of these drugs have been reviewed (7–12) and will not be included in this report because there are few new developments in the application of these agents.

In addition to high activity against Gram-positive cocci and bacilli, the action of penicillin G also includes moderately high activity against *Neisseria,* relatively modest activity against *Hemophilus,* and low-level activity against *Enterobacteriaceae* such as *Escherichia coli* and *Salmonella* (see Table 1). However, early

attempts at treatment of *Hemophilus* meningitis with penicillin G in moderate doses were not particularly successful, and primary treatment of serious *Hemophilus* infection with large doses has not been examined in recent years. Massive doses of penicillin have been used to treat Gram-negative septicemia (13); the results, though uncontrolled, were not conclusive and were complicated by penicillin neurotoxicity (14). Thus, except for Stamey's suggestion of penicillin G prophylaxis for recurrent cystitis (15), penicillin G treatment of infection due to Gram-negative bacilli is not widely recommended. Therefore, improved antimicrobial activity against Gram-negative bacilli (particularly *Hemophilus,* enterics, and *Pseudomonas*) and improved pharmacologic efficiency have been the other main objectives in developing semisynthetic penicillins and cephalosporins. This report reviews the present status of the "expanded-spectrum" penicillins and of newer cephalosporins. It has not been possible to include all compounds reported. [We have excluded, for example, two promising compounds, pivampicillin (16) and cephanone (16a, 16b), because development of these agents has apparently been delayed.]

NEWER "EXPANDED-SPECTRUM" PENICILLINS

Ampicillin, D-α-aminobenzyl penicillin, described in 1961, showed increased activity against enteric bacilli and *Hemophilus.* It was the first such agent to receive extensive clinical trial and has since achieved wide use and probable overuse. The microbiologic activity, pharmacology, and clinical applications have been reviewed (17–25) and will not be detailed here. For comparison, summaries of the antibacterial spectrum, relative activity, and clinical pharmacology of ampicillin are included in Tables 1–3, which summarize selected data for penicillins G and V and ampicillin for comparison with more recently developed compounds. Examples of drugs generally resembling ampicillin in spectrum, without clinically significant activity against penicillinase-producing staphylococci or against *Pseudomonas,* include hetacillin, amoxicillin, epicillin, azidocillin, and cyclacillin. Compounds with some activity against *Pseudomonas* include carbenicillin sodium, idanyl carbenicillin, and ticarcillin.

Hetacillin and Ampicillin

CLASSIFICATION Hetacillin was produced by reacting ampicillin with acetone (22), producing a compound resembling ampicillin with the inclusion of a dimethylimidazolidinyl structure in the side chain (Figure 1). Hetacillin is rapidly and virtually quantitatively hydrolyzed both in vitro and in vivo so that the active agent remaining is apparently ampicillin.

ANTIMICROBIAL ACTIVITY Because hetacillin is hydrolyzed to ampicillin the activity is that of ampicillin, including high activity against pneumococci, streptococci, and penicillin sensitive staphylococci, in the same range as penicillin G and V, but with significant activity also against *Hemophilus* and certain *Enterobacteriaceae* (See Table 1) but not against *Pseudomonas.*

CLINICAL PHARMACOLOGY Conversion to ampicillin in the process of gastro-intestinal absorption or uptake from intramuscular sites takes place rapidly, with little

Table 1 Antibacterial activity of penicillin G and representative "expanded spectrum" staphylococcal β-lactamase-susceptible semisynthetic penicillins

Bacterial Species	Penicillin G		Ampicillin		Amoxicillin		Azidocillin	Carbenicillin		Ticarcillin	
	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)
Strep. pneumoniae	0.01(≤0.01-0.02)	(0)	0.02(≤0.01-0.1)	(0)	0.04(0.01-0.05)	(0)	<0.01	0.4(0.1-1)	(I)[b]	1(0.6-2.5)	(0)
Strep. pyogenes (A)	<0.01(≤0.01-0.02)	(0)	0.01(≤0.01-0.2)	(0)	0.01(≤0.01-0.2)	(0)	<0.01	0.2(0.1-1)	(I)	0.8(0.3-2.5)	(0)
Staph. aureus (Non-Pase)	0.06(0.02-0.2)	(0)	0.1 (0.04-0.3)	(0)	0.1 (0.04-0.3)	(0)	0.06(0.01-0.5)	5(1-10)	(I)	2.5(1-10)	(I)
Enterococci	3(2-5)	(I)	1.25(0.5-5)	(I)	1.25(0.5-5)	(I)	(0.25-4)	50	(100)	25	(100)
N. gonorrhoeae	0.05(≤0.01-2.5)	(v)[c]	0.02 (0.01-1.0)	(v)	0.02(0.01-0.3)	(v)					
N. meningitidis	0.06	(0)	0.03	(0)	0.02			0.1			
H. influenzae	0.6 (0.1-3)	(I)	0.2 (0.05-1.0)	(5)	0.2 (0.02-1.0)	(5)	0.6 (0.1-3)	(0.5-125[a])			
E. coli	(16->125)	(30[a])	3(<1->125)	(20[a])	3(<1->125)	(25[a])	(32->125)	5(2->125)	(20[a])	3(1->125)	(10[a])
Salmonella	(2-64)		1(0.4->125)	(10[a])	1(<0.5->125)	(10[a])		(4-16)		(2-8)	
Proteus mirabilis	8(2->125)		1(0.5->125)	(10[a])	0.5(0.2->125)	(10[a])	(16-128)	1(0.5->125)	(10[a])	1(0.2->125)	(<10[a])
Proteus (other)	(16->250)	(90[a])	125(32->125)	(90[a])	125(50->125)	(90[a])	125	2(0.5->125)	(15[a])	2(0.2->125)	(10[a])
K pneumoniae	>250		12(4->125)	(80[a])	12(25->125)	(90[a])	>125	>125(50->125)	(100)	>125(50->125)	(100)
Enterobacter	>250		50(25->125)	(85[a])	>125		>125	12(6->125)	(25[a])	6(3->125)	(25[a])
Pseudomonas	>250		>250		>250		>125	32(8->250)	(20+[a])	16(2->250)	(15+[a])

[a] "Resistant" to serum concentrations of drug achieved with "normal" dosage. Proportion may vary markedly depending on strain selection, nosocomial origin, and testing methodology including inoculum size.

[b] I = Many strains intermediate in susceptibility.

[c] v = Variable proportion of strains (approximately 5-30%) with MICs at high end of range, depending on population studied.

Table 2 Clinical-pharmacologic characteristics of penicillin G, V and selected "expanded spectrum" semisynthetic penicillins

Drug	Proportion of Oral Dose Absorbed (%)	Protein-Bound (%)	Route of Admin.	Maximum Serum Level 0.5 g Dose Mode (Range) (μg/ml)	Serum Half-Life (hr.)	Recovery in Urine (% of Dose)
Penicillin G (benzyl)	20-30	20-60	oral	2.5 (2-6)	0.6	15-25
			im	4.5 (2-6)	0.5-1	90-100
			iv-inf.	10	0.4	90-100
Penicillin V (phenoxymethyl)	25-50	70-80	oral	2.5	0.5	35-50
Ampicillin	30-60	16-20	oral	3.5 (1.5-6)	1-2	35-45
			im	7.5 (6-9)	1.1	75
			iv-inf.	12	0.6-1.0	75
Amoxicillin	50-80	15-25	oral	8 (3-20)	1	60-90
Epicillin		10-30	oral	5 (2-9)	1	40
Azidocillin	75	85	oral	5-7	0.5	60-70
			im	6-9	1.0	85
Carbenicillin sodium	–	50	im	10-18	1.5	80-98
			iv-inf.	40 est.	1	
Carbenicillin indanyl	40	50	oral	5-7	1	50
Ticarcillin	–	45	im	22 (14-32)	2	85-98
			iv-inf.[a]	40 est.	1.1	

[a] 5 g given iv in 15-30 min will produce peak serum levels >300 μg/ml.

or no delay in absorption-excretion kinetics compared with administration of ampicillin. There are only minor variations in clinical pharmacology between ampicillin and hetacillin. One study showed slightly higher hetacillin serum levels following iv administration (23), while others (22) showed slightly lower levels compared with ampicillin following oral or intramuscular administration. Kirby & Kind noted slight delay in excretion and suggested that these resulted from greater acid stability of hetacillin together with a slight time lag for hydrolysis of hetacillin to ampicillin in vivo (25). Hetacillin was slightly more resistant than ampicillin to in vivo inactivation, presumably by the liver, and both ampicillin and hetacillin show lower renal clearance compared with penicillin G (23–25).

CLINICAL EFFECTIVENESS Treatment of a variety of infections with hetacillin has produced results which approximate those expected for ampicillin, including meningitis (26), respiratory infections (27), and typhoid fever (28–29). Hence, there is no

Table 3 Estimated minimum therapeutic ratio for penicillin G, V and selected "expanded spectrum" penicillins against common pathogens

Drug	Route of Admin. of 0.5 g Dose	Ratio (minimum peak serum level[a]/MIC[b])									
		Str. pn.	*Str. A*	*St. aur.* (N-Pase)	*Enterococ.*	*H. infl.*	*E. coli*	*Klebs*	*Pr. mirab.*	*Prot.* Other	*Pseudo.*
Penicillin G (benzyl)	oral	100	100	10-50	1	1	0.2	0	0.1	0	0
	im	100	100	10-50	1	1	0.2	0	0.1	0	0
	iv-inf.	1000	1000	50-100	3	3	1	0	0.5	0	0
Penicillin V (phenoxymethyl)	oral	75	75	10-25	1	1	0.02	0	0.2	0	0
Ampicillin	oral	20	10	10	0.5	2	1[c]	0.1[c]	1[c]	0	0
	im	30	20	30	1.5	6	2[c]	0.3[c]	3[c]	0	0
	iv-inf.	60	40	60	3	10-15	4[c]	1[c]	6[c]	0	0
Amoxicillin	oral	50	100	10	1	3	1[c]	0.1[c]	1[c]	0	0
Azidocillin	oral	500	500	10	1	1	0.2[c]	0	0.2[c]	0	0
	im										
Carbenicillin sodium	im	10	10	1	0.2		1[c]	0	5[c]	2[c]	0.2[c]
	iv-inf.[d]	40	40	4	1		4[c]	0	20[c]	10[c]	1[c]
Carbenicillin indanyl	oral	5	5	0.5	0.1		0.5[c]	0	2[c]	1[c]	0.1[c]
Ticarcillin	im	5	5	1.5	0.5		2[c]	0	6[c]	3[c]	0.5[c]
	iv-inf.[d]	50	50	5	1		10[c]	0	20[c]	10[c]	1[c]

[a] Minimum value from reported range of peak serum levels, unadjusted for duration of level, volume of distribution, etc.

[b] MIC = minimum inhibitory concentration (Maximum of range of MICs for species or strains considered "susceptible" to therapy, unadjusted for protein-binding, tissue diffusion, etc; used in deriving the ratio estimate.)

[c] Higher dosage would achieve higher ratios with some strains but a variable proportion are quite resistant and would not be amenable to any therapy. Others are inhibited at high levels such as achieved in urine.

[d] For treatment of *Pseudomonas septicemia* higher dosage necessary, e.g. 4-5 g infusions.

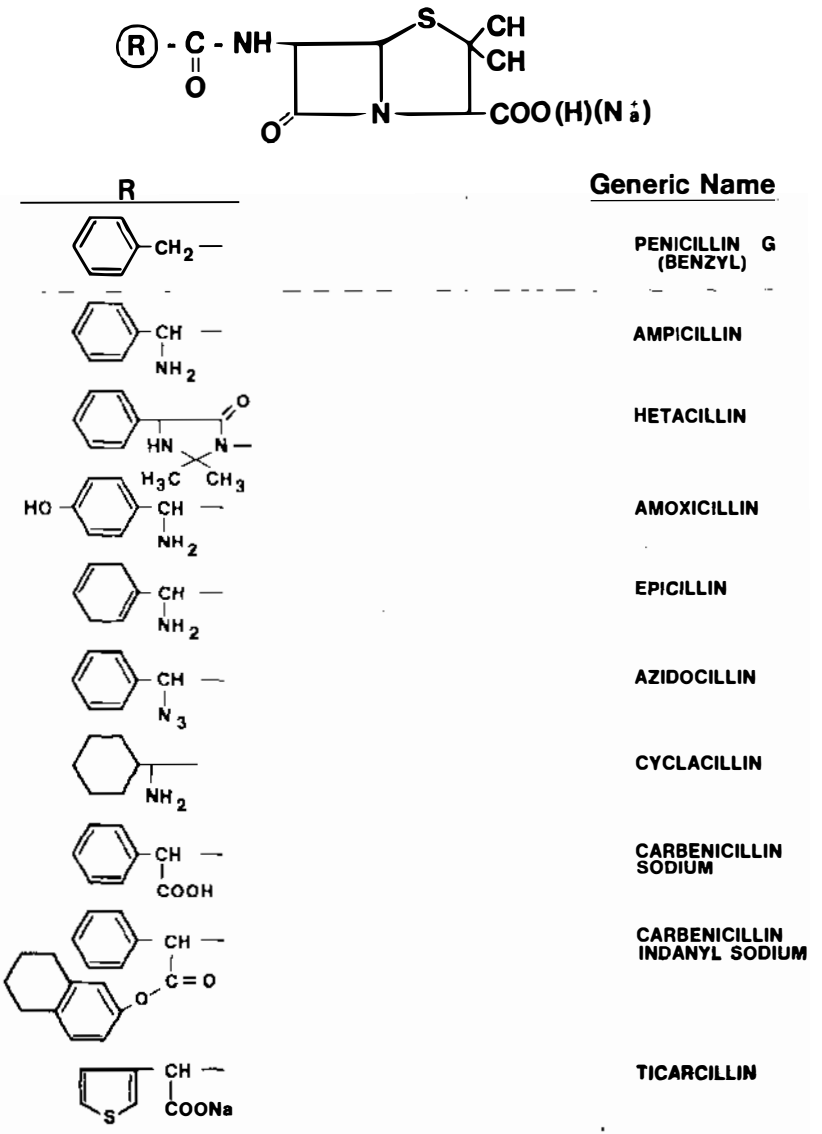

Figure 1 Structure of penicillin G, penicillin V, ampicillin, and representative newer, "expanded" spectrum, (penicillinase-susceptible), penicillins.

reason to suspect that hetacillin shows any advantage warranting its use instead of ampicillin.

TOXICITY AND HYPERSENSITIVITY Direct pharmacologic toxicity should be almost nonexistent for hetacillin, as for ampicillin and penicillin, and would probably be limited to encephalopathy such as recorded with massive doses of penicillin (14) or ampicillin (30), particularly in the presence of renal failure.

The incidence of skin rashes, usually macular or maculopapular, and occasionally morbilliform, is clearly higher following ampicillin compared with the other penicillins (31) and is even higher in patients also receiving allopurinol (32), and in patients with infectious mononucleosis the incidence is so high as to be suggestively diagnostic (33). Bierman et al (34) studied hemagglutinating antibody and skin-test reactivity to benzyl penicillin, benzyl penicillaote, benzyl penicilloyl polylysine, ampicillin, and hetacillin in patients with a history of rashes induced by ampicillin or hetacillin. Their results indicated that few of the maculopapular type of eruptions were demonstrable as true immunologic allergy and seldom recurred on rechallenge, whereas urticarial reactions were much more likely to be immunologic in origin (34). The mechanism of these "toxic" rashes is not clear. Clinical data are not extensive enough to determine whether the other newer penicillin and ampicillin analogs will be associated with similar eruptions. Bierman's study (34) included hetacillin testing, and although details are not presented, it is likely that here again hetacillin is behaving essentially as ampicillin.

Amoxicillin

CLASSIFICATION As indicated in Figure 1, the structure of amoxicillin, or α-amino-*p*-hydroxybenzyl-penicillin differs from ampicillin only in the addition of the parahydroxy group. Similar to ampicillin, amoxicillin is relatively insoluble in water but is soluble in pH8 phosphate buffer (35). It shows greater stability to gastric juice pH of 1.5 than ampicillin (half-lives of 17 hr for amoxicillin and 12 hr for ampicillin).

ANTIMICROBIAL ACTIVITY In vitro activity of amoxicillin is virtually identical with that of ampicillin, both in its spectrum and relative activity (excellent activity against penicillin-sensitive Gram-positive pathogens and moderate activity against enterococci and certain Gram-negative bacilli). There is essentially complete cross-resistance between ampicillin and amoxicillin against a number of strains and species of Gram-negative enteric bacilli. Neither amoxicillin or ampicillin are active against *Pseudomonas* (35–37).

CLINICAL PHAMACOLOGY Compared with ampicillin, amoxicillin shows remarkably improved absorption following oral administration (37–43). The pattern of renal excretion is similar to that of ampicillin, indicating that the higher serum levels and more complete recovery in the urine (70% in 6 hr for amoxicillin compared with 40–50% for ampicillin) are the result of more complete oral absorption rather than other basic differences in pharmacokinetics (Table 2, 40–42).

The effect of food on absorption of amoxicillin is not great, but peak serum levels are somewhat lower and the time of peak levels delayed in nonfasting subjects. Middleton et al (44) noted greater variability in serum levels in patients, compared with data from normal subjects (38–41), as might be anticipated because of difficulty controlling clinical variables such as food intake and gastrointestinal disorders in patient populations. Probenecid produced modest delay in urinary excretion and somewhat higher serum levels (37).

Because of the generally better absorption after oral dosing, with serum levels significantly higher compared with ampicillin, it is evident that amoxicillin theoretically should provide an improved "therapeutic ratio," as indicated in Table 3, which presents an arbitrary ratio between the lower end of the range of expected peak serum levels and the minimum inhibitory concentrations (MICs) of common pathogens. (No attempt has been made to adjust these ratios by taking into account additional, more complex factors, such as protein binding, tissue diffusion, lipid solubility, and membrane transport. Table 3 therefore provides only an arbitary reference ratio based on direct assays of serum levels and should not be taken to imply that such ratios can necessarily be translated into differences in clinical efficacy.)

Administration of amoxicillin and ampicillin to animals produced similar serum levels after parenteral administration but much higher levels following oral administration of amoxicillin (40), similar to the human phamacologic findings. In treatment of experimental infections, amoxicillin proved significantly superior to identical doses of ampicillin; however, the differences were evident not only after oral drug, which was expected, but also after parenteral administration, which was not anticipated in view of the similar serum levels and similar MICs of the infecting organism. It did not appear likely that differences in protein binding were responsible for the apparent paradox, and no other explanation was yet evident (40).

CLINICAL APPLICATION No clinical evidence has appeared to prove that the pharmacologic advantage of improved absorption has necessarily resulted in better clinical response compared with ampicillin or with other drugs effective against similar pathogens. Satisfactory clinical and bacteriologic response has been recorded in uncontrolled studies of urinary tract infections (44) and in streptococcal infections of upper respiratory tract and skin (45). Additional clinical experience, including controlled trials, will be required to determine whether the pharmacologic advantage of improved absorption of amoxicillin can be fully used clinically by employing lower dosage or by substitution of oral instead of the parenteral dosage now required when high serum levels of ampicillin are needed.

Epicillin

CLASSIFICATION Epicillin (amino-cydohexadienyl penicillin) is an acid-stable semisynthetic penicillin similar in structure to ampicillin (Figure 1). The low, reversible serum protein binding (46) and susceptibility to degradation by staphylococcal β-lactamase (47) are also similar to ampicillin.

ANTIMICROBIAL ACTIVITY The antibacterial activity of epicillin is sufficiently close to that of ampicillin so that the characteristic MIC values are not listed separately in Table 1. In summary, epicillin shows high activity against Group A streptococci, pneumococci, non-penicillinase-producing staphylococci, and penicillin-sensitive anaerobes and *Neisseria,* and moderate activity against *Hemophilus* and against selected ampicillin-sensitive strains of enteric bacilli, notably *Proteus mirabilis* and *E. coli.* In addition, epicillin shows somewhat greater activity than ampicillin against certain strains of *Pseudomonas* and indol-positive *Proteus* (46), but this activity is less than that of carbenicillin against these strains and is not likely to be of clinical value. Otherwise, cross-resistance and spectrum seem virtually identical between epicillin and ampicillin.

CLINICAL PHARMACOLOGY The clinical pharmacology of epicillin is similar to ampicillin (Table 2) with similar rates of oral absorption and a serum half-life of about 1 hr. Some 30% of the oral dose is recovered in the urine within 6 hr in full active form. Serum levels and total absorption following oral administration appear to be slightly less than for ampicillin, but it is unlikely that these differences would be significant clinically.

CLINICAL APPLICATION A variety of infections in adults and children have been treated with parenteral and oral epicillin. These largely uncontrolled trials have included patients with infections of the upper and lower respiratory tact, *Salmonella* and *Shigella* infections, soft-tissue infections, and urinary tract infections (48–50). Clinical results appear as good as could have been anticipated. However, in the absence of detailed analyses of clinical pharmacologic and microbiologic data in individual patients or of controlled trials, further conclusions cannot be drawn beyond the apparent similarity to ampicillin.

Azidocillin

CLASSIFICATION Azidocillin (α-azidobenzyl-penicillin) is also similar generally to ampicillin in structure (Figure 1), activity (Table 1), and pharmacology (Table 2). Its acid stability is similar to penicillin V, better than penicillin G, but somewhat less than ampicillin (51). It differs from ampicillin in the much greater protein binding (80–85%), compared with 15–20% for ampicillin (51).

ANTIMICROBIAL ACTIVITY Against Gram-positive cocci the antibacterial activity of azidocillin is also generally similar to ampicillin and penicillin. Minor differences are as follows: against *Streptococcus pneumoniae, Strep. viridans,* and *Strep. pyogenes* it is slightly more active than ampicillin or penicillin G; against penicillin sensitive *Staphylococcus aureus* it is slightly less active than penicillin or ampicillin; and against *Haemophilus influenzae* and *H. parainfluenzae* it is similar to penicillun G but shows slightly higher MICs than ampicillin. It is susceptible to staphylococcal penicillinase and therefore is inactive against penicillin-resistant *Staph. aureus.* The activity against enterococci is similar to ampicillin but apparently fourfold better than penicillin G (52,53).

Azidocillin is not significantly active against Gram-negative enteric bacilli, showing similar or less activity against *E. coli* and *Proteus* than penicillin G or V, and is clearly less active than ampicillin against enteric bacilli (52, 53).

CLINICAL PHARMACOLOGY Azidocillin (Table 2) shows good (about 75%) oral absorption, more complete than ampicillin or penicillin G or V. Peak serum levels, reached within 1 hr after oral doses, are somewhat higher than either penicillin G, V, or ampicillin, and appear equally rapidly after oral or im administration. Some 70% appears in the urine after oral administration compared with 85% after im doses (54, 55). Peak serum levels are slightly higher than penicillin G, V, or ampicillin following oral doses; however, this combination of slightly higher peak serum levels, together with MICs, which are only slightly lower against streptococci and pneumococci, produces theoretical therapeutic ratios against these pathogens which exceed those of any of the other penicillins (Table 3). This greater therapeutic margin would be offset in theory by the somewhat greater protein-binding of azidopenicillin, and it is unlikely that the theoretical ratio difference would prove clinically significant.

In studying experimental *H. influenzae* meningitis, Lithander found azidocillin and benzyl-penicillin levels in cerebrospinal fluid (CSF) slightly lower than ampicillin (56) and confirmed earlier studies in meningitis patients that suggested that ampicillin reaches slightly higher levels in CSF than does penicillin (24).

CLINICAL APPLICATION Azidopenicillin is under clinical trial for respiratory infections (57) with the objective of determining the clinical efficacy of this active penicillin which shows good pharmacologic characteristics together with high activity against respiratory pathogens, but like penicillin G or V, remains narrow spectrum in its limited activity against facultative enteric bacilli. Indeed, should azidopenicillin produce fewer reactions, or because of its lower activity against enterics and more complete upper GI absorption produce less change in lower intestinal flora than ampicillin, then such decreased side effects might represent a potential therapeutic advantage. Unfortunately, this expectation was not realized in one 6-month placebo-controlled trial of ampicillin and azidocillin for continuous prophylaxis in 40 children with severe chronic bronchitis and bronchiectasis (57). One third of the patients carried ampicillin- and cephaloridine-resistant *E. coli* at the beginning of the trial; this proportion did not change in the placebo group (who reported somewhat more respiratory symptoms), but the number with resistant coliforms doubled in both the ampicillin and azidocillin-treated groups. Kerrebigin's findings suggested that exposure to the 6-APA nucleus was sufficient stimulus to induce and/or select penicillinase producing strains of *E. coli* (57).

Cyclacillin

CLASSIFICATION AND ANTIMICROBIAL ACTIVITY Cyclacillin (amino-cyclohexane penicillin) is an acid-stable penicillin that shows moderate activity in vitro against a spectrum of organisms similar to penicillin and ampicillin. It is somewhat more resistant to degradation by staphylococcal penicillinase, but despite partial effective-

ness in experimental infections, it is not likely that the drug warrants clinical application in treatment of infections due to penicillinase-producing staphylococci. The activity against pneumococci, Group A streptococci, and nonpenicillinase-producing *Staph. aureus* is clearly less than ampicillin or penicillin G or V but is similar to that observed for cephalexin (58,59). Activity in vitro against selected Gram-negative bacilli is manyfold less than that of ampicillin, and from limited published data appears in the range expected for penicillin G or V (58, 59).

PHARMACOLOGY AND EXPERIMENTAL INFECTION From limited published data, cyclacillin appears to be reasonably well absorbed (60, 61), producing serum levels similar to penicillin V, but not as high as cephalexin (60, 61). Protein binding is a low 20%, similar to ampicillin, and produces a similarly small effect on MIC endpoints (58, 60).

The notable feature of cyclacillin is the marked discrepancy between its modest in vitro activity and its striking in vivo effectiveness in experimental infections particularly with Gram-positive pathogens. Not only were highly significantly lower ED_{50} values recorded for treatment of a variety of infections in mice, but the duration of effectiveness of single doses far exceeded that of ampicillin or penicillin (61). It seemed unlikely that low protein binding and good tissue diffusion were sufficient explanation for the differences between in vitro and experimental in vivo activity (61). This prolonged activity in vivo suggested the possibility that a metabolic product with residual antibacterial activity might be excreted slowly, such as the slow excretion of aminocyclopentane carboxylic acid found by Christensen in man and rat (62). Prolonged retention of such a metabolite would, if confirmed, also suggest careful study to rule out any unexpected tissue toxicity, for example, in the kidney which showed high levels of cyclacillin in animal tissue assays (58).

CLINICAL APPLICATIONS Clinical applications of cyclacillin are not well defined, and caution is indicated in view of the modest in vitro activity. Nevertheless, one controlled study of Group A streptococcal pharyngitis demonstrated equivalent effectiveness for cephalixin, penicillin V, and cyclacillin (63).

Carbenicillin Sodium

Disodium carbenicillin has been marketed extensively and has been the subject of recent reviews and symposia (64–67); the following summarizes the current status of parenteral carbenicillin.

CLASSIFICATION AND ANTIMICROBIAL ACTIVITY Carbenicillin (disodium α-carboxybenzyl-pencillin) is the first semisynthetic penicillin to reach extensive clinical application specifically because of its enhanced activity against selected Gram-negative bacilli, primarily *Pseudomonas* and indol-positive *Proteus*. It shows relatively modest activity against other Gram-positive and Gram-negative pathogens comprising an overall spectrum similar to that of ampicillin (68–72).

RESISTANCE OF PSEUDOMONAS AND ENTEROBACTERIACEAE TO CARBENICILLIN While most investigators have found that three fourths or more of *Pseudomonas*

strains are inhibited by 100 μg/ml or less, a part of the variability in various studies results from differences in methodology. Variation in endpoints results from differences in inocula, media, and test systems. On the other hand, the emergence of increasing proportions of resistant strains was predicted from early in vitro studies (71, 72). One common pattern of resistance observed in many strains seems to be a stable heterotypic manifestation not associated with production of specific inactivating enzymes, but manifest for example in discrepancies between inhibitory and bactericidal endpoints. A second mechanism for resistance has also been demonstrated. Episomal R-factors mediating linked resistance to carbenicillin, probably via carbenicillin β-lactamase, and to other antibiotics, have been transferred between *Pseudomonas* and other *Enterobacteriaceae* in vitro (73, 74), in vivo, and in burn wound infections with *Pseudomonas* and *Klebsiella* in mice (73), and such strains have emerged as major clinical problems (67, 73).

SYNERGISM BETWEEN CARBENICILLIN AND GENTAMICIN Carbenicillin and gentamicin show apparent synergism against many (probably one half to two thirds) strains of *Pseudomonas;* and in the remainder of isolates, these drugs are either addictive or are indifferent (75, 76). Combined therapy might hopefully 1. provide optimal therapeutic ratios in vivo, particularly in immuno-suppressed patients, 2. decrease the chance that resistant variants would emerge either in the individual patient, or 3. be selected epidemiologically, and 4. decrease the chances of gentamicin toxicity by lowering the gentamicin dosage required to achieve "adequate" serum bactericidal activity. It is unlikely that all of these goals will be achieved by combination therapy. Despite combined therapy, superinfections occur with other resistant Gram-negative bacilli, and resistant *Pseudomonas* variants have emerged (67). Final resolution of data suggesting effective results with carbenicillin alone (65) compared with findings of more effective response with combined therapy when the two drugs are synergistic (77), must await further definition of the pharmacologic-microbiologic findings in such series, hopefully prospectively controlled. Nevertheless, statistically improved results (82% "clinical success") when synergism was demonstrated versus 53% when the drugs used were not synergistic (77) and the weight of present evidence seems to favor combined therapy at least for severe infections with *Pseudomonas* when the infecting strain is synergistically inhibited in vitro (77, 82, 83).

CLINICAL PHARMACOLOGY Carbenicillin sodium is relatively unstable in acid pH and must be administered parenterally; it is approximately 50% protein bound and like penicillin G, is not a notably lipid-soluble compound, yet achieves reasonable tissue distribution. It is rapidly excreted in the urine, with most of the active drug recovered in the urine (Table 2). Following 0.5 g im doses, peak serum levels of 10–18 μg/ml are achieved. Intravenous infusions of 4 or 5 g can be given, producing rapid peak serum levels of several hundred μg/ml, and with levels 1 hr later still at 200 μg/ml. This exceeds the MIC of the majority of strains of *Pseudomonas,* but

because many isolates show MICs in the range of 64–256 μg/ml (Table 1), it is clear that for such strains only marginal therapeutic ratios would be achieved (Table 3) and would be maintained only for the first hr following the infusion.

The serum half-life of approximately 1 hr is slightly longer than penicillin or ampicillin. Thus, hepatic excretion and/or degradation of carbenicillin is slower than other penicillins. This is reflected also in longer half-lives in anuric patients (Table 7): 10–16 hours for carbenicillin compared with 3–4 hr for penicillin G and 8–9 hr for ampicillin. Primary hepatic failure also increases the serum half-life of carbenicillin up to 2 hr (78), but the severity of impairment in hepatic function was not correlated with the carbenicillin half-life (except in patients who also had impaired renal function). Kunin found the half-life of penicillin G was also markedly prolonged in patients with combined hepatic as well as renal failure (79). Probenecid delays renal secretion, elevating and prolonging the peak serum levels (80).

CARBENICILLIN INACTIVATION BY GENTAMICIN In view of the recommended combination of carbenicillin plus gentamicin therapy for serious Gram-negative infection, the report of apparent inactivation of gentamicin by carbenicillin in vivo as well as in vitro (81) has raised continuing concern. Several investigators have negated the in vivo implications of the original report, and Riff & Jackson have summarized further in vitro and in vivo data (84–87). Carbenicillin and gentamicin interact when mixed in vitro resulting in mutual inactivation, with higher rates of inactivation at higher temperatures, at high ratios of carbenicillin:gentamicin, and in water solution compared with saline (with the least reaction in serum). In vivo, however, Jackson found inactivation only in patients in severe renal failure with the expected gentamicin half-life $>$ 60 hours; the half-life of a dose of gentamicin was decreased to 24 hr by concomitant carbenicillin (87).

CLINICAL APPLICATIONS Clinical applications of sodium carbenicillin have been reviewed (67). The primary use of carbenicillin is for serious *Pseudomonas* infection, either alone or in combination with gentamicin, including septicemia (64), severe burns (88), osteomyelitis (89), meningitis (90), urinary tract infections (91a), and pulmonary infections (91). Many patients who develop *Pseudomonas* infections, of course, have serious underlying disease, and evaluation of the response to antibiotic therapy is difficult, particularly in pulmonary infections. Nevertheless, despite the relatively high MICs of many strains of *Pseudomonas,* carbenicillin is the only available penicillin analog with significant activity against *Pseudomonas,* and the only other available agents are gentamicin with its potential for toxicity, and the polymyxins, which probably are of limited value in systemic treatment of serious tissue infection. Carbenicillin is the only "nontoxic" antibiotic with demonstrated reasonable clinical efficacy in serious *Pseudomonas* infection. Similarly, carbenicillin is the only alternative or adjunctive nontoxic drug available for treatment of serious infection due to nonmirabilis *Proteus* or due to occasional additional tetracycline, ampicillin, and cephalosporin-resistant Gram-negatives that are often nosocomial in origin.

Indanyl Carbenicillin

CLASSIFICATION AND ACTIVITY Indanyl carbenicillin is the indanyl ester of carbenicillin (Figure 1). Sodium carbenicillin is not absorbed after oral administration, but the indanyl ester is stable at 37°C for 1 hr in gastric juice pH2, and as indicated in Table 2, some 40% absorbed. Specific assay for the ester shows an early transient peak in the serum at 30 min. Following absorption the ester is promptly cleaved by serum and tissue esterases to yield the primary antibiotic carbenicillin plus free indanol, and by 90 min the ester is no longer detectable in serum (92). The free indanol is conjugated as glucuronide and sulfate esters and is excreted almost completely in the urine (93). The indanyl ester is the most lipophilic of the penicillins and is highly protein bound (94). It has intrinsic antimicrobial activity which is similar to disodium carbenicillin for Gram-negatives, but which is significantly more active against Gram-positive pathogens, apparently as the result of the modified physical-chemical properties of the ester. Hydrolysis of the ester to carbenicillin takes place over a period of hours in broth but occurs quite rapidly in vivo, hence the actual activity in vivo is that of carbenicillin. The MIC and therapeutic ratio values listed in Tables 1 & 3 thus are those assayed as carbenicillin, not as the indanyl ester.

CLINICAL PHARMACOLOGY AND APPLICATIONS Some 40% is absorbed orally from 0.5 g doses, producing serum levels in the range of 5–10 μg/ml (102, 103). Higher dosage and multiple dose schedules produced increased levels, up to doses of 16–26 g/day which produced nausea, some vomiting and diarrhea, which limited further absorption. Serum levels reached 40 μg/ml and urine levels up to 7000 μg/ml on the large oral doses (94). On dosage schedules tolerated by most patients, however, the serum levels are not high enough to provide significant therapeutic ratios against Gram-negative organisms (see Table 3), and effective levels are achieved only in the urine. Indanyl carbenicillin therefore is indicated only for treatment of urinary tract infections where the drug provides unique therapeutic advantage against those organisms that are uniquely susceptible to carbenicillin among the "nontoxic" drugs —namely against *Pseudomonas,* nonmirabilis *Proteus,* and a few other selected enteric Gram-negative bacilli. The clinical efficacy of indanyl carbenicillin in treatment of urinary tract infection has been well documented (95–99). Cox has reviewed the clinical-pharmacologic paradox, however, that confronts the clinician attempting to manage patients with *Pseudomonas* or "persistent" *Proteus* urinary tract infections. Such patients too often have chronic renal disease and are already in renal failure (creatinine clearance under 15 ml/min), such that urinary concentrations of indanyl carbenicillin (or of other antibiotics) are too low to permit successful treatment (100, 101).

Ticarcillin

Ticarcillin (or α-carboxyl thienylmethyl-penicillin, Figure 1) is a semisynthetic penicillin that is unstable in acid solution and must be administered parenterally. The spectrum of organisms inhibited and the mechanisms and degree of activity are similar to sodium carbenicillin, with therapeutic utility also because of its activity

specifically against *Pseudomonas,* nonmirabilis *Proteus* species, and selected other Gram-negative bacilli usually resistant to other antibiotics except gentamicin or kanamycin. It is also synergistically active with gentamicin.

Early studies of ticarcillin show two potential advantages over carbenicillin sodium. First, its in vitro activity against a variety of organisms, but particularly against *Pseudomonas,* is slightly greater than carbenicillin (104–106). Secondly, it shows slightly advantageous pharmacologic characteristics in that serum levels are slightly higher and serum half-life slightly longer (107–109). These differences (see Tables 1 and 2) are therefore sufficient to produce a theoretically slight advantage in Therapeutic Ratio compared with carbenicillin sodium, as summarized in Table 3. Data from clinical applications of this compound have not yet been published.

CEPHALOSPORINS

An expanding series of semisynthetic cephalosporins have been produced from cephalosporin C, one of the three natural products originally derived from a strain of *Cephalosporium acremonium,* the other two antibiotics being cephalosporin N and a steroid antibiotic similar to fusidic acid. The 7-amino-cephalosporanic acid nucleus of course is related closely in structure to the penicillin nucleus, but has a fused dihydrothiazine instead of a fused thiazolidine betalactam ring (110). Production of 7-amino-cephalosporanic acid from cephalosporin C (5, 6) permitted evolution of a large number of derivatives with varying physical, biological, and antimicrobial properties. This group has been reviewed (111–115). We will comment on the "older" cephalosporins as a base for comparison with "newer" cephalosporins.

Cephalothin and Cephaloridine

Sodium cephalothin (thiophene-acetamido-cephalosporanic acid, Figure 2) was the first derivative marketed, and cephaloridine (with two side chains added, thienyl- and pyridylmethyl) soon followed. The cephalosporins antibacterial activity is via mechanisms similar to the penicillins interference with cell-wall synthesis and is also usually bactericidal. Cephalothin and cephaloridine have similar spectra of antimicrobial activity, including good activity against Gram-positive cocci and bacilli and against a broad (but not complete) spectrum of Gram-negative organisms. Important exceptions, such as *Pseudomonas* and *Enterobacter* species, are often resistant by virtue of production of β-lactamase (or "cephalosporinases") with varying substrate affinities and specificities (116–121).

Gram-negative β-lactamases can be inhibited or inactivated by binding if simultaneously exposed to a penicillinase-resistant penicillin such as cloxacillin (122, 123). Combined therapy with such a combination (e.g. cloxacillin plus ampicillin, or cloxacillin plus cephaloridine) has been accomplished in vivo (124–126) as well as in vitro, but this approach now is clinically useful or necessary only rarely, especially with the availability of carbenicillin.

Resistance to staphylococcal penicillinase is a major advantage of the antimicrobial activity of the cephalosporins. Cephalothin is highly resistant to hydrolysis

by staphylococcal penicillinase. Cephaloridine is sufficiently less resistant than cephalothin to penicillinase that use of cephaloridine for staphylococcal endocarditis has been questioned (116a). However, the predominant clinical experience has been favorable, including therapy of serious staphylococcal disease (115).

Table 4 summarizes the antibacterial activity of cephalothin and cephaloridine as well as the newer analogs. There is considerable variation in modes and ranges of MICs reported from various laboratories, depending upon methodology, inoculum size, strain selection, etc. This is particularly relevant in comparing data for many of the Gram-negative organisms for which a change in inoculum size may shift MIC endpoints twofold to eightfold and produce markedly different interpretation of susceptibility, as implied in the "Therapeutic Ratio" estimated in Table 6. For example, a three-dilution, methodology-induced variation in MIC endpoint of a *Streptococcus viridans* to cephalothin from 0.01 to 0.08 μg/ml need not raise therapeutic concern because of the high therapeutic ratio even at an MIC of 0.08 (Table 6); the therapeutic ratio for cephalothin in an *E. coli* tissue infection on the other hand is marginal at best (Table 6) and a three-dilution shift in MIC endpoint, from 2 to 16 μg/ml, might carry different implications concerning the susceptibility of that strain to therapy. This in part explains the variations reported in "percent susceptible" of various Gram-negative organisms to the various cephalosporins. Standardization of methodology and of interpretive standards for susceptibility testing is in need of improvement (see below).

Selected clinical-pharmacologic characteristics of cephalothin and cephaloridine are summarized in Table 5. Neither is significantly absorbed orally. Cephaloridine produces twice the serum levels of equivalent dosage of cephalothin, and the clearance of cephaloridine is slower, with a half-life of 1 hr compared with one-half hr for cephalothin. Therapeutic levels thus may be present in serum for only a brief period if cephalothin is given at 6 hr intervals. Both drugs are excreted in the urine in high concentrations.

Cephalothin is a weakly ionized salt, with a pK of about 2.8 similar to the pencillins, and a large component of the renal clearance of cephalothin is via tubular secretion. Cephaloridine is a zwitterion, relatively nonpolar, and renal clearance is equivalent to the glomerular filtration rate. Therefore, probenecid markedly delays urinary secretion of cephalothin, producing higher, more prolonged serum levels, whereas cephaloridine clearance is either unaffected (113) or only slightly delayed (111) by probenecid. Although cephalothin is 50–65% protein bound compared with only 25% for cephaloridine, and although neither is highly lipid soluble, both drugs appear in tissues and body fluids (114) and show 18 and 16 L/1.73 m^2 volumes of distribution, respectively (117a). CSF levels are poor, however, particularly for cephalothin (118a) and, while pneumococcal meningitis has been successfully treated with cephaloridine, cephalothin and cephaloridine have failed to clear meningococcal meningitis adequately despite in vitro susceptibility of the organism (119a).

Successful clinical application of cephalothin and cephaloridine have been extensive and comprise infection in most organ systems and with virtually all susceptible pathogens. Meningitis, particularly meningococcal, is an exception already mentioned. Septicemia or serious tissue infection, aside from pyelonephritis, due to

Table 4 Antibacterial activity of representative cephalosporin antibiotics

Bacterial Species	Cephalothin		Cephaloridine		Cefazolin		Cefoxitin		Cephaloglycine		Cephalexin	
	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)	MIC Mode (Range) (μg/ml)	Prop. "Resist."[a] (%)
Strep. pneumoniae	0.1(0.02-0.4)	(0)	0.03(0.01-0.2)	(0)	(0.1-0.3)	(0)	3		0.1(0.05-0.8)		2(0.1-12)	(1)[b]
Strep. pyogenes (A)	0.12(0.05-0.5)	(0)	0.01(0.002-0.1)	(0)	(0.1-0.3)	(0)	<0.8		0.2(0.05-2)		0.6(0.2-6)	(1)
Staph. aureus (Non-Pase)	0.1 (0.08-0.8)	(0)	0.1 (0.04-1)	(0)	0.1(0.06-2)	(0)	3		1.6(0.2-8)		2-6(0.5-16)	(1)
Staph. aureus (Pase)	0.2 (0.06-2)	(0)	0.5 (0.06-8)	(0)	0.3(0.06-8)	(0)	3		3(0.5-8)		2-9(0.5-16)	(1)
Enterococci	24(8-32)	(100)	16(4-32)	(100)	32(15-50)	(100)			50(16-128)		100(32-256)	(100)
N. gonorrhoeae	(0.25-3)	(1)	1.5	(1)	1(0.1->50)	(1)					3(0.1-6.3)	(1)
H. influenzae	(2-8)	(1)	(4-16)	(1)	(2-12)	(1)					>100(12.5->100)	(100)
E. coli	4(2-128)	(15[a])	2(1-256)	(15[a])	2(1-256)	(5[a])	3(1-25)	(5[a])	1(0.5-12.5)		4(1-32)	
Salmonella	(1.5-12)		(3-12)		2(1-6.25)						5(4-50)	(20[a])
Proteus mirabilis	2(0.5-12)	(10)	2(1-25)	(15)	1(0.5-5)	(5)	1(0.5-6)	(0)	3(1-25)		8(4-50)	
Proteus other	(32->256)	(100)	(64->256)	(100)	50(2.5-100)	(60[a])	6(3-25)	(10)	16->256		>100(25->100)	(100)
K. pneumoniae	4(1-8->256)	(15[a])	4(1-8->256)	(15[a])	2(1-8->256)	(15[a])	3(0.8->256)	(10[a])	1(0.25-4->256)	(10[a])	12(1->100)	(30[a])
Enterobacter	>100(2->256)	(90[a])	>100(2->256)	(90[a])	>100(2->256)	(80[a])	50(2->256)	(75[a])			>100(50->100)	(100[a])
Pseudomonas	>256		>256		>256		>256		>256		>256	

[a] "Resistant" to serum concentrations of drug achieved with "normal" dosage. Proportion may vary markedly depending on strain selection, nosocomial origin, and testing methodology including inoculum size.

[b] I = Many strains intermediate in susceptibility.

Table 5 Clinical-pharmacologic characteristics of selected cephalosporin antibiotics

Drug	Proportion of Oral Dose Absorbed (%)	Apparent Volume of Distribution ($L/1.73\ M^2$)	Protein-Bound (%)	Route of Admin.	Maximum Serum Level 0.5 g Dose Mode or Range (μg/ml)	Serum Half-Life (hr)	Renal Clearance / Creatinine Clearance (Ratio)	Recovery in Urine (% of Dose)
Cephalothin (CT)	2	18	50-80	im	6-11	0.8		50-75
				iv	30-40 (18[a])	0.5[a]	2.4[a]	50-65
Cephapirin	–		44-50	im	8	0.8		65
				iv-inf.	30	0.5		
Cephacetrile (CCT)	–		38	im	12[b]		2.2[a]	88
				iv-inf.	35[b] (16-28[a])	1.3[a]		
Cephaloridine (CR)	5	16	20-35	im	18-22	1.1-1.5		60-90
				iv	60 (25[a])	1.1[a]	1.0[a]	85[a]
Cefazolin (CZ)	–	10	74-86	im	40	1.8		70-80
				iv-inf.	120	1.8[a]		96[a]
Cephaloglycine	20-30		15	oral	2-4.5	2		8-25
Cephalexin (CX)	80+	15	12-15	oral	10-18	0.6-1.2		70-100
				im	8-10	0.9		
				iv-inf.	40 (27[a])	(0.6-0.9)[a]	1.7[a]	96[a]
Cephradine	95		15	oral	9-13	0.8		98
Cefoxitin				im	11			
				iv-inf.	47	0.8		78

[a]Data following continuous iv infusion to achieve steady state (CT and CX = 0.5 g/hr; CR = 0.25 g/hr; CCT = 0.4-0.5 g/hr).

[b]Estimated by extrapolation from levels after 1 g doses.

Table 6 Estimated minimum therapeutic ratios for cephalosporin antibiotics against common pathogens

Drug	Route of Admin. of 0.5 g Dose	Ratio (minimum peak serum level[a]/MIC[b])									
		Str. pn.	*Str. A*	*St. aur.* (Pase)	*St. aur.* (N-Pase)	*Enteroc.*	*E. coli*[c]	*Klebs.*[c]	*Enterob.*[c]	*Pr. mirab.*[c]	*Prot.* other[c]
Cephalothin	im	15	12	3	10	0.2	1	0.5	0	1.5	0.2
	iv-inf.	50	40	10	20	1	2.5	2.5	0	2	1
Cephapirin	im	30	25	3	10		0.7	0.8	0	1	0.2
	iv-inf.	100	75	10	20		2	2.5	0	3	1
Cephacetrile	im		12	2	5	0.5	4	1		1	
	iv-inf.		35	6	15	1.5	12	3		3	
Cephaloridine	im	100	200	2.5	20	1	5	2	0	5	0.2
	iv-inf.	300	600	8	60	3	15	6	0	15	1
Cefazolin	im	120	120	5	20	1	10	5	0	10	1
	iv-inf.	400	400	40	60	3	30	15	0	30	2
Cephaloglycine	oral	2.5	1	0.3	0.3	0.04	1	0.5	0.04	1	0.1
Cephalexin	oral	1	1.5	0.7	0.7	0.1	1	0.7	0	1	0
	im	1	1.5	0.7	0.7	0.1	1	0.7	0	1	0
	iv-inf.	4	6	2	2	0.5	4	3	0	3	0
Cephradine	oral	1	1.5	0.7	0.7	0.1	0.7	0.4	0	1	0
Cefoxitin	im	3	20	3	3		2	2	0.2	5	1
	iv-inf.	12	80	12	12		8	8	0.8	20	4

[a] Minimum value from reported range of peak serum levels, unadjusted for duration of level, volume of distribution, etc.

[b] MIC - Minimum inhibitory concentration - (Maximum of range of MICs for species or strains considered "susceptible" to therapy, unadjusted for protein-binding, tissue diffusion, etc.; used in deriving the ratio estimate.)

[c] Higher dosage would achieve higher ratios with some strains but a variable proportion are quite resistant and would not be amenable to any therapy. Others are inhibited at high levels such as achieved in urine.

Gram-negative bacilli such as *E. coli* or *Klebsiella* which appear susceptible to cephalosporins, show variable outcomes, only partly successful. Fatal or unsatisfactory outcome is usually caused by serious underlying or complicating disease. Nevertheless, caution is needed in interpretation of therapeutic results with serious tissue Gram-negative bacillary infection treated with cephalosporins, as well as penicillins, because of the narrow therapeutic margins for the cephalosoporins, even in those strains that are not highly resistant by virtue of cephalosporinase production. Use of large doses, when possible, improves the ratios, but many investigators prefer to employ kanamycin or gentamicin instead or along with the cephalosporin.

Significant renal toxicity has occurred in a small number of patients treated with large doses of cephaloridine (120a) and this drug induces renal lesions in animals, whereas little reaction is seen with cephalothin (121a). Cephaloridine dosage must, therefore, be limited to approximately 4 g per day and be adjusted downward in the presence of markedly impaired renal function (120a).

Primary allergic and hypersensitivity reactions occur with these drugs, just as with the penicillins. Immunologic cross-reactivity between the penicillins and the cephalosporins is demonstrable both clinically and experimentally (122a, 123a). However, cross-allergy is sufficiently incomplete that numerous patients with a history of allergy to penicillin have received cephalosporins without reaction; indeed, cephalothin or cephaloridine have been considered excellent drugs for treating serious Gram-positive coccal infections such as endocarditis in patients allergic to penicillin (124a). Nevertheless, the incidence of reaction to cephalothin or cephaloridine is higher in patients with than in those without a history of penicillin allergy (125a); therefore, caution is still advisable in evaluating indications and initiating therapy in such patients.

Cephalogycline

Cephaloglycine (α-amino-phenyl cephalosporanic acid) was the first marketed cephalosporin with marginal but clinically useful oral absorption. Protein binding is low. However, only some 10–25% is absorbed, and serum levels remain too low for effective systemic therapy (126a) (Tables 5, 6). It is only because of good renal clearance by both filtration and tubular secretion that urinary levels are adequate to treat urinary tract infections (127). A large portion of the drug is converted to the desacetyl derivative that is excreted in the urine. Cephaloglycine is somewhat unstable in vitro, particularly at neutral or slightly alkaline pH (128), explaining some of the variability in reported MICs and in bioassay of serum levels. The drug shows moderate activity against a spectrum of Gram-positive cocci and Gram-negative bacilli similar to that of cephalothin. Activity in experimental infection is higher than predicted from the low serum activity, suggesting that the desacetyl product might show some intrinsic additive antibacterial activity in vivo (128). Clinical application of cephaloglycine has been limited to treatment of urinary tract infection, but it now has limited use even for this indication in view of the later development of cephalexin and cephradine, and the availability of other drugs that also show better serum and tissue activity.

Cephalexin

Cephalexin (7-α-amino-α-phenylacetamido-3-methylcephemcarboxylic acid) is minimally protein bound, acid stable and well absorbed (80% or better) following oral administration. Virtually all of the absorbed drug is recovered in the urine in unchanged, active form (129). Serum half-life from steady-state iv administration is 0.6–0.9 hr, intermediate between cephalothin and cephaloridine (130). Renal clearance includes some tubular secretion as well as filtration (130); probenecid will therefore enhance the duration of serum levels.

There has been considerable variation in the ranges of MICs for cephalexin reported by various investigators. For example, Braun et al reported median MICs for penicillinase-producing *Staph. aureus* of 12.5 μg/ml (131), whereas other laboratories report siginificantly lower modes and ranges (126–130, 132–134). Differing methodology again undoubtedly accounts for these differences. Oral cephalexin in fact has produced good clinical responses even in staphylococcal septicemia (135). Furthermore, efficacy equivalent to that of penicillin V has been demonstrated in controlled trials of streptococcal pharyngitis therapy (136, 137), despite higher MICs of streptococci to cephalexin. These clinical experiences suggest that even relatively low therapeutic ratios, if coupled with at least fair tissue distribution, as has been demonstrated for cephalexin (138) and reasonable drug distribution volumes equivalent to those of cephalothin and cephaloridine (130), can produce adequate response. It is clear, however, that regardless of the exact MIC values, cephalexin is comparatively less active than penicillin G or V, cephalothin, or cephaloridine against streptococci, pneumococci, and penicillin-sensitive staphylococci, and less active than nafcillin, the isoxazolyl penicillin, cephalothin, or cephaloridine against penicillinase-producing *Staph. aureus* (126–134). Therefore, it is doubtful that cephalexin should be recommended as standard therapy for serious staphylococcal infection.

Against "susceptible" Gram-negative bacilli the activity of cephalexin is often less than that of cephalothin or cephaloridine, but usually in the same range (Table 4). Levels in the urine are high and usually adequate to achieve satisfactory clinical response against organisms with reasonably low MICs. Even in renal failure, adequate levels of cephalexin are usually achieved in the urine for treatment of urinary tract infections. Clark noted that in 17 of 49 patients being treated for urinary tract infection, bacteriuria did not clear (139)—this was not a controlled study but represented a higher failure than anticipated in that patient group. A variety of other Gram-negative infections have been successfully treated with cephalexin usually in uncontrolled studies (e.g. 140, 141).

Cephradine

CLASSIFICATION AND ANTIMICROBIAL ACTIVITY Cephradine is 7-amino-cyclohexadienyl-acetamido-(cephalosporanic acid) with structure, activity, and pharmacology very similar to cephalexin. It is acid stable and shows low protein binding. Antibacterial spectrum and relative activity are also similar to that of cephalexin.

Against pneumococci, streptococci, and *Staph. aureus* cephradine, as well as cephalexin, has moderately high activity but less than cephalothin or cephaloridine. Against noncephalosporinase-producing Gram-negative bacilli its activity, as cephalexin, is only moderate, with many strains of *E. coli, Proteus mirabilis* and *Klebsiella* inhibited by 3 to 12 μg/ml but with a number of strains slightly (e.g. one dilution) more susceptible to cephalexin (142). Bactericidal activity is relatively good, with usually only one dilution separating inhibitory and bactericidal endpoints (142).

CLINICAL PHARMACOLOGY AND CLINICAL APPLICATION Like cephalexin, cephradine is well absorbed orally; serum levels ranged from 9–13 μg/ml but were a little lower than recorded for cephalexin. During treatment even of Gram-negative infections, serum inhibitory titers were usually at least 1:2 on 2–3 g dosage per day provided the MIC of the pathogen was <3 μg/ml. The serum half-life (0.8 hr) is similar to that of cephalexin, and high levels of active drug appear in the urine. Few studies of clinical efficacy have yet appeared, but available uncontrolled data indicates that, just as for cephalexin, a variety of respiratory, soft tissue, wound and urinary tract infections due to Gram-positive and Gram-negative pathogens should respond to treatment (143). Uncontrolled cephradine therapy in treatment of *Salmonella* and *Shigella* gastroenteritis was difficult to evaluate (144) as would be expected. Super-infections occurred (142), again as anticipated following therapy with any broad-spectrum antibiotic. There is no indication to date that side effects or toxicity will differ from those from cephalexin. Cephradine appears equivalent clinically to cephalexin, but if any minor theoretical difference is notable, it is that the combination of slightly lower serum levels and slightly higher MIC values for some enteric organisms may produce some slightly lower estimated therapeutic ratios (Table 6).

Cephapirin

CLASSIFICATION AND ANTIBACTERIAL ACTIVITY Cephapirin (7-pyridylthioacetamid-cephalosporonate) is a semisynthetic cephalosporin that is similar to cephalothin in activity, phamacology, and application. It is only slightly less serum bound (44–50% compared with 65% for cephalothin), and is not orally absorbed but is stable for 8 hr at room temperature in standard iv fluids. Antibacterial activity against pneumococci and Group A streptococci is excellent, in the range 0.01 to 0.06 μg/ml, and is two- to fourfold more active than cephalothin (145–147). Resistance to *Staph.* penicillinase is excellent, and activity against *Staph. aureus* is comparable to that of cephalothin. Against Gram-negative bacilli, cephapirin shows moderate activity, comparable to that of cephalothin, but where minor twofold differences have been noted such as with *E. coli, Klebsiella,* and *Proteus mirabilis,* the differences favored cephalothin (145, 146). Like cephalothin the drug is not active against *Enterobacter,* nonmirabilis *Proteus, Enterococci,* or *Pseudomonas. H. influenzae* is only moderately susceptible to cephalosporins, and Khan (148) noted failure of cephapirin to clear the organism from pulmonary infections in children.

CLINICAL PHARMACOLOGY AND CLINICAL APPLICATION Serum levels of cephapirin following iv and im administration are comparable to cephalothin (Table 4), and the drug is rapidly cleared, serum $T\frac{1}{2}$ 0.5–0.8 hr, with high urinary level, as with cephalothin (149, 150). A number of early reports have shown satisfactory clinical response in treatment of a similar spectrum of serious infections due to Gram-positive coccal and Gram-negative organisms as expected for cephalothin. Inadequate information is yet available to establish any differences in reaction rates [e.g. eosinophilia noted by Gordon (145)]. However, less pain upon im injection has been noted compared with cephalothin (146), and two prospective controlled studies recorded less phlebitis from iv cephapirin than from cephalothin (151, 152).

Cefazolin

CLASSIFICATION AND ANTIMICROBIAL ACTIVITY Cefazolin is a semisynthetic cephalosporin that differs from cephalothin and cephaloridine in that it has both a tetrazolylacetyl side chain at the amino linkage and a methyl-thiadiozolyl-thiomethyl group at R_2, the 3-position of the 7-aminocephalosporanic acid (Figure 2). Cefazolin is some 75% protein bound, similar to cephalothin but considerably higher than cephaloridine. Antibacterial activity against streptococci, pneumococci, and staphylococci is excellent, approximately the same as cephalothin, severalfold more active than cephalexin, but two- or fourfold less active than cephaloridine. With α strep. and *Staph. epidermidis* from patients with endocarditis, Quinn (153) found cefazolin less active than cephalothin or cephaloridine, whereas cefazolin was comparable to the other compounds in activity against *Staph. aureus*.

Activity of cefazolin against susceptible Gram-negative pathogens, although variable, as with other cephalosporins, is usually similar or somewhat greater than the activity of cephalothin and cephaloridine, although in one series (154) cefazolin did not inhibit heavy inocula of proteus mirabilis. *Pseudomonas* are quite resistant, and cefazolin shows little activity against other *Proteus, Enterobacter,* and enterococci. Studies of cephalosporinase activity from several specific hospital-isolated strains of Gram-negative bacilli indicated that cefazolin was the most labile of the cephalosporins studied (119). Further experience is needed to determine the degree of variability in cephalosporinases from a wider sampling of strains in different locations and their stability and reproducibility, especially in view of their transmissibility by episomal R-factors (116–121).

CLINICAL PHARMACOLOGY Cefazolin shows several marked differences in pharmacokinetics compared with cephalothin and cephaloridine (Table 5), (154, 155, 161, 162). A number of studies have demonstrated the highest serum levels following im injection of cefazolin compared with any of the cephalosporins, approximately twice as high as cephaloridine and four times the levels of cephalothin. Experimental renal toxicity is minimal (163). Plasma and renal clearance is much slower than most of the other cephalosporins, with a serum half-life of 1.8 hr determined following continuous infusion to achieve a steady-state baseline (155). Cephanone is the only cephalosporin with a longer half-life (2.5 hr). The apparent pharmacologic advantages of high serum levels and longer half-life may theoreti-

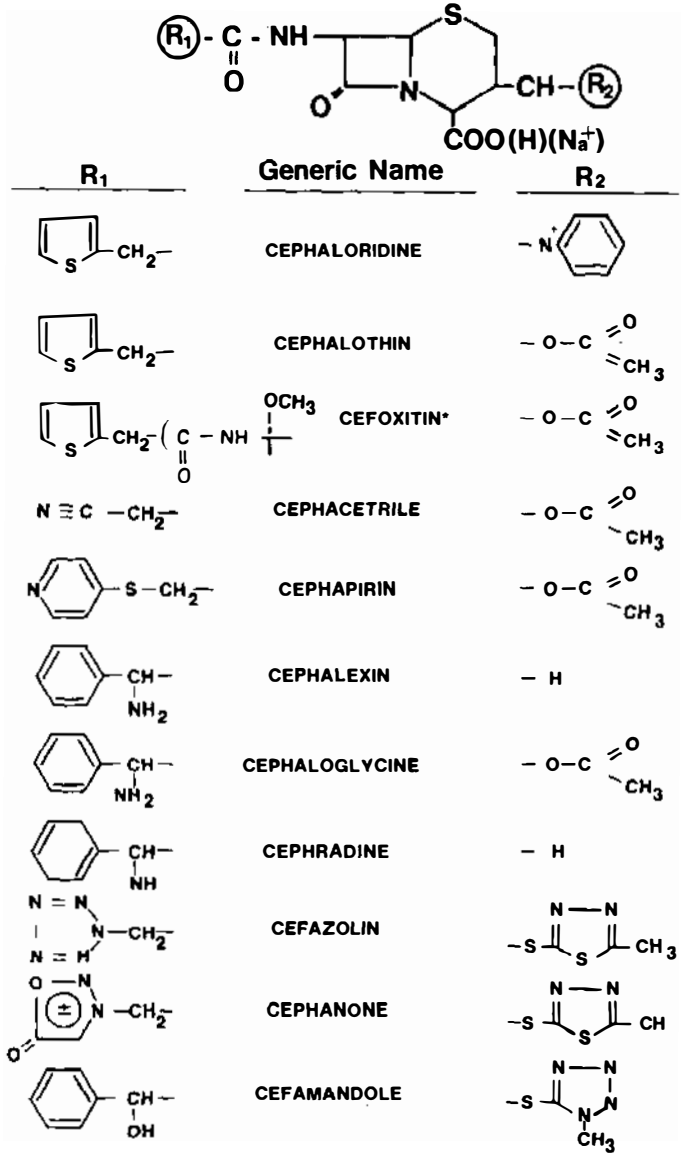

Figure 2 Structure of cephalothin and representative newer cephalosporin antibiotics
* = Derivative of cephamycin series of naturally occurring 7-methoxylated cephalosporin antibiotics.

cally be contradicted in clinical application by the higher protein binding of cefazolin and the smaller volume of distribution. It is possible that cephaloridine or cephalexin, with low protein binding and larger volumes of distribution, may have greater concentrations of free drug available in tissue fluids. This possibility is not borne out by animal studies showing high levels of cefazolin in bile and in other tissues (156, 157). It is not known whether these apparently paradoxical findings can be extrapolated to humans. Cefazolin is not transported into uninflamed meninges (154), but is found in the inflamed synovial fluid, and to a lesser extent is excreted in bile (154).

CLINICAL APPLICATIONS Limited studies have demonstrated effective therapy by cefazolin for urinary tract infections, a variety of respiratory infections including notably one bacteremic *H. influenzae* infection, skin and soft-tissue infections, and bone and joint infections (154, 158–161). Several of these patients were bacteremic, and the cure of a number of cases of endocarditis (153) would further substantiate that cefazolin is established as an effective agent against susceptible organisms. Thorough evaluation of the results to be expected as a sole agent in treatment of Gram-negative bacillary septicemia will require much additional data.

Cephacetrile

CLASSIFICATION AND ANTIMICROBIAL ACTIVITY Cephacetrile, (7-cyan-acetamido-cephalosporanic acid, Figure 2), is a semisynthetic cephalosporin that is not absorbed orally and resembles cephaloridine in protein binding. Knusel recorded 38% protein binding for cephacetrile, compared with 35% for cephaloridine and 62% for cephalothin (164). Cephacetrile resembles cephalothin and cephaloridine in spectrum and degree of antibacterial activity, with median MICs against *Staph. aureus* slightly higher than cephalothin or cephaloridine, although cephalothin was more resistant than the other two drugs to in vitro hydrolysis against penicillinase produced by two specific strains (165). Methicillin-resistant strains of *Staph. aureus* showed resistance to cephacetrile, as to cephalothin and cephaloridine (164, 165). Cephalothin gave more stable endpoints to changing inoculum size of *Staph. aureus* strains. Against both cephalosporinase and noncephalosporinase-producing strains of *E. coli,* inoculum size strongly influenced the MIC endpoints for cephacetrile, cephalothin, and cephaloridine. Overall distribution of *E. coli* MICs for cephacetrile was intemmediate between the other two drugs, with a modal MIC of approximately 3 μg/ml. *Proteus* species showed a similar distribution for all three drugs, with modal values approximately 6–10 μg/ml for cephacetrile being slightly higher. Enterococci were only moderately sensitive, with Knusel's endpoints of ~ 3 μg/ml intermediate between cephalothin and cephaloridine (164).

CLINICAL PHARMACOLOGY Cephacetrile must be administered parenterally, producing serum levels of 20–25 μg/ml after *1* g doses. Serum half-life ranges from 0.5 to 0.6 hr following single rapid iv infusions, up to 1.3 hr for calculated $T_{1/2}$ after continuous iv infusions to achieve steady-state conditions (166). Most of the active drug is recovered in urine (approximately 88%), and calculation of renal/creatinine

clearances gave a ratio of 2.2, similar to the 2.4 ratio for cephalothin, indicating significant tubular secretion (166). Little drug was found in human bile following single doses (167). Severe renal failure increased serum half-life to 24 hr (166), Table 7.

Detailed studies in dogs revealed no nephrotoxicity for cephaloridine or cephacetrile, even with concomitant furosemide (168). Both cephaloridine and cephacetrile showed significant levels in renal lymph when plasma concentration was high, but cephacetrile was much lower at low plasma levels (168). Overall, the data indicates that cephacetrile should be a comparably effective drug to cephaloridine and cephalothin, with comparable therapeutic ratios (see Table 6).

CLINICAL APPLICATIONS Clinical results in uncontrolled evaluation of treatment of 27 patients comprising soft tissue infections, respiratory infections, and urinary tract infections suggest comparable results to those anticipated for cephalothin or other cephalosporins (169). Hodges et al found no renal toxicity, but did encounter phlebitis, some pain on injection, eosinophilia, and benign thrombocytosis [which Olef (170) has reported during convalescence from infection.] Transient benign direct Coombs positivity was also noted, as previously seen with cephalothin and cephaloridine (171, 172).

Cefoxitin

CLASSIFICATION AND ANTIBACTERIAL ACTIVITY The cephamycins are a series of natural occurring 7-methoxylated cephalosporin antibiotics originally derived from strains of *Streptomyces* (173). From among cephamycins A, B, and C, cephamycin C showed greater resistance to specific β-lactamases and greater activity primarily against Gram-negative organisms. Synthetic modification of cephamycin C was aimed at enhancing the Gram-positive spectrum, while retaining β-lactamase resi-

Table 7 Effect of severe renal failure on clearance of penicillins and cephalosporins

Drug	Serum Half-Life (Hours)	
	Normal Subjects	Patients in Severe Renal Failure (Anuric or Creatinine Clearance under 5 ml/min)
Penicillin G	0.4-0.6	3-4
Ampicillin	0.6-1	8-12
Carbenicillin	1.0	10-16
Cephalothin	0.5-0.8	3
Cephaloridine	1.1-1.5	8-24
Cephacetrile	1.3	24
Cefazolin	1.8	25-45
Cephalexin	1.7	20-30

tance and Gram-negative activity. Cefoxitin is 7-α-methoxyl, 7-thienyl-acetamido cephalosporanic acid (see Figure 2). It is more active than cephalothin against Gram-negative bacilli. Cefoxitin particularly shows unique activity among the cephalosporins in that it inhibits *Serratia* at 6–50 μg/ml and *Proteus morgagni* at 3–12 μg/ml, two species that are usually resistant to cephalothin. Cefoxitin is also two- to fourfold more active than cephalothin against Gram-negative bacilli such as *E. coli* and *Klebsiella*. Only a minor portion of *Enterobacter* strains are inhibited, and all *Pseudomonas* are resistant. Activity against Gram-positive cocci is distinctly less than cephalothin or cephaloridine but still should be adequate for effective therapy. In summary, cefoxitin shows a unique antibacterial spectrum advantage in its activity against *Serratia* and *Proteus morgagni;* its somewhat improved activity against other Gram-negative bacilli is also of interest and will require clinical evaluation (174–177).

CLINICAL PHAMACOLOGY (Table 5). Serum levels following 0.5 g doses im and iv reach an average of 11 and 47 μg/ml respectively, in the same range as cephalothin and cephacetrile, but not as high as cephaloridine or cefazolin. Serum and urinary clearance is rapid, with a serum half-life of 0.8 hr, similar to cephalothin, cephapirin, and im cephalexin. Renal excretion is via both glomerular filtration and tubular secretion (178–180).

COMMENT—SELECTED PROBLEMS

Inactivation of Cephalosporins and Penicillins by β-Lactamases

β-Lactamases produced by different bacterial species show different chemical properties, substrate specificities, etc, and these characteristics are relevant in determining resistance to penicillins and cephalosporins (116–123). For example, Jackson (119) recently reported starch-gel electrophoretic study of six cephalosporins, grouped by side-chain structure, as test substrates for β-lactamases extracted from hospital strains of *Klebsiella, Enterobacter, E. coli* and *Pseudomonas,* both penicillin-induced and noninduced. Variable specificities were confirmed. Cephalosporinase from a *Klebsiella* strain degraded cephaloridine at the least rate and cefazolin some 11 times greater, with cephacetrile and cephalothin intermediate, but avidity and activity of the *Klebsiella* enzyme were greatest for penicillin. In contrast, an *Enterobacter* strain produced enzyme that was a much more active cephalosporinase than penicillinase. Jackson's and Fraher's findings further suggest that resistance may relate better to avidity of enzyme for drug, than to substrate reaction velocity (119, 123). The penicillin-induced *Pseudomonas* β-lactamases exhibited high avidity and activity for both penicillins and cephalosporins.

Jackson's findings indicated that against the *Klebsiella* enzyme, the side-group diazole (cephanone) was more stable than the tetra-azole group, (cefazolin) in the R-1 position (Figure 2). Against *Enterobacter* β-lactamase, the cyano group at R-1 (cephacetrile, Figure 2) was the most stable, but against the *Klebsiella* enzyme, the R-1 thiophene group in cephalordine and cephalothin was more stable than the cyano-(cephacetrile) group (119). Further development of semisynthetic cephalosporin and penicillin antibiotics of course are being aided by such studies relating

natural inactivating enzyme avidities and kinetics to specific chemical side-chain moieties (116–121).

Standardization and Interpretation of Antimicrobial Susceptibility Testing

In the past, various procedures have been used in clinical microbiology laboratories for routine susceptibility testing of antimicrobial agents, and often the disc-diffusion methods have not been well controlled. Shortcuts in technique such as lack of standardization of inoculum size and failure to measure the size of the zone of inhibition have led to errors and inconsistencies. Misleading information has also resulted from testing of inappropriate drugs and testing of organisms that are not rapid-growing pathogens or organisms for which susceptibility tests do not assist and may even confuse clinical management. The US Food and Drug Administration has now officially required that antibiotic discs include a package insert describing standard methodology, either the "Kirby-Bauer" method (181), or standardized modifications (182), as recommended by the National Committee for Clinical Laboratory Standards. Improved standardization of microbiologic methodology used even in research laboratories engaged in clinical-pharmacologic investigation of newer antibiotics would also help avoid the significant discrepancies in data reported from different centers. Adoption of standard reference antibiotic testing methods, as recommended by the Report of an International Collaborative Study (183), would result in less conflicting microbiologic data, facilitate coordinated evaluation of new agents, and assist in deriving standards for interpretation.

Once standardization of procedures has been achieved in clinical laboratories, further revisions are needed in deriving more appropriate standards for interpretation of susceptibility testing results. Present guidelines (181) divide the ranges of MICs estimated from the disc test into three categories: Sensitive, Intermediate, and Resistant. This interpretation is partly misleading in that the Sensitive category is extremely broad, e.g. placing a Sensitive staphylococcus with an MIC to cephalothin of 0.1 μg/ml in the same interpretive category as an *E. coli* which is a hundredfold less susceptible, with a cephalothin MIC of 10-15 μg/ml. For the *E. coli,* this MIC can be exceeded with a reasonable average Therapeutic Ratio of 5 or 10 or more only in the urine, with low, "standard" doses, or else requiring high doses for achieving adequate serum levels for treatment of tissue infection (see Table 6). Much more directly relevant would be the adoption of four interpretive categories (183): (*a*) highly sensitive (*b*) moderately sensitive (*c*) slightly sensitive, and (*d*) completely resistant. With these guidelines, testing, for example, of a *Klebsiella* from a urinary tract infection with an MIC to cephalothin of 32 μg/ml could quite appropriately be evaluated as group *c* or slightly sensitive, implying that with normal dosage it would be amenable to inhibition only by the high levels achieved in the urine.

Evaluation of Antibiotics—Role of Tissue Levels

The pharmacologic findings reviewed in sections A and B and the summary data in Tables 1–7 rely heavily on pharmacologic kinetics of blood levels. Probably of greater physiologic importance may be the levels actually attained and maintained

in the infected tissue, with the blood levels of indirect importance. The pharmacokinetics of delivery of antibacterial agents into tissue or interstitial fluid is complex, and must take into account more information than merely protein binding and serum and urine level kinetics. For newer antibiotics, further data should be derived concerning more detailed aspects of lipid solubility, ionization constants, and membrane transport in order to compare effective tissue levels. For example, lipid solubility and tissue diffusion of the penicillins and cephalosporins, most of which are weakly ionized, is generally only moderate in the absence of inflammation (184), whereas higher tissue levels should be achieved with lipid soluble drugs such as the tetracyclines, chloramphenicol, or erythromycin. Experimental models for sampling of skin, tissue fluid, or lympatics in man or animals give somewhat variable results, with different sampling systems showing differing time-diffusion kinetics and serum/tissue concentration ratios, and variable correlation with protein binding. Furthermore, the relationship of such experimental systems to natural infection is unsettled and clinical confirmation is needed. For example, Calnan's perforated plastic cylinders produce "physiologic" tissue fluid (188, 189), but the integrity of blood supply has been questioned (191). Further studies of methods for measuring tissue diffusion in relation to clinical pharmocology and clinical effectiveness of antibiotics would aid in evaluation of newer agents (185–187, 190).

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