MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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STILL NEWER ANTIBIOTICS

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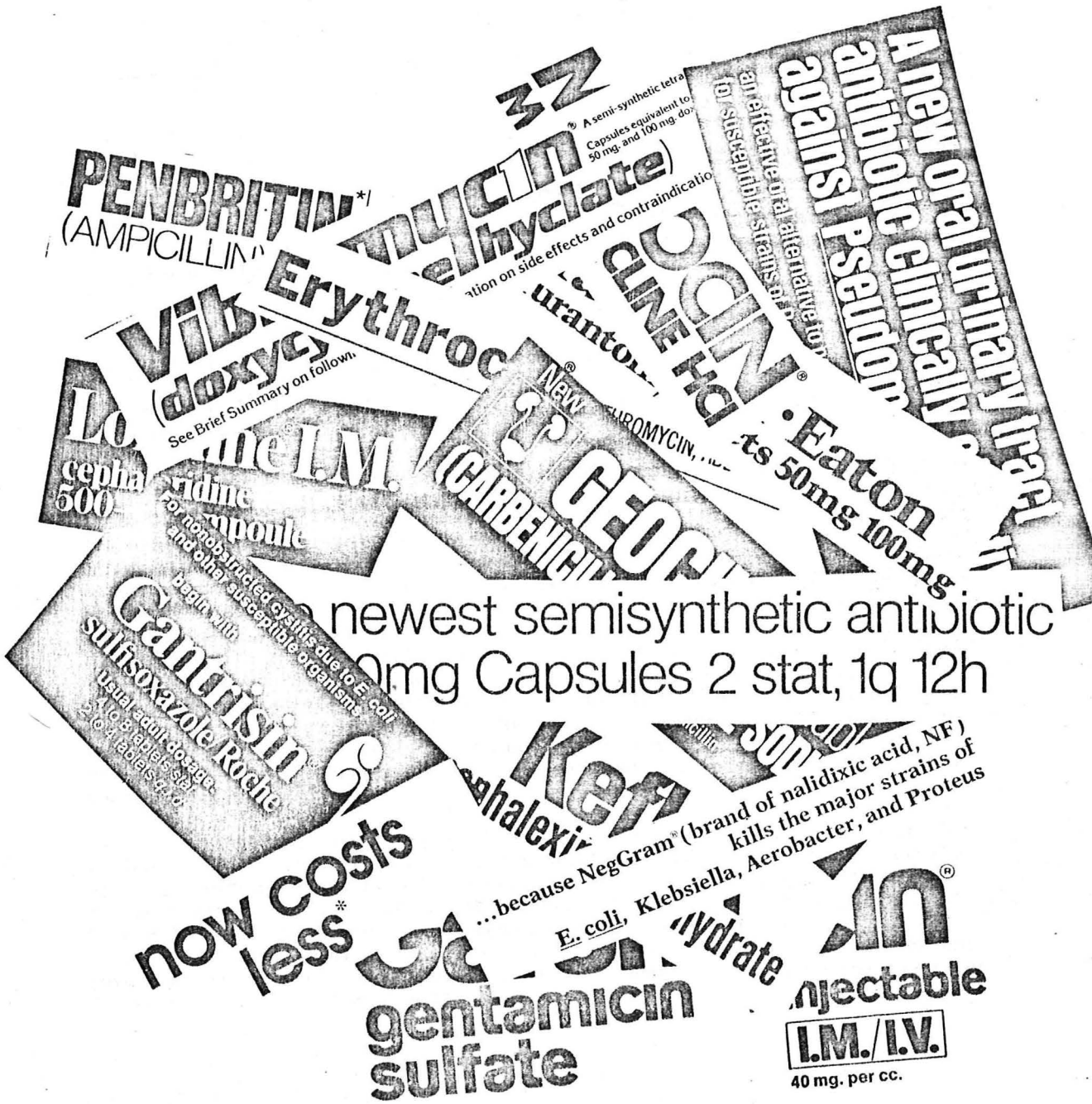


"STILL NEWER ANTIBIOTICS"

The continuing introduction of new antimicrobial agents provides the health professions with a greater capability to manage infections, yet, concomitantly, makes the rational and appropriate use of antibiotics more complex. Not only has selection of an optimal antibiotic become more complex, but just as environmental pollution has assumed general recognition, antibiotic pollution is becoming appreciated and likely will come under voluntary or regulatory control, thus also making the decision to initiate antibiotic therapy more complex.

The extent of antibiotic pollution is reflected by data from the Food and Drug Administration, which is required to certify antibiotics prior to distribution. According to Dr. C. E. Edwards, in 1971 the FDA certified 2,000,000,000 tetracycline capsules and approximately 20,000,000,000 (billion) doses of antimicrobial agents for human use (1). It seems obvious that this represents overusage; What is the potential health hazard of this practice? Is this responsible at least in part for the increasing prevalence of gram-negative bacillary infections? Is this responsible for the progressive decline in susceptibility of the anaerobe *Bacteroides fragilis* to tetracycline? Has a similar phenomenon in Mexico been responsible for the appearance of chloramphenicol-resistant strains of *Salmonella typhi* in Mexico? These questions are unanswered, but of obvious significance. There is evidence that curtailment of antibiotic usage within closed environments such as hospitals can greatly modify the patterns of antimicrobial susceptibility found in bacterial isolates, with elimination of selected antibiotics being associated with an increased prevalence of susceptible isolates (2, 4). However, it has required only brief reintroduction to select multiply resistant isolates (4).

The Joint Commission on Accreditation of Hospitals requires Infection Control Committees to "review periodically the use of antibiotics as they relate to patient care within the hospital" (5). In the Dallas County Hospital District, the usage of selected antibiotics has been assembled (Table 1). Are these rates of usage at Parkland excessive? From the standpoint of control, the evidence suggests that patterns of antibiotic usage influence not only the recipients of the drugs, but other patients within the hospital who may acquire an infection caused by a resistant organism. Thus, individual control in the use of antimicrobials with increased reliance on other measures, e.g., aseptic practices, isolation procedures, drainage of closed space infections, is assuming an increased importance if regulatory control is to be minimized. Even when appropriate individual antibiotic usage is practiced, there may be circumstances whereby within the hospital setting, which includes its outpatient facilities, it is advantageous to reserve the use of specific agents for infections due to specific organisms in specific patient groups.

It is against this background, as well as the individual considerations of efficacy, lack of toxicity, ease of administration and cost, that some of the newer antimicrobial agents will be reviewed and compared. The review will follow two approaches: first, a comparison of "newer" agents with the agents which might be considered as standards; and second, an assessment of the role of "newer" agents in the treatment of selected infectious disease problems. The problems have been selected either because the "newer" agents appear to be the agents of choice or because they are in the vogue.

TABLE 1

ANTIBIOTIC USAGE - DALLAS COUNTY HOSPITAL DISTRICT
(Parkland Memorial and Woodlawn Hospitals) - 1971

ANTIBIOTIC	UNIT	NO. UNITS USED	ASSUMED AV. COURSE*	NO. COURSES OF THERAPY	NO. UNITS PER 1000 DISCHARGED PATIENTS†	NO. COURSES PER 100 DISCHARGED PATIENTS
Cephalothin	1.0 gm	31,440	56 gm	561.4	1020	1.82
Gentamicin	2.0 ml (80 mg)	14,306	1680 mg	681.2	4644	2.21
Carbenicillin	1.0 gm	10,318	140 gm	73.7	335	0.24

* Cephalothin 8.0 gm/day for 7 days
Gentamicin 240 mg/day for 7 days
Carbenicillin 20 gm/day for 7 days

† Discharges for 1971: 30,807

I. COMPARISON OF "NEWER" WITH STANDARD AGENTS

PENICILLINS

TABLE 2

PENICILLINS

First Generation Newer Penicillins versus Penicillin G

a. Penicillinase-Resistant Penicillins

Standard: None *Newer*: Methicillin
Nafcillin
Oxacillin
Cloxacillin
Dicloxacillin
Flucloxacillin

b. "Broad Spectrum" Penicillinase-Susceptible Penicillins

Standard: Penicillin G *Newer*: Ampicillin

c. Anti-Pseudomonal Broad Spectrum Penicillinase-Susceptible Penicillins

Standard: None *Newer*: Carbenicillin

Methicillin was the first of the penicillins which was significantly resistant to staphylococcal penicillinase and as such represented a major advance in antistaphylococcal therapy. Since it was introduced into clinical practice during the apogee of occurrence of staphylococcal disease in the late 1950s (1960), it enjoyed immediate widespread use. With the subsequent introduction of other penicillinase-resistant penicillins, it is appropriate to compare this group of agents (Table 3).

From review of Table 3, it is apparent that there are three major determinants in the selection of one or more penicillinase-resistant semisynthetic penicillins: 1) oral versus parenteral administration, 2) extent of protein binding, 3) potential for producing nephropathy and if other aspects are essentially equal, cost.

Serum albumin was shown to interfere with the antibacterial activity of sulfonamides by Davis and Tompsett, Shultz and McDermott demonstrated interference with the antibacterial activity of penicillin (11,12). Clinically it was noted that commercial lots of penicillin containing large amounts of penicillin K, which is highly bound to serum albumin, were less effective in the treatment of syphilis than amorphous penicillin which contained only a small amount of penicillin K (13). In view of these observations, evaluation of new antimicrobials must include an assessment of the effects of proteins on antimicrobial activity. With the penicillins, binding in serum takes place almost entirely with the albumin fraction. While there is no significant difference in extent of binding between sera of different human subjects, there are differences in the degree of binding between sera of different animal species, e.g., oxacillin in dog serum is 35% free while

TABLE 3

COMPARISON OF PROPERTIES OF PENICILLINASE RESISTANT SEMISYNTHETIC PENICILLINS (7-10)

AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			ADVANTAGES	DISADVANTAGES
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY		
	SENSITIVE	RESISTANT			1/4 hr 1 hr 6 hr			
METHICILLIN (Staphcillin)	Staph. aureus Staph. albus Group A strep Viridans strep Neisseria D. pneumoniae	Enterococci H. influenzae (±) Gm-negative bacilli Bacteroides fragilis	37%	IM or IV	2000 mg IV 72 19 0	Similar to pen G, eosinophilia, leucopenia, nephropathy, Coombs + hem. anemia	Lowest degree of protein binding of PRSP	Cannot be given orally; nephropathy
NAFCILLIN (Unipen)	Same as methicillin--more active on weight basis vs staph, group A strep, D. pneumoniae, equal vs neisseria, less vs H. influenzae		90%	po, IM or IV	1000 mg po — 3-6.3 0.15	Similar to pen G, ↑ in SGOT (ASx)	Nephropathy not reported; Oral, IM & IV	High degree of protein binding
OXACILLIN (Prostaphlin, Resistopen)	Same as nafcillin		94%	po, IM or IV	500 mg po — 2.6-4.9 0	Similar to pen G, ↑ in SGOT (ASx), leucopenia, anemia, transient hematuria (infants)	Nephropathy not reported; Oral, IM & IV	High degree of protein binding
CLOXACILLIN (Tegopen)	Same as nafcillin		95%	po	500 mg po — 2.5-9.2 0	Similar to pen G, ↑ in SGOT (ASx), leucopenia	Nephropathy not reported; Serum antibacterial activity twice oxacillin and dicloxacillin	High degree of protein binding; po only

TABLE 3 (Continued)

AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			ADVANTAGES	DISADVANTAGES
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY		
	SENSITIVE	RESISTANT			1/4 hr 1 hr 6 hr			
DICLOXACILLIN (Veracillin, Dynapen, Pathocil)	Same as nafcillin		98%	po	250 mg po — 1.1-9.3 0	Similar to pen G, ↑ in SGOT (ASx), leucopenia	Nephropathy not reported	High degree of protein binding; po only
FLUCLOXACILLIN (Floxapen)	Same as nafcillin		95%	po or IM	500 mg po — 14.5 — 250 mg po — 8.8 —	Not well defined. Similar to pen G, ↑ SGOT (ASx) in 1/5	Superior absorption with maximal free levels	Unavailable in U.S.

in human serum it is only 6-7% free (14). The importance of binding to therapy is indicated by the following properties of drug-albumin complexes (15).

Distribution: complexes tend to be retained in the intravascular space

Activity: protein-bound drug has little or no antibacterial activity

Renal Clearance: glomerular filtration is almost entirely restricted to free drug. Active tubular secretion is so efficient that even highly bound drugs may be cleared rapidly

Thus, protein binding determines the level of free (active) drug in the serum which in turn determines the level available for diffusion into tissues. The concentration of free antibiotic in tissues cannot be higher than the peak level of free drug in the serum since this is the maximal concentration gradient for passive diffusion. The differences between 95% and 98% binding may not seem great; however, since it is the free drug which is active, if two agents had total levels of 10 μg/ml, drug A would have free (active) levels of 0.5 μg/ml while drug B would have 0.2 μg/ml, i.e., less than one-half as much. The effect of protein on the efficiency of three penicillins is illustrated in Table 4 (16):

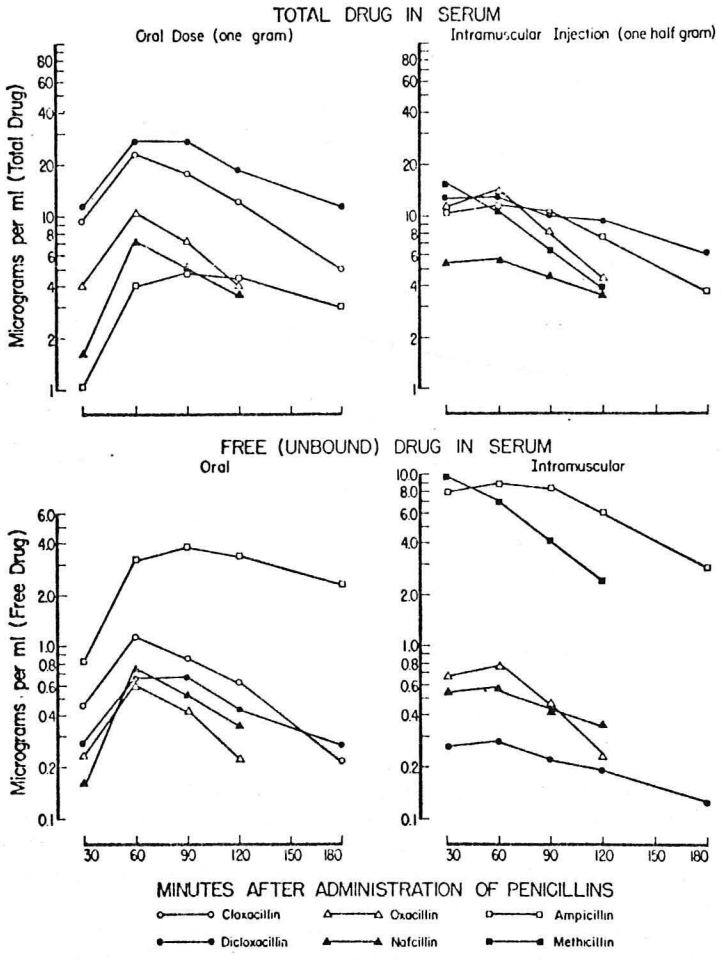
TABLE 4

EFFECT OF PROTEIN BINDING ON ANTIBACTERIAL ACTIVITY OF PENICILLINS AGAINST A STRAIN OF STAPH. AUREUS

Diluent	Average MIC (μg/ml) (% efficiency)		
	Penicillin G	Oxacillin	Methicillin
Trypticase soy broth	0.021 (100%)	0.156 (100%)	0.936 (100%)
Human serum	0.079 (27%)	2.03 (8%)	1.09 (86%)

It is common to find studies in the literature that equate achievement of higher blood levels with more effective gastrointestinal absorption when the observed differences may be explained largely by the extent of protein binding. A useful approach is comparison of blood levels after equal doses are given orally and by injection; the more highly bound drug would be expected to yield higher blood levels even when given in the same dose even when the gastrointestinal tract is bypassed. The value of such studies is illustrated in Figure 1 (from Kunin, ref. 15).

FIGURE 1



Concentrations of total and free (unbound) penicillin analogues achieved in the serum of a group of healthy young men given each drug by oral and intramuscular routes.

Note (in upper left panel), dicloxacillin gave the highest concentration of total drug after an oral dose. However, estimation of the free drug in serum revealed highest concentrations for ampicillin (22% protein bound) and cloxacillin (lower left panel). When given by injection, free methicillin concentrations were at least 10-fold higher than the other penicillinase-resistant penicillins. The relationships of levels of "free" penicillin following a given oral dose of oxacillin, cloxacillin, dicloxacillin and flucloxacillin are 1:2:2:4 (10).

It is on the basis of these considerations that we have continued to use methicillin parenterally despite the greater, albeit small, risk of nephropathy and to use cloxacillin orally.

Ampicillin was the first of the semisynthetic penicillins, with increased activity against gram-negative bacilli, being approximately one order of magnitude more effective against certain strains of gram-negative bacilli than is penicillin G. Percival et al. found penicillin G to be hydrolyzed more than 10 times as rapidly as ampicillin and suggested that this resistance accounted for ampicillin superiority (17). However, Sabath and Finland found this difference in susceptibility to hydrolysis is not the only factor in determining differences in antimicrobial activity (18).

More recently, three additional "broad spectrum" penicillins (each of which is susceptible to staphylococcal penicillinase and not effective against strains of *Pseudomonas aeruginosa*) have been marketed or are in clinical trial (Table 5):

TABLE 5

SECOND GENERATION PENICILLINS VERSUS FIRST GENERATION NEWER PENICILLINS

"Broad Spectrum" Penicillinase-Susceptible Penicillins

Standard: Ampicillin *Newer*: Hetacillin
Pivampicillin
Amoxicillin

Hetacillin is closely related to ampicillin, being made by the reaction of acetone with ampicillin. In the presence of water, the reverse reaction takes place liberating ampicillin and acetone. The antibacterial spectra and *in vitro* activities of hetacillin and ampicillin are identical and it is probable that the antibacterial activity of hetacillin is that of its hydrolysis product ampicillin (22). Electrophoretic studies of serum after the administration of hetacillin indicated the majority of circulating antibiotic to be in the form of ampicillin. While Bunn and Tuano et al. found equivalent or slightly higher blood levels with hetacillin than with ampicillin, in cross-over studies Sutherland and Robinson found ampicillin to produce consistently and substantially higher peak blood levels (19,20,22). Also, urinary excretion over 6 hours was less with hetacillin than ampicillin. Thus, there appear to be few if any advantages to hetacillin.

Despite its relatively good acid stability, the gastrointestinal absorption of ampicillin is far from complete, as indicated by the observation that 75% of an IV dose is excreted in the urine by 6 hours, whereas only 25 to 35% of an orally administered dose is recovered in the same interval (23). Pivampicillin is an acyloxymethyl ester of ampicillin which is hydrolyzed under the influence of nonspecific esterases present in blood and tissues to ampicillin (Figure 2). Cross-over studies in volunteers showed pivampicillin to be better absorbed than ampicillin with higher peak ampicillin concentrations in serum and a higher rate of urinary recovery (Table 6) (24,25). Two capsules of pivampicillin (358 mg ~ to 250 mg of ampicillin) given orally results in drug levels comparable to 500 mg of ampicillin intramuscularly (25). In toxicology studies, there has been some evidence of hepatotoxicity; thus, clinical studies have been delayed.

TABLE 6

COMPARISON OF PROPERTIES OF "BROAD SPECTRUM" PENICILLINASE SUSCEPTIBLE PENICILLINS (22-28)

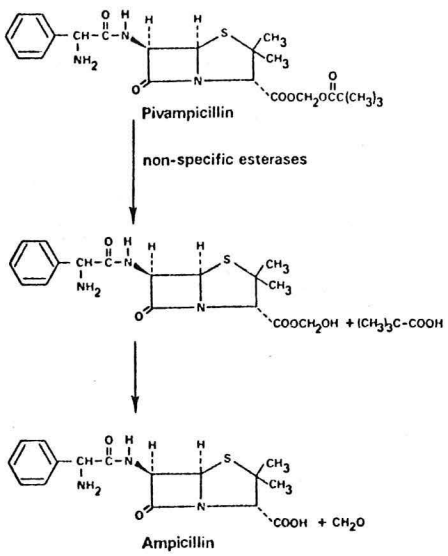
AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			COMPARISON WITH AMPICILLIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1/4 hr 1 hr 6 hr			
PENICILLIN G	H. influenzae ≤ 1.0 μg/ml E. coli ≤ 20 μg/ml + Proteus mirabilis ≤ 8 μg/ml + Salmonella sp. ≤ 5 μg/ml + Shigella		59-65%	po, IM or IV	500 mg/hr IV (800,000 u/hr) 16	—	—	—
AMPICILLIN	Group A strep D. pneumoniae Pen'ase-neg. staph Viridans strep Enterococci Neisseria H. influenzae E. coli Proteus mirabilis Salmonella sp. Shigella sp. Listeria sp. Bacteroides ±	Klebsiella sp. Enterobacter sp. Indole (+) proteus Serratia sp Pseudomonas sp	18-22%	po, IM or IV	250 mg po — 1.7-3.8 0.5 500 mg po — 2.3-4.9 0.5 500 mg/hr IV — 29	GI, skin rash (esp. in patients with infectious mono), fever, ↑ SGOT (rare), anaphylactoid reaction, convulsions (excess N), nephropathy	—	—
HETACILLIN (Versapen)	Same as ampicillin		16	po	500 mg po — 1-3 0.5 500 mg/hr IV 36	Same as ampicillin	After po, blood levels rise more slowly, persist longer; More resistant to hepatic destruction than ampicillin	Probably lower blood levels

TABLE 6 (Continued)

AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			COMPARISON WITH AMPICILLIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1/4 hr 1 hr 6 hr			
PIVAMPICILLIN	Same as ampicillin		18-22%	po	250 mg po — 4.8-5.0 <0.5 500 mg po — 8.4-9.1 0.5	Mild nausea, (?) hepatotoxicity	Blood levels 2-3x higher than ampicillin trihydrate	? Hepatotoxicity
AMOXICILLIN (BRL 2333)	Same as ampicillin		17%	po	250 mg po — 5.1 0.4 500 mg po — 6.7-10.8 1.0	Not yet defined	Blood levels and duration ~ to pivampicillin	

FIGURE 2

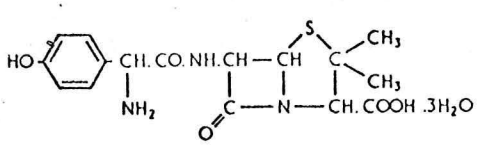
HYDROLYSIS OF PIVAMPICILLIN



Amoxicillin is a new semisynthetic penicillin with an antibacterial spectrum similar to that of ampicillin (Figure 3).

FIGURE 3

STRUCTURE OF AMOXICILLIN



Mol. wt. 419·46

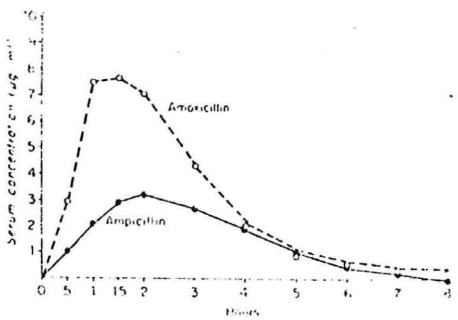
Amoxycillin, BRL 2333

D(-)-α-amino-p-hydroxybenzylpenicillin trihydrate

Penicillin-sensitive strains of staphylococci, streptococci and pneumococci are sensitive to $\leq$ 0.1 µg/ml (26-28). Strains of *H. influenzae* are inhibited at $\leq$ 0.5 µg/ml, while most strains of *E. coli, Proteus mirabilis, Salmonella sp.* and enterococci were sensitive to $\leq$ 5.0 µg/ml. Shigella strains were more variable in susceptibility, while penicillinase producing *Staph. aureus, Ps. aeruginosa,* indole positive proteus, *Klebsiella sp., Enterobacter sp.* and *Serratia sp.* were resistant to $\geq$ 50 µg/ml. Oral administration to volunteers produced serum concentrations which were twice as high as those obtained with similar doses of ampicillin (Fig. 4, Table 6). Absorption was not greatly influenced by food. Early clinical trials suggest efficacy at least comparable with ampicillin and no increased toxicity. If borne out by further trials, amoxicillin may well become the oral "ampicillin" of choice, especially in the management of infections due to *H. influenzae*.

FIGURE 4

MEAN SERUM CONCENTRATIONS OF AMPICILLIN AND AMOXICILLIN FOR 8 FASTING VOLUNTEERS, AFTER 500 mg ORAL DOSES



Recently, two additional "broad spectrum" penicillins (which are susceptible to staphylococcal penicillinase, but are effective against strains of *Pseudomonas aeruginosa*) have been marketed or are in clinical trial (Table 7).

TABLE 7

ANTI-PSEUDOMONAL BROAD SPECTRUM PENICILLINASE SUSCEPTIBLE PENICILLINS

Standard: Carbenicillin *Newer*: Carbenicillin, indanyl sodium
BRL 2288

Carbenicillin cannot be administered orally as it is poorly absorbed and/or acid labile. The 5-indanyl ester of carbenicillin is acid stable and well absorbed from the GI tract, then rapidly hydrolyzed *in vivo* to carbenicillin (29). While blood levels are low, urinary concentrations (274-2160 µg/ml) exceed the MICs for *E. coli, Pr. mirabilis,* indole (+) proteus, *Ps. aeruginosa,* some but not all *Enterobacter sp., Klebsiella sp.* and enterococci (30,31). Clinically it is effective in the treatment of urinary tract infections, 19/26 patients showing

eradication of bacteriuria during therapy; however, in two patients initial isolates acquired increasing resistance during treatment (31). Its place is perhaps best summarized by Wallace et al.:

> "Although most patients with infections confined to the bladder can be successfully treated with the indanyl ester of carbenicillin, for practical purposes it performs not better than a host of drugs already available for the treatment of most urinary tract infections. In addition, its widespread use may limit the usefulness of the parenteral form of carbenicillin by causing selection of resistant strains of pseudomonas in hospitalized patients." (31)

BRL 2288 is a new semisynthetic penicillin, which is similar in structure to carbenicillin (Table 8) (32).

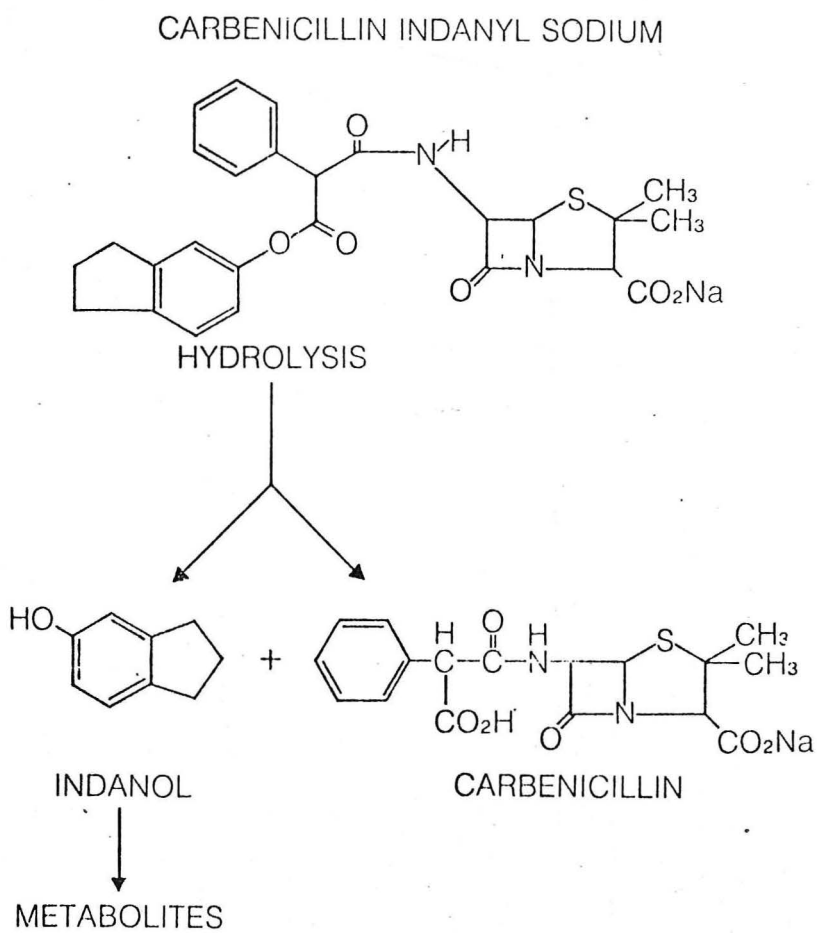


TABLE 8

COMPARISON OF PROPERTIES OF ANTI-PSEUDOMONAL BROAD SPECTRUM PENICILLINASE SUSCEPTIBLE PENICILLINS (29-32)

AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			COMPARISON WITH CARBENICILLIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1/2 hr 1 hr 6 hr			
CARBENICILLIN (Geopen, Pyopen)	Pen'ase neg. staph Group A strep D. pneumoniae Enterococci E. coli Indole + & - proteus Enterobacter sp Pseudomonas sp (+) H. influenzae Shigella Salmonella Bacteroides fragilis	Klebsiella Serratia (±) Pen'ase pos. staph Flavobacterium Aeromonas	49%	IM or IV	1 gm IV 120 57 0 5 gm IV over 2 hrs 300 210 145	Hypersensitivity, ↑ SGOT, neutropenia, hemolytic anemia, convulsions (high dose with renal failure), abn. coagulation tests (high dose in patients with uremia) hypokalemia (4.7 mEq Na^+/gm)	Effective vs Ps. aeruginosa, Enterobacter sp.; Not nephrotoxic	Pseudomonas requires large dose IV--cost. Emergence of resistance seen with pseudomonas
CARBENICILLIN, INDANYL SODIUM (Geocillin)	Same as carbenicillin, approved only for use in treatment of urinary tract infections due to E. coli, Pr. mirabilis and pseudomonas		49%	po	500 mg po 2.1 4.9-9.3 0	Bitter taste, GI (nausea, diarrhea, flatulence, cramps, vomiting), pruritus, mild leucopenia, eosinophilia. ↑ SGOT	High urine levels after oral administration	Low blood levels; may be associated with emergence of carbenicillin resistant pseudomonas

TABLE 8 (Continued)

AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES				COMPARISON WITH CARBENICILLIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS		TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1/2 hr 1 hr 6 hr				
BRL 2288	Ps. aeruginosa (2-4x more active than carbenicillin) Indole pos. proteus Enterobacter Pr. mirabilis E. coli Salmonella Shigella Gm-positive cocci (less active than ampicillin)	K. pneumoniae Serratia Enterococci	45%	IM or IV	500 mg IM 22 21 4.7 1000 mg IM 22 34 16.5 1000 mg IV 63 38 5.7		Not yet defined	Appears to produce higher levels than carbenicillin; May be more active against strains of pseudomonas	

CEPHALOSPORINS

While there have been a number of recent penicillins, there have and will be an even greater number of cephalosporin derivatives (Tables 9, 10 [33-46], Fig. 5):

TABLE 9

NEWER CEPHALOSPORINS VERSUS CEPHALOTHIN

Standard:	Cephalothin	*Newer*:	Cephaloridine
			Cephaloglycine
			Cephalexin
			Cephapirin
			Cephanone
			Cefazolin
			Cephacetrile
			Cephamycin C

TA. . 10

COMPARISON OF PROPERTIES OF CEPHALOSPORINS (33-46)

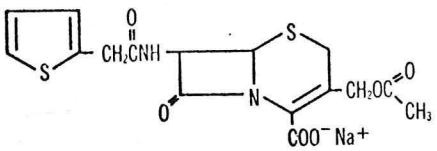
AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			COMPARISON WITH CEPHALOTHIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1 hr 6 hr			
CEPHALOTHIN	Staph, Group A strep, D. pneumoniae, E. coli, Klebsiella, indole (-) proteus, salmonella, shigella, neisseria	H. influenzae ± Enterococci (many) Enterobacter Indole (+) proteus Serratia Providencia Pseudomonas Citrobacter Herellea Bacteroides sp.	53-79%	IV or IM	500 mg/hr 10-30	Phlebitis (17-50%), rash, fever, eosinophilia, ↑ SGOT, neutropenia, anemia, thrombocytopenia, nephrotoxicity		Has acetyl group which can be hydrolyzed to desacetyl form less active
CEPHALORIDINE	As cephalothin except that staph may be more resistant and H. influenzae		0-31%	IM	1.0 gm 38	~ to ceph + renal toxicity (necrosis proximal tubules in rabbit)	Less pain on injection; Not deacetylated; Less protein binding	Nephrotoxicity; less effective vs pen'ase + staph than cephalothin
CEPHALOGLYCIN	Many Gm + (including enterococci) and Gm - organisms	Pseudomonas		po	500 mg po ≥ 0.6 0 with 10/15 ≥ 1.0 peak 4.8	GI (22%), hypersensitivity, eosinophilia, fever, dizziness, (?) balanitis	None	Erratic absorption--no blood levels
CEPHALEXIN	As cephalothin	H. influenzae more resistant	12	po	1.0 gm 32	~ to ceph	Oral administration; not deacetylated	Cost

TABLE 10 (Continued)

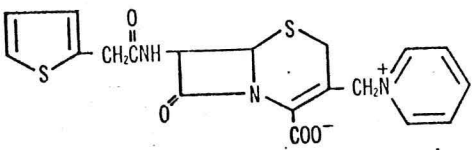
AGENT	IN VITRO PROPERTIES			IN VIVO PROPERTIES			COMPARISON WITH CEPHALOTHIN	
	ANTIBACTERIAL SPECTRUM		PROTEIN BINDING (AVG.)	ROUTE OF ADM.	BLOOD LEVELS	TOXICITY	ADVANTAGES	DISADVANTAGES
	SENSITIVE	RESISTANT			1 hr 6 hr			
CEPHAPIRIN (Bristol) BL-P1322	Similar to cephalothin 80% klebsiella		Less than cephalothin 44-50%	IV or IM	1.0 gm 5.7-17.0 0 $\bar{x}$ 11.3 500 mg/hr 6.6-48	Same as cephalothin (26%) Pain $\bar{p}$ IM, ↑ SGOT, eosinophilia, leucopenia, ↑ BUN	Less phlebitis, 2/10 vs 8/10 on cephalothin	Hydrolyzed to desacetyl form
CEPHANONE (Lilly)	Similar to cephalothin		42%	IV or IM	1.0 gm 64 14	—	Higher blood levels	Not defined
CEFAZOLIN (SKF)	Similar to cephalothin		74	IV or IM	0.5 gm 24-34 6-7		? More prolonged blood levels	
CEPHACETRILE (Ciba)	As cephalothin, enterococci may be more sensitive		—	IM or IV	1-2 gm IV 13-40 < 2--5.6 1-2 gm IM 13-15	Not well defined--less phlebitis than cephalothin, less nephrotoxicity than cephaloridine. Red urine	(?) Less toxicity	Not defined
CEPHAMYCIN C (MSD)	Klebsiella Indole (-) proteus Indole (+) proteus Providencia	Enterobacter E. coli Pseudomonas D. pneumoniae Staph		Not reported in humans			(excreted by glomerular filtration)	

FIGURE 5

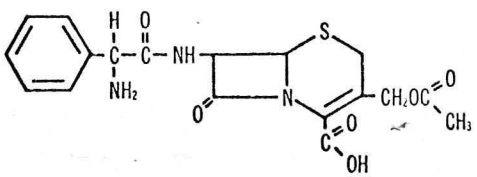
STRUCTURE OF CEPHALOSPORINS



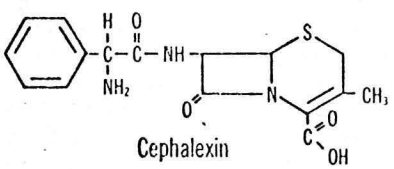
Sodium Cephalothin



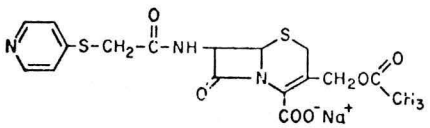
Cephaloridine



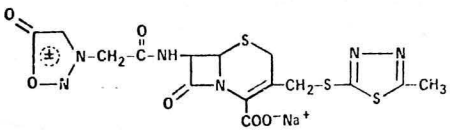
Cephaloglycin



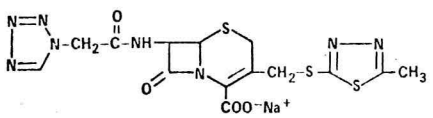
Cephalexin



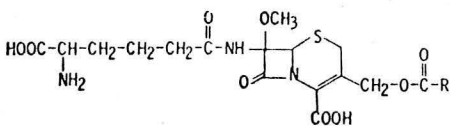
Cephapirin

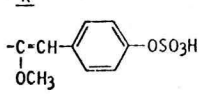
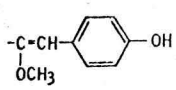


Cephanone (CSY)



Cefazolin (CEZ)



Cephamycin	R
A	
B	
C	$-NH_2$

Review of the table from the standpoint of advantages and disadvantages suggests that cephapirin may have advantages over cephalothin in view of less phlebitis and cephanone may have advantages over cephaloridine in producing higher blood levels, although the higher degree of protein binding may negate this possible advantage.

There are several other general comments regarding the cephalosporins which should be emphasized. From the standpoint of spectrum of antimicrobial activity, the cephalosporins (with the possible exception of cephaloglycin and cephacetrile) have unpredictable activity against enterococci. Cephalothin should not be employed as the alternative agent in the management of penicillin allergic patients with enterococcal endocarditis. The cephalosporins also are less active than many other agents against *Bacteroides fragilis* , hence should not be used in lieu of penicillins as alternative agents in the management of infections associated with fecal spillage or the female genital tract. Recently there has been increasing evidence that cephalothin alone or in combination with known nephrotoxic agents may show nephrotoxicity (21,47). Finally, the cephalothin should not be used as the alternative agent in the management of bacterial meningitis in penicillin allergic patients, as the desacetyl form, which penetrates into the CSF, has 2 to 16 times less antibacterial activity against both pneumococci and meningococci and failures can be expected (48-50).

AMINOGLYCOSIDIC ANTIBIOTICS

AMINOGLYCOSIDIC ANTIBIOTICS WITH ANTIPSEUDOMONAL ACTIVITY

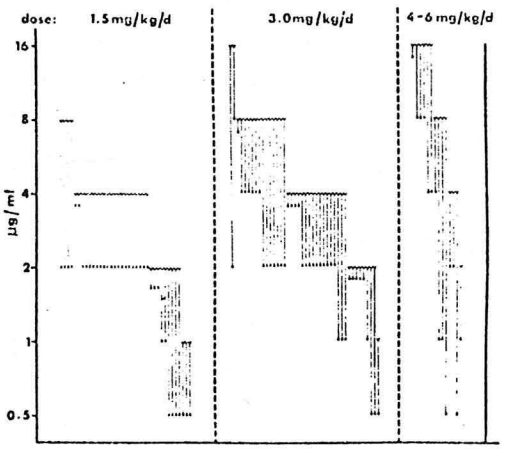
Standard: Gentamicin *Newer*: Tobramycin

Gentamicin has achieved a major role in the management of serious aerobic gram-negative bacillary infections. In a combined series of 152 adults with bacteremia, the mortality in patients treated with gentamicin in a usual dosage of 2.5 to 5.0 mg/kg/day was 32%, with ranges between 80% and 15%. The most common form of toxicity has been nephrotoxicity, with a prevalence of approximately 5%.

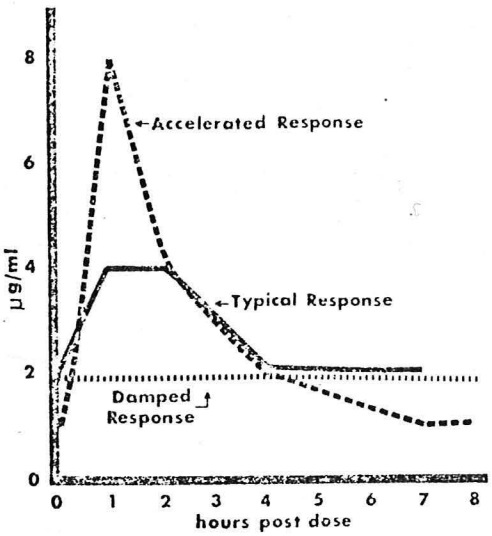
The patient with acute leukemia represents a special constellation of circumstances. In a combined series of 102 patients with bacteremia complicating acute leukemia, treated with gentamicin alone or in combination with other agents, usually carbenicillin or cephalothin, the mortality from infection was 50%. Bodey and associates have noted that combination of gentamicin and carbenicillin was particularly effective against infections caused by *Pseudomonas sp.* and *Proteus sp.*, while effectiveness was less against *E. coli, Klebsiella sp., Enterobacter sp.* and *Serratia sp.* (51). The effectiveness of gentamicin also was related to the patients' neutrophile counts, being effective in 57% of patients with neutrophile counts of $\geq 1000/mm^3$ but being effective in only 22% of patients with neutrophile counts of $< 100/mm^3$ (52). In contrast, carbenicillin is effective even in severely neutropenic patients (52). In these patients, toxicity occurred with a higher frequency than in other groups of patients: nephrotoxicity in 30%, auditory toxicity 3%, one patient developed an erythematous rash and three patients developed bullous lesions which subsequently became necrotic at sites where the gentamicin infiltrated into the skin (52).

These variations in the frequency of toxicity may reflect marked differences in blood levels of gentamicin (Fig. 6) (52A).

FIGURE 6



Peak and Trough Levels of Gentamicin in Serum in Patients With Normal Renal Function



Responses to Dosage in Patients With Normal Renal Function. Maintenance Therapy was 3 mg of Gentamicin per kg per Day

Despite standard dosage regimens, serum levels have been observed to vary between 0.8 and > 6.7 µg/ml 30 minutes after an 80 mg intramuscular dose (53) or 1.5 to 6.2 µg/ml 60 minutes after a 40 mg intramuscular dose (54). To achieve adequate therapeutic levels and minimize the likelihood of toxicity, it is becoming more apparent that therapy with aminoglycosides should be monitored with blood level determinations, especially in patients with renal impairment or older patients.

The antimicrobial spectrum of gentamicin does not predictably include pneumococci, enterococci (*Streptococcus fecalis*) or most anaerobic organisms such as *Bacteroides sp.* Hence, when these organisms are likely etiologic possibilities, alternative agents must be administered instead of or in addition to gentamicin. Failure to recognize this requirement has resulted in fatal pneumococcal sepsis, enterococcal endocarditis and peritonitis secondary to fecal contamination.

Nebramycin is another aminoglycoside antibiotic complex, reported in 1967. Nebramycin factor 6, which was found to possess the greatest antibacterial activity, was designated tobramycin in 1970. Tobramycin has undergone extensive *in vitro* testing and is now in clinical trial (55-63). The *in vitro* susceptibilities of 1,456 isolates from Parkland are listed in Table II (64).

TABLE 11

DISC DIFFUSION SUSCEPTIBILITIES OF 1,456 ISOLATES (64)

BACTERIAL ISOLATES	NO. OF STRAINS	PER CENT SUSCEPTIBLE											
		T*	G	CB	Te	CL	P	PB	S	K	Am	CF	C
P. aeruginosa	141	98	96	69	3	73	0	86	5	9	1	1	3
E. coli	135	99	99	86†	65	64	0	50	64	93	83	79	96
K. pneumoniae	116	95	99	1§	71	70	0	69	50	72	5	89	85
E. aerogenes	106	93	100	58	83	65	0	72	61	84	6	5	92
E. cloacae	116	97	98	71	69	60	0	57	71	87	12	9	91
S. marcescens	108	82	100	48	8	8	0	6	59	65	1	0	69
Salmonella sp.	26	100	100	92	81	96	0	92	54	92	88	88	92
Shigella sp.	113	99	97	93	88	95	1	92	78	96	93	98	96
Citrobacter freundii	36	96	100	61	83	72	0	72	75	92	22	31	92
P. mirabilis	125	99	100	98	1	0	24	0	88	96	97	99	94
P. morganii	59	95	97	92	57	2	0	0	52	92	9	3	71
P. rettgeri	26	73	88	92	4	4	4	4	42	96	27	15	35
P. vulgaris	15	93	100	73	27	0	0	0	100	100	7	0	93
Prov. stuartii	20	75	100	100	0	0	0	0	50	95	55	5	30
S. aureus	103	99	100	-	83	3	24	36	95	97	23	100	100
Enterococcus	108	8	61	96	19	1	19	0	2	28	98	28	74
Herellea sp.	103	97	100	18	52	65	0	68	69	88	7	0	6

* T = tobramycin; G = gentamicin; CB = carbenicillin; Te = tetracycline; CL = colistin; P = penicillin G; PB = polymyxin B; S = streptomycin; K = kanamycin; Am = ampicillin; CF = cephalothin; C = chloramphenicol

† 42 strains

§ 88 strains

Of particular interest are the susceptibilities of strains of *Ps. aeruginosa* to lower concentrations of tobramycin than to gentamicin and the susceptibility of some "gentamicin resistant" strains of *Ps. aeruginosa* to tobramycin. In contrast, gentamicin is effective against more strains of *Serratia marcescens* than is tobramycin.

II. ROLE OF "NEWER" AGENTS IN THE TREATMENT OF SELECTED INFECTIOUS DISEASE PROBLEMS

Infections due to Anaerobes

Non-Sporulating Gram-Negative Bacilli:

In recent years, there have been reports of an increase in the number of tetracycline resistant bacteroides (65,66). For example, in studies by Sutter, Kwok and Finegold, prior to 1960, 14 of 15 strains were sensitive to tetracycline, 12 of 22 isolated from 1960 to 1969 and only 24 of 63 (38%) isolated from 1970 were susceptible (67). In view of these observations, the increasing awareness of the importance of anaerobes, especially *Bacteroides sp.*, in clinical infections and the recognition that many strains were sensitive *in vitro* to erythromycin, lincomycin and clindamycin, there has been major interest in the management of anaerobic infections with newer agents.

The antimicrobial susceptibility of a group of anaerobic bacteria is summarized in Table 12. Noteworthy was the observation that only metranidazole was consistently bactericidal. Published clinical observations on the efficacy are limited but have supported the validity of the *in vitro* effectiveness of lincomycin and clindamycin. Tracy and associates reported 6 patients, three of whom failed to respond to tetracycline, five of whom rapidly responded to lincomycin (71). Bartlett, Sutter and Finegold reported the treatment of 25 patients with lincomycin (11 cases) and clindamycin (14 cases) with favorable responses in all but one of the patients on lincomycin (72). The average dose of lincomycin was 2.8 gm/day (IM), while for clindamycin it was 1.3 gm/day (po in 9 cases and IM in 5 cases). The manufacturer's summary catalogues 84 cases of anaerobic infection with 57 excellent results, 19 good and 8 poor (73). With the availability of parenteral clindamycin phosphate, we would recommend its use in a dosage of 600 mg (diluted in 100 ml) intravenously over a 20-minute period administered every 6 hours, i.e., 2.4 gm/day. The dosage does not have to be modified with either moderate renal or hepatic disease. In addition to its efficacy against these anaerobes, Mohr, Rhoades and Muchmore have reported four patients with actinomycosis treated successfully with lincomycin (74).

While therapy with lincomycin and clindamycin appears to offer considerable promise in the area of anaerobic infections, recent observations of acute colitis syndromes associated with their use should introduce a note of caution. Norgaard has observed 7 such cases (2 on lincomycin and 5 on clindamycin) at Methodist Hospital (75).

TABLE 12

ANTIMICROBIAL SUSCEPTIBILITY OF ANAEROBIC BACTERIA (% INHIBITED-MIC)

	PENICILLIN G (0.8)	CEPHALOTHIN (12.5)	TETRACYCLINE (3.1)	CHLORAMPHENICOL (12.5)	ERYTHROMYCIN (1.6)	LINCOMYCIN (6.2)	CLINDAMYCIN (6.2)	KANAMYCIN (12.5)	GENTAMICIN (6.2)	RIFAMPIN (25)	COLISTIMETHATE (25)	METRONIDAZOLE (?6.25)	Relative Frequency (%) (601 Strains)(1)
Bacteroides fragilis (1)	1	4	36	100	66	95	100	0	0	100	-		32
(2)	-	-	38	-	-	-	-	-	-	-	-	100*	
(3)	0	18	38	100	56	100	100	0	0	100	0		
Fusobacterium	100	78	83	100	89	100	100	27	5	100			3
Cl. perfringens	97	100	82	100	97	100	91	0	0	100			6
Peptococcus	96	98	59	98	58	96	95	13	30	98			24
Peptostreptococcus	98	99	73	100	73	100	100	23	33	94			12
Veilonella	100	100	85	100	23	100	100	38	31	100			2
Proprionobacterium acnes	100	100	100	100	88	100	100	19	56	100			2
Eubacterium	64	64	71	100	85	100	100	64	85	93			2
Bacteroides melaningenicus	65	93	79	100	96	96	100	34	45	96			5

(1) Ref. 68

(2) Ref. 67

(3) Ref. 69

* Ref. 70

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