Internal Medicine Grand Rounds
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Advances in Antimicrobial Therapy

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The major determinant factor in the therapeutic activity in penicillin is the aggregate time, not necessarily continuous, for which the drug remains at bactericidal levels. Of importance also is the fact that after the concentration of penicillin has fallen below those effective levels the surviving bacteria do not immediately recover from the toxic effects of the drug.

Eagle, et al. Am. J. Med. 1950;IX:280

In contrast to penicillin, the bactericidal activities of aminoglycosides and fluoroquinolones are concentration dependent. The pharmacokinetic parameter which best measures these activities is $\frac{C_{MAX}}{MIC_{50}}$.
Optimum bactericidal activity is achieved when the peak concentration is approximately 10 times the MIC.

Adapted From: Nicolau, et al., *Antimicrob. Agents Chemother.* 1995;39:650

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PHARMACOKINETICS OF PENICILLIN AND AMINOGLYCOSIDE DOSING

In 1950 Dr. Harry Eagle first established that the determinate factor in the therapeutic activity of penicillin is the aggregate time, not necessarily continuous, at which the drug remains at bactericidal levels (Figure 1). This is referred to as time

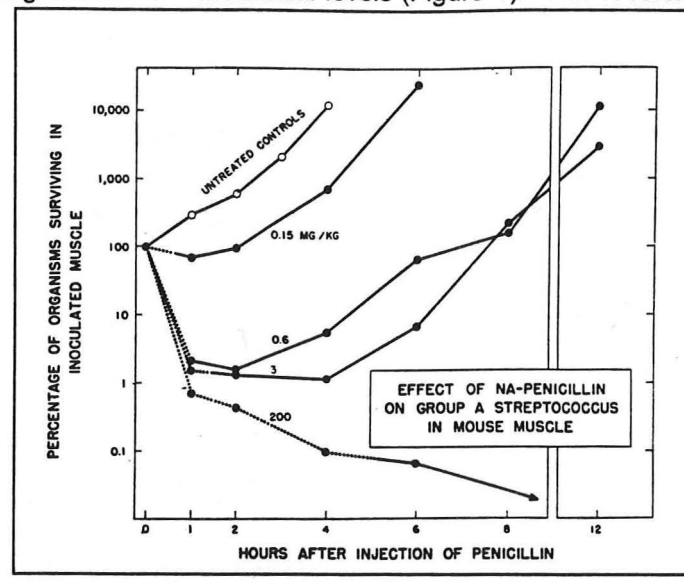

Figure 1

dependent killing. Dr. Eagle also called attention to the post-antibiotic effect, i.e., when the concentration of penicillin had fallen below effective levels, the surviving bacteria do not immediately recover from the toxic effects of the drug. Even though concentrations of penicillin were increased manyfold above the MBC, the rate of bacterial cell death was constant. Increase in the length of the effect was seen at higher concentration levels because of the persistence of the drug. When the concentrations of the drug fell below the MBC, the post-antibiotic effect occurred and afterwards there was bacterial regrowth. The clinical ramifications of this time dependent killing for penicillins and cephalosporins are important. In 1949, Dowling and his associates reported lowering of the case fatality rate in pneumococcal meningitis from 75% to 35% by increasing the amount of penicillin from 1 to 12 million units per day. They had, however, achieved the maximal killing rate, since despite our capacity to give more penicillin to patients with pneumococcal meningitis, the case fatality rate has remained essentially the same in 1997. Stated in a different way, it is impossible to kill bacteria more rapidly by simply increasing penicillin or cephalosporin concentrations. The post-antibiotic effect on different organisms varies

between antimicrobial drugs. Practically, in dosing with a penicillin or a cephalosporin,it is desirable to have the drug concentration in serum above the MIC for the particular organism at least 50% of the time (Tables 1 and 2) (Quintiliani et al.). An example of the applicability of these principles is the recent change in the dosage of amoxicillin/clavulanate. In volunteers, the serum concentration was above the MIC for most pertinent organisms with either a dose of 875 mg of amoxicillin and 125 mg of potassium clavulanate given every 12 hours, or with 500 mg of amoxicillin and 125 mg of potassium clavulanate given every 8 hours. The twice daily dosing promoted compliance and afforded less side effects in terms of diarrhea, yet the clinical effects were essentially similar.

Table 1

MICs of oral cephalosporins against common pathogens

	MIC_{90} (mg/L)					
Cephalosporin	*H. influenzae*[a]	*M. catarrhalis*[a]	*E. coli*	*S. pneumoniae*	*S. aureus*[b]	Group A streptococci
Cephalexin/ cephradine	16	16	16	4	4	1
Cefadroxil	16	4	16	8	8	0.5
Cefaclor	4	2	4	2	16	0.25
Cefuroxime axetil	2	2	4	0.12	2	0.25
Cefixime	0.25	0.25	0.5	1	>16	0.25
Loracarbef	4	2	4	2	4	0.12
Cefprozil	8	2	4	0.25	2	0.06
Cefpodoxime proxetil	0.12	0.5	1	0.03	2	≤0.06
Ceftibuten	0.12	2	0.5	4	>16	1

Table 2

Comparative pharmacokinetics of oral cephalosporins

Cephalosporin	Dosage (mg)	C_{max} (mg/L)	T_{max} (h)	AUC (mg/L • h)	$t_{1/2}$ (h)	F (%)	24-h urinary excretion (%)	Protein binding (%)	Food affects AUC?
Cephalexin/ cephradine	500 q6h	14.2-21.4	0.5-1.3	29.0-32.8	0.6-1.3	90-100	85-100	10-19	No
Cefadroxil	500 q12h	10.1-17.9	1.0-1.6	40.6-50.8	1.2-1.7	85-100	85-100	20	No
Cefprozil	500 q12h	9.3-11.5	1.2-2.0	25.7-33.4	0.9-1.4	71-94	57-70	36-45	No
Cefaclor	500 q8h	8.1-16.7	0.5-1.0	16.1-29.5	0.6-1.0	95	43-75	20-25	No
Loracarbef	400 q12h	10.6-18.7	1.2	38	0.7-1.0	90	90	25	
Cefuroxime axetil	500 q12h	3.6-9.0	1.8-2.4	13.5-30.3	1.0-2.0	36-52	32-48	33-50	
Cefpodoxime proxetil	400 q12h	3.6-4.5	2.4-3.1	20.5-26.5	2.2-2.8	29-53	24-32	30	
Cefixime	400 q24h	3.6-4.9	3.7-4.9	30.4-40.0	3.1-3.8	40-45	16-19	48-69	No
Ceftibuten	400 q24h	17.0	1.8-2.2	79.2	1.1-2.7	90-95	90-94	67-77	

In contrast to penicillin, aminoglycosides and fluoroquinolones exert their bactericidal effect primarily in a concentration dependent fashion. The pharmacokinetic parameter that best predicts the response to therapy is the peak serum level of these drugs divided by the minimum inhibitory concentration of the organism or C_{MAX}/MIC_{50} or AUC/MIC_{50}. Aminoglycosides and fluoroquinolones also exert a post antibiotic effect when the organisms do not grow in absence of the drug in serum. Recognition of the fact that the aminoglycosides and fluoroquinolones kill in a concentration dependent manner has allowed once daily dosing with some of these drugs. The relationship

between the maximal peak antibiotic level/MIC ratio to the rate of clinical response is shown (Table 3 and Figure 2). A ratio of 10 or greater in this study of 236 patients with a proven gram negative bacterial infection inferred a response rate that approximated 90%. In once daily aminoglycoside dosing, the therapeutic goal is to have some part of the day where drug cannot be detected in serum. This corresponds to the time when the post-antibiotic effect would be operative (Moore et al.).

Table 3

Associations of aminoglycoside levels and MICs with clinical response to therapy.

Concentration factor	Response (n = 188)	No response (n = 48)	P*
Maximal peak	8.2 ± 2.8	7.1 ± 2.6	.013
Mean peak	6.4 ± 1.7	6.1 ± 2.1	.30
Maximal trough	4.4 ± 2.8	4.7 ± 2.2	.15
Mean trough	3.1 ± 1.7	3.9 ± 1.7	.002
Maximal GM	5.6 ± 2.5	5.6 ± 2.3	.99
Mean GM	4.0 ± 1.7	4.7 ± 1.8	.04
MIC	2.1 ± 2.1	3.3 ± 3.4	.02
Maximal peak/MIC	8.5 ± 5.0	5.5 ± 4.6	.00001
Mean peak/MIC	6.6 ± 3.9	4.6 ± 3.6	.0001
Maximal trough/MIC	4.3 ± 3.3	3.8 ± 3.5	.17
Mean trough/MIC	3.1 ± 2.4	3.1 ± 2.5	.90
Maximal GM/MIC	4.3 ± 2.7	3.5 ± 2.5	.09
Mean GM/MIC	3.1 ± 2.0	3.0 ± 2.3	.62

* By nonparametric Wilcoxon rank-sums test.

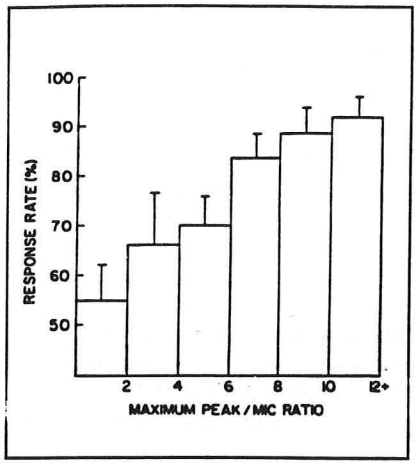

Figure 2

In contrast to the bactericidal killing capacity of aminoglycosides, the toxicity of these drugs is time dependent. Receptors in the proximal convoluted tubule are conceived to have a low avidity for the aminoglycoside. After ligand-receptor interaction, the aminoglycosides are internalized. They are also being extruded and the extrusion can occur best when aminoglycosides are absent from the proximal convoluted tubule. As a consequence of this phenomenon, concentrations of aminoglycosides in proximal convoluted tubular cells are higher with dosing every 8 hours than when with once daily dosing (Figure 3) (Nicolau et al.). The original emphasis for changing to once daily aminoglycoside dosing came from the desire to prevent nephrotoxicity and hearing loss. Once daily aminoglycoside dosing is also the most effective way for the drugs to be operative with respect to their bactericidal capacity.

Recent publications by the Hartford Hospital Group have generated the widely used Hartford Nomogram (Figure 4). The problem organism that one would like to kill optimally is *Pseudomonas aeruginosa*. In that hospital, the MIC_{50} for *Pseudomonas aeruginosa* is two micrograms per mL. To achieve a peak maximal concentration to MIC ratio (C_{MAX}/MIC_{50}) of 10, it is necessary to give 7 mg/kg of gentamicin over a one-half hour period. The start of the infusion dictates when the serum antibiotic level should be drawn, i.e., 10-14 hours after starting. The initial antibiotic dose depends upon the patient's creatinine clearance and the dosing weight.

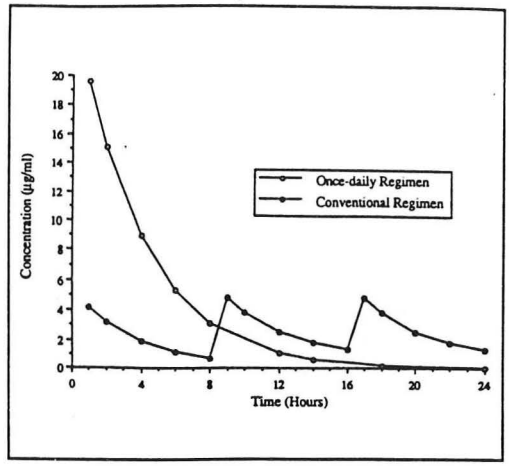

Figure 3

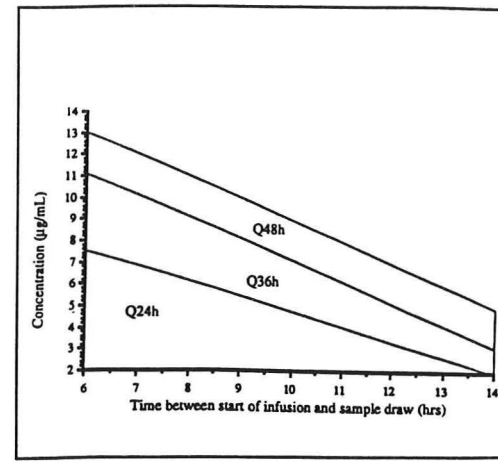

Figure 4

The creatinine clearance can be estimated by knowing four parameters: the age and sex of the patient, the dosing weight in kilograms, and the serum creatinine. C_{CR} = (140-age) x dosing (weight in kilograms)/ serum creatinine x 72. For women, multiply the calculated C_{CR} by 0.85. To calculate the dosing weight, a correction for obesity must be made. For males, the ideal body weight = 50 kg + 2.3 kg/inch over 5 feet. For females, the ideal body weight = 45 kg + 2.3 kg/inch over 5 feet. To correct for obesity, (greater than 20% of the ideal body weight (IBW), the dosing weight = IBW + 0.4 (actual weight - IBW). Ten to 14 hours after the infusion is started, a random aminoglycoside level is drawn and plotted on the Hartford Nomogram. This then determines whether the dosage should be repeated every 24 hours, every 36, every 48 hours, or whether another means of dosing the patient should be initiated. In certain patients, there may be an altered volume of distribution (V_D) or the creatinine clearance may be abnormally high, and once daily aminoglycoside dosing should not be undertaken in these patients. Such persons include these with >20% body surface burns, heavily traumatized patients, patients on dialysis, cirrhotic patients, pregnant patients, pediatric patients and in persons with resistant streptococcal endocarditis. In neutropenic patients, the post-antibiotic effect is shortened and if once daily aminoglycoside dosing is undertaken, it must be coupled to the administration of a potent β-lactam antibiotic.

Commonly encountered errors with once daily aminoglycoside dosing are as follows: 1) Peak and trough levels are ordered. All that is needed is a single random level drawn 8 - 14 hours after the start of infusion (assuming use of the Hartford Nomogram); 2) No correction is made for obesity. If patients are more than 20% overweight, a dosing weight must be calculated; 3) Initial orders should adjust for creatinine clearance; ≥60 ml/min. once every 24 hours, 40-60 ml/min. once every 36 hours, 20-40 ml/min. once every 48 hours, <20 ml/min. follow serial levels; 4) The aminoglycoside dose that should be used is 7 milligrams per kilogram for gentamicin and tobramycin and 15 milligrams per kilogram for amikacin. For use in the Nomogram, the random level of the amikacin is divided in half. Of note, is the fact that random levels 8-14 hours after the start of infusion are quite similar whether one is utilizing a dose of 4.5 milligrams per kilogram

or 7 milligrams per kilogram. The peak concentration with 7 milligrams per kilogram is much higher. With the use of once daily aminoglycoside dosing, gentamicin should be used most commonly followed by tobramycin; amikacin dosing should be utilized infrequently.

Commonly Encountered Errors with ODA Use

1. "Peak and trough" levels are ordered. All that is needed is a single random level drawn 8 - 14 hours after the start of the infusion (assuming use of the Hartford Nomogram).
2. No correction is made for obesity. If patients are > 20% overweight, make the following adjustment: Dosing weight = Ideal Body Weight + 0.4 (actual body weight - IBW)
3. Initial orders should adjust for creatinine clearance:

≥ 60 ml/min	Once every 24 hours
40 - 60	36
20 - 40	48
≤20	Follow serial levels

4. The aminoglycoside dose that should be used is 7 mg/kg for GM,T and 15 mg/kg for amikacin. Random levels 8 - 14 hours later are similar whether 4.5 mg/kg or 7 mg/kg are given. The absolute peak at 7 mg/kg; however, is much higher.
5. Do not use in Pediatrics, Pregnancy, Burns (> 20%), Ascites, Dialysis, Enterococcal Endocarditis. Remember the PAE is shortened in neutropenic patients.

In order to minimize further aminoglycoside nephrotoxicity and hearing loss, every attempt should be made to ascertain the etiology of the infection, obtain susceptibilities on the organism and place the patient on the simplest specific regimen possible. Oftentimes, this may be an oral drug. An example in this regard is the patient with acute pyelonephritis. A common way to treat these patients is with the combination of ampicillin plus a once daily aminoglycoside. The ampicillin and the aminoglycoside synergize against an organism like the Enterococcus and the gentamicin covers gram negative rods. This is a highly effective means of treatment of the patient, but depending upon blood and urine cultures and the susceptibilities of the organisms isolated, the antibiotic can be switched to oral drug once the patient is afebrile and the antibiotic is then continued to complete a 14 day treatment course. Once daily aminoglycoside dosing decreases the number of aminoglycoside levels that are obtained, and the work associated with administration of the drug since the infusion need be only given once a day. The serum creatinine should be drawn every 3 days while the patient is on the aminoglycoside therapy and if there is an alteration, then new dosing parameters should be sought.

PROBLEM:

A 40 year old woman has a large vulvar squamous cell carcinoma. One month prior to entry into the hospital, she began having fever and drenching sweats. In the hospital, she continued to have daily temperature spikes to 40°C. Exam showed a 220 pound woman who was 5 feet 2 inches tall. The carcinoma is large and necrotic. Cultures of blood and urine are negative. Serum creatinine is 0.8 mg/dL. A CT scan of the pelvis extending through the tumor is planned. She is begun on naproxyn sodium 375 mg BID. Empiric antibiotic therapy is planned. In this woman the optimal once daily GM dose is:

A. 0 mg
B. 350 mg
C. 490 mg
D. 700 mg
E. None of the above

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LEVOFLOXACIN

Several new fluoroquinolones are being introduced into practice. These include levofloxacin and sparfloxacin. Both have enhanced activity against gram positive cocci that are pathogens in the respiratory tract as well as atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*. Sparfloxacin has the capacity to induce photosensitivity reactions in about ten percent of those given the drug, it can cause QT_c prolongation and laboratories do not do routine susceptibility testing at present. Since ofloxacin is being tested in susceptibility tests at present and the results are usually applicable to levofloxacin, this drug will be discussed in detail. Levofloxacin is the L-rotatory isomer of ofloxacin which is the racemic mixture of D- and L-optic isomers. Fluoroquinolones, like aminoglycosides, exert their effect in a concentration dependant manner. The best pharmacokinetic parameters that predict their efficacy in clinical situations is the C_{MAX} divided by the MIC_{50}, or the AUC divided by the MIC_{50}. Although the C_{MAX}/MIC_{50} most closely approximates the efficacy of the aminoglycosides, it is impossible to separate the C_{MAX}/MIC_{50} from the AUC/MIC_{50} because, in essence, they are describing the same phenomena. Figure 5 depicts the C_{MAX} and the AUC for patients given 750 mg. and 1000 mg. of levofloxacin on day one, and day ten of therapy (Chien et al.). Table 4 shows the calculated C_{MAX}/MIC_{50} and the AUC/MIC_{50} ratios of selected pathogens. Since the C_{MAX}/MIC_{50} is ≥ 9, the presumption is that these organisms are susceptible and this would lead to the expectation that all of these pathogens could be treated in patients successfully. However, levofloxacin will, in actuality, be given as a dose of 500 mg. once a day, and the MIC_{90} for *Streptococcus pneumonia* is 1.91 micrograms per ml (Table 5) (Adapted after Davis et al.). At a 500 mg. dose, the C_{MAX} would approximate 6.5, and when divided by 1.91 yields an answer that approximates 3.4, rather than the value of 10 that should be expected to result in successful treatment.

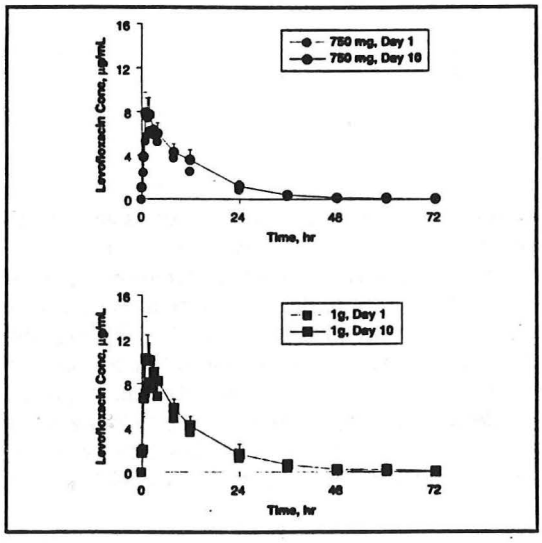

Figure 5

Table 4

Pathogen	MIC_{50} (mg/L)	Levofloxacin Once-Daily Dose 750 mg C_{max}/MIC_{50}	750 mg AUC/MIC_{50}	1000 g C_{max}/MIC_{50}	1000 g AUC/MIC_{50}
Escherichia coli	0.03	287	3024	393	3934
Klebsiella pneumoniae	0.06	143	1517	198	1980
Haemophilus influenzae	0.016	538	5688	738	7376
Moraxella catarrhalis	0.10	86	910	118	1180
Pseudomonas aeruginosa	1.0	9	91	12	118
Staphylococcus aureus	0.25	34	364	47	472
Group A streptococci	0.5	17	182	23	236
Group B/C streptococci	1.0	9	91	12	118
Streptococcus pneumoniae	1.0	9	91	12	118

Table 5

Organism	Mean MIC_{90} value (mg/L) Levofloxacin	Ofloxacin	Ciprofloxacin
Staphylococcus aureus (methicillin-susceptible)	0.41	1.06	1.40
Streptococcus pneumoniae	1.91	3.77	2.78
Enterococcus faecalis	1.89	4.53	1.95
Escherichia coli	0.07	0.15	0.03
Serratia marcescens	7.42	14.84	5.40
Campylobacter jejuni	0.58	0.78	0.78
Haemophilus influenzae	0.02	0.05	0.02
Neisseria gonorrhoeae	0.03	0.07	0.02
Pseudomonas aeruginosa	3.70	5.80	0.92
Bacteroides fragilis	3.52	6.53	14.99

Fluoroquinolones exert a post-antibiotic effect but in 10% of pneumococci after serum levels had gone below 1.9 micrograms per ml. for a period of time, regrowth should occur, and would involve predominantly the most resistant isolates. Levofloxacin has been evaluated in a neutropenic mouse thigh model with penicillin non-susceptible *Streptococcus pneumoniae* (PNSP). Levofloxacin was effective in such a model, and presumably would be effective in human patients. The point is that although therapy might be potentially initially successful, resistant isolates might be selected, particularly if levofloxacin were to be widely used (Figure 6) (Preston et al.). In therapeutic trials, levofloxacin has been found to be equivalent therapy to amoxicillin/clavulanate in acute sinusitis and to cefaclor in the treatment of acute bacterial exacerbations of chronic bronchitis (Table 6).

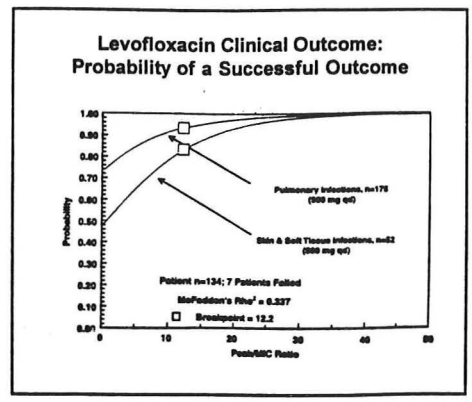

Figure 6

It has been found to be as effective as ciprofloxacin in the therapy of skin and soft tissue infections. In complicated urinary tract infections, it was found to be as effective as ciprofloxacin and ofloxacin in the therapy of acute pyelonephritis. In a large, multi-center randomized study comparing the efficacy and safety of intravenous and oral levofloxacin versus ceftriaxone and cefuroxime axetil in the treatment of adults with community-acquired pneumonia, levofloxacin was found to be at least equivalent to ceftriaxone, cefuroxime axetil in the treatment of community-acquired pneumonia. In the ceftriaxone, cefuroxime axetil arm of the study erythromycin could be added if atypical organisms were suspected. In the levofloxacin arm, no further drugs were added. It was found effective in treatment of chlamydial and mycoplasma pneumonias; there were five legionella pneumonias that were treated, four of which were cured, and one of which was improved with levofloxacin. Levofloxacin has the capacity to enter into phagocytic cells, and reach higher concentrations in these cells than in serum. Levofloxacin has been found to be active against *Mycobacterium tuberculosis* in a mouse model of that disease; by extrapolation from the mouse model, an 800 mg. dose once a day in humans would be as effective as 300 mg. isoniazid per day in the treatment of tuberculous infections.

To date, results of clinical studies of levofloxacin in prostatitis have not been reported. Results of its efficacy in sexually transmitted diseases also have not been reported. Ofloxacin has an indication in prostatitis and can be used to treat *Chlamydia trachomatis* and *Neisseria gonorrhea*. Ofloxacin has just received an indication for the treatment of pelvic inflammatory disease, although previously ofloxacin was used either with clindamycin or metronidazole for the treatment of that condition. Since levofloxacin is the active component of ofloxacin, it should be expected that once these studies are done, that levofloxacin would have the same indications as ofloxacin. Potential drawbacks to levofloxacin include its relative inactivity against *Enterococcus fecalis*, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* (Table 5).

In summary, new fluoroquinolones have been developed which are just coming on the market. These are levofloxacin and sparfloxacin. sparfloxacin has problems associated with photosensitivity reactions (10%) and prolongation of the QT_c interval.

Table 6
INDICATIONS AND USAGE
(Levofloxacin)

Acute maxillary sinusitis
Acute bacterial exacerbations of chronic bronchitis
Community - acquired pneumonia
Uncomplicated skin and skin structure infections
Complicated urinary tract infections
Acute pyelonephritis

Susceptibility testing would be a problem since the drug is not yet routinely included in testing panels. Levofloxacin is the active L-isomer of the racemic mixture of D- and L-isomers found in ofloxacin. It is scheduled to be given as 500 mg. once a day, and has been approved for use in acute sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia, and pyelonephritis (Table 6). It is expected to have indications in sexually-transmitted diseases, and could have an effect in tuberculosis. To date, most infections with penicillin resistant *Streptococcus pneumoniae* would appear to be able to be treated with levofloxacin, but since quinolones, in particular ciprofloxacin and ofloxacin have by their extended use resulted in resistant strains of *Neisseria gonorrhea*, it is to be expected that resistant strains of *Streptococcus pneumonia* could develop, and could limit the effectiveness of this antibiotic, if used unwisely. A ten day treatment of levofloxacin course would cost the patient $68. If levofloxacin is to be an effective agent in infections, it would have to be utilized wisely, and in a mix with other antimicrobial agents. If utilized too extensively, it could result in the emergence of resistant organisms, and with their spread to other persons it would render further development of other fluoroquinolones more difficult.

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CEFEPIME

Cefepime has been considered to be a fourth-generation cephalosporin (Table 7). It passes through bacterial cell membrane porins quickly and binds to multiple penicillin-binding proteins. It resists degradation by β-lactamases, including Bush Group 1 β-lactamases produced by Enterobacter and Citrobacter species. It has a low β-lactamase inducing capacity and an antimicrobial spectrum that equals ceftriaxone plus ceftazidime. It is as effective as ceftazidime against *Pseudomonas aeruginosa* but is more effective against Enterobacter and Citrobacter species. It has antistaphylococcal activity against methicillin susceptible *Staphylococcus aureus*, but it is not effective against *Listeria monocytogenes*, the Enterococcus, and has a limited anaerobic spectrum (Table 8) (Adapted after Cunha). Cefepime is not effective against methicillin resistant *Staphylococcus aureus* or methicillin resistant coagulase negative staphylococci. It has been utilized to treat hospital-acquired pneumonia, other serious infections, and febrile patients with neutropenia. It has been utilized as a single agent in the treatment of neutropenic patients with fever, and is as successful as ceftazidime in this regard (Table 9) (Eggimann et al.). Since it has a gram positive spectrum, the use of vancomycin might be able to be avoided by selecting cefepime over ceftazadime. In neutropenic patients with fever, who did not respond to cefepime, the addition of vancomycin, an aminoglycoside, a drug with anaerobic coverage or amphotericin B may be necessary. Cefepime can cross into the cerebrospinal fluid, and has been shown in childhood to be as efficacious as ceftriaxone in the treatment of childhood meningitis. There is only limited experience with the drug in adult meningitis (Table 10).

Table 7
CEFEPIME
A Fourth Generation Cephalosporin?

1. Activity = Ceftriaxone + ceftazidime
2. More rapidly penetrates the gram negative cell
3. Binds to multiple PBPs
4. Resists degradation by Bush Group 1 β-lactamases (Enterobacter sp., Citrobacter sp.)
5. Low β-lactamase inducing capacity

The drug is given as 1 to 2 grams q 12 h. In central nervous system infections in adults or in neutropenic patients, it would be given as 2 grams q 8 h. Its expected average wholesale price would approximate $9 - $14 per gram. If utilized in serious infections as 2 grams twice a day, it would be less expensive than ceftazadime when used as 2 grams q 8 h. Because of cost considerations, the extended spectrum of cefepime, the lack of induction of β-lactams, and its efficacy against Enterobacter and Citrobacter species which are becoming resistant to ceftazidime, it has been suggested that ceftazidime be replaced in the hospital formulary by cefepime (Table 11) (Paladino et al.). However, insufficient numbers of adult patients with meningitis have been treated

with cefepime so that substitution cannot be made at present. Although cefepime, unlike ceftazidime can resist the action of Bush group 1 β-lactamases, it is capable of being degraded by certain extended spectrum β-lactamases, and so resistance to the drug could occur and be spread in the hospital environment.

Table 8
COMPARATIVE ANTIMICROBIAL ACTIVITY OF THIRD-GENERATION AND FOURTH-GENERATION CEPHALOSPORINS (MIC_{90})

Microorganism	Ceftriaxone (μg/mL)	Ceftazidime (μg/mL)	Cefepime (μg/mL)
Escherichia coli	0.06	0.27	0.05
Citrobacter freundii	27	81	1.3
Enterobacter aerogenes	17	21	0.34
Pseudomonas aeruginosa	>128	6.3	5.7
Staphylococcus aureus			
Methicillin susceptible	3.8	14	3.2
Enterococcus faecalis	>128	>128	>128
Streptococcus pneumoniae	0.05	0.37	0.07

Table 9
OUTCOMES OF PATIENTS WITH FEBRILE NEUTROPENIA IN EITHER THE CEFEPIME OR COMPARATOR

Parameters	Cefepime	Comparator
Afebrile in ≤ 4 days	60/103 (58%)	63/105 (60%)
Study therapy alone	38/45 (84%)	33/42% (79%)
With modification	22/58 (38%)	30/63 (48%)
Afebrile at the end of study therapy	74/100 (74%)	77/101 (76%)
Survived >30 days after therapy	98/109 (90%)	98/107 (92%)
Median duration of study therapy	9 days	11 days
No additional antibacterial therapy added	46%	41%
Additional antiinfective therapy added:		
Vancomycin	45%	53%
Aminoglycosides	6%	8%
Other antibacterial agents	30%	33%
Systemic antifungals	34%	36%

Table 10
CLINICAL USES OF CEFEPIME

Monotherapy
- Serious gram-negative bacillary infection
  - Central nervous system infections (in meningeal doses)
  - Community-acquired pneumonias
  - Skin and soft tissue infections
  - Bone and joint infections
  - Urinary tract infections

Combination Therapy
- Intra-abdominal infections (plus metronidazole or clindamycin)
- Nosocomial pneumonias
- Febrile leukopenic compromised hosts

Table 11
SUMMARY OF THE OVERALL COSTS OF CEFEPIME AND CEFTAZIDIME

Drug	Costs			
	Level II ($US)		Level III ($US)	
	mean ± SEM	median	mean ± SEM	median
Cefepime	281 ± 8	210	6,839 ± 111	6,212
Ceftazidime	398 ± 12	312	7,309 ± 142	6,456

CEFEPIME
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MEROPENEM

Meropenem is a carbapenem that is different from imipenem in that it does not have to be coupled to cilastatin to prevent nephrotoxicity (Table 12). Imipenem is hydrolyzed by the tubular enzyme renal dehydropeptidase to an active moiety which is a nephrotoxin. To prevent nephrotoxicity, it is necessary to give imipenem with cilastatin. Meropenem, in contrast, can be given alone without the induction of nephrotoxicity. Meropenem also is different from imipenem in that it can be given to patients without the induction of seizures. In controlled trials comparing meropenem to cefotaxime in the treatment of meningitis, the development of seizures in the two groups were comparable; thus, meropenem lacks the neuroepileptogenic activity of imipenem. Because of its ionic charge, meropenem passes through porins in the bacterial cell membrane more easily and is less prone to the induction of resistance through changes in porin structure. Some *Pseudomonas aeruginosa* isolates that are insensitive to imipenem will be sensitive to meropenem. Meropenem retains the anti-aerobic activity of imipenem, loses some gram positive coverage in that it no longer can effectively treat *Enterococcus faecalis* infections but has more activity than imipenem against *Pseudomonas aeruginosa* and against members of the family Enterobacteriaceae (Table 13) (Adapted after Edwards et al., SJID).

Table 12
DIFFERENCES BETWEEN IMIPENEM AND MEROPENEM

1. Imipenem requires cilastatin to avoid nephrotoxicity
2. Meropenem = cefotaxime in seizure potential
3. *In vitro*, meropenem > imipenem against Enterobacteriaceae (*E. coli*, Citrobacter sp., Enterobacter sp.)
4. Resistance in *Ps. aeruginosa* develops more slowly to meropenem
5. Loss of activity of meropenem against *E. fecalis*
6. In children and adults, depending on future studies, meropenem may be an agent of first choice in bacterial meningitis

Table 13
ANTIMICROBIAL ACTIVITY OF MEROPENEM AND IMIPENEM AGAINST AEROBES AND ANAEROBES

	MIC_{90}(mg/L)	
Organism (n)	Meropenem	Imipenem
Staphylococcus aureus (MS) (3417)	0.25	0.13
Staphylococcus epidermidis (MS) (1317)	4	1
Streptococcus pneumoniae (PR) (143)	1	0.25
Enterococcus faecalis (1698)	8	2
Listeria monocytogenes (155)	0.25	0.25
Haemophilus influenzae (1343)	0.13	0.06
Escherichia coli (3683)	<0.06	0.5
Citrobacter freundii (656)	0.13	1
Enterobacter cloacae (1201)	0.25	2
Pseudomonas aeruginosa (3018)	4	>8
Berkholderia cepacia (166)	8	32
Bacteroides fragilis (1686)	0.5	1

Since meropenem can cross the blood-brain barrier and lacks the seizure inducing capacity of imipenem, studies have been performed evaluating the efficacy of meropenem in meningitis. These studies have indicated that meropenem is equivalent to ceftriaxone and can treat gram negative bacillary meningitis in a manner similar to ceftazidime. Of interest is the fact that meropenem is effective against *Listeria monocytogenes* and has efficacy against penicillin-resistant *Streptococcus pneumoniae*. This includes strains of the pneumococcus which have high levels of resistance to penicillin (Table 14) (Adapted after Spangler et al.). If further studies substantiating the efficacy of meropenem in meningitis can be performed, it could be considered as

Table 14
SUSCEPTIBILITY OF PNEUMOCOCCI TO ANTIMICROBIAL AGENTS

Antimicrobial agent and stain	Cumulative % of strains inhibited at MIC (μg/ml) of:									
	≤0.015	0.03	0.06	0.125	0.25	0.5	1.0	2.0	4.0	8.0
Penicillin G										
S	49.0	68.7	98.0	100						
I	0	0	3.8	18.0	40.0	66.0	100			
R	0	2.0	2.0	4.0	6.0	8.0	10.2	71.4	96.0	100
Cefepime										
S	17.6	41.2	72.6	94.1	98.0	100				
I	2.6	10.2	28.6	49.4	52.0	93.5	100			
R	2.0	2.0	6.1	16.3	24.5	46.9	73.5	97.9	100	
Ceftriaxone										
S	23.5	50.9	92.2	98.0	100					
I	6.5	23.4	35.1	45.5	72.7	94.8	100			
R	0	6.1	6.1	12.3	26.5	51.0	69.4	95.9	100	
Meropenem										
S	78.4	90.2	96.0	100						
I	36.4	45.5	68.8	92.2	97.4	100				
R	4.1	24.5	33.3	53.1	77.8	95.6	100			
Vancomycin			4.0	14.1	45.2	100				

the initial antibiotic choice in the treatment of purulent meningitis in both pediatrics and adult medicine. Meropenem has been used in abdominal surgery and in abdominal wounds containing multiple organisms including anaerobes. Its role in such treatment is equal to that of imipenem. It has been used in febrile neutropenic patients at a dosage level of 2 grams q 8 h and has been found to be as effective as imipenem. If patients fail meropenem therapy when they are neutropenic, an aminoglycoside or vancomycin or amphotericin B may be added as a next step. Meropenem is considered to be such a potent anti-anaerobic agent that it is not necessary to add metronidazole or clindamycin. If there is a high likelihood that *Pseudomonas aeruginosa* is causing the infection, an aminoglycoside should be included to cover this organism more effectively and to prevent the development of resistance. Meropenem like imipenem is hydrolyzed by metallo-β-lactamases. Such enzymes are produced by *Stenotrophomonas maltophilia*. Meropenem has no efficacy against *Enterococcus sp.* Unlike imipenem, it has some but limited against *Berkholderia cepacia*. It also has no efficacy against MRSA or coagulase-negative staphylococci that are resistant to methicillin. If widely used in the hospitals, organisms like *Stenotrophomonas maltophilia* can be selected by antibiotic pressure and spread from patient to patient resulting in epidemics especially in intensive care units. Its adverse effect profile is similar to that imipenem with the exceptions that it does not cause seizures and lacks any nephrotoxic potential.

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CLARITHROMYCIN AND AZITHROMYCIN

Clarithromycin and azithromycin are new macrolide antibiotics that have the same effect as erythromycin, but they also have an effect against *Haemophilus influenzae*, including species that produce β-lactamases. Like erythromycin, clarithromycin and azithromycin have an effect against *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*, although clinical experience with the newer drugs in treating this latter infection is limited. Both of these drugs and particularly azithromycin are taken up by phagocytic cells, including fixed and circulating macrophages and polymorphonuclear leukocytes. They are basic compounds and become entrapped in phagocytic cells in acidic endosomes. High concentrations of drug accumulate inside these cells. Their tissue concentrations far exceed serum concentrations and the actions of azithromycin can extend for days after its administration. One feature of azithromycin is its capacity with a single 1 g dose to be effective for extended periods on genital and conjunctival surfaces where it can eliminate *Chlamydia trachomatis*. This includes *Chlamydia trachomatis* in serogroups A - C which affect the eye and cause trachoma and serogroups D - K which affect the genital tract and cause sexual transmitted diseases. There is no published experience with azithromycin in treating lymphogranuloma venereum. The capacity to treat *Chlamydia trachomatis* infections has been utilized on a pilot basis to treat whole villages to eliminate trachoma. It could furnish the basis for treating sexually transmitted diseases more easily since the total treatment could be accomplished at one visit and not require the seven days of doxycycline presently necessary. Azithromycin has also an indication to treat chancroid in men with a single dose; there is insufficient data indicating that it could be effective in women.

Clarithromycin and azithromycin have revolutionized the treatment of MAC infections in HIV infected persons and other atypical mycobacterial infections in immunological normal and immunosuppressed hosts. Before the advent of clarithromycin and azithromycin, MAC infections were poorly treated if at all. With accumulation of these drugs in fixed and circulating macrophages, it is possible both to control and prevent infections due to MAC. To treat these infections, it is only necessary to add another drug like ethambutol and/or rifabutin to prevent the development of resistance. On a therapeutic level, clarithromycin combined with ethambutol is now commonly used to treat MAC infections and it has been found more effective if rifabutin also is added (Figure 7) (Shafran et al.).

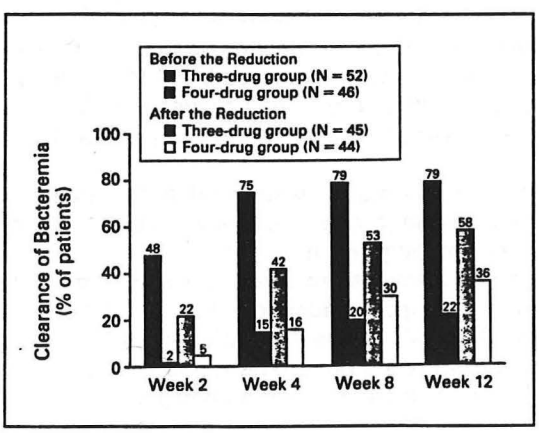

Figure 7

The combination of rifabutin and clarithromycin necessitates a reduction in the amount of rifabutin that can be given since uveitis can result if rifabutin serum levels are high. Rifabutin, clarithromycin, and azithromycin have all been found to be effective in prophylaxing HIV infected patients from developing MAC infections. However, in persons receiving clarithromycin 500 mg BID who failed therapy, 59% of the isolates were determined to be resistant to clarithromycin. Azithromycin, rifabutin, and the combination of azithromycin and rifabutin were all found to be effective in the prophylaxis of MAC infections, with the combinations of rifabutin and azithromycin being the most efficacious (Figure 8) (Havlir et al.).

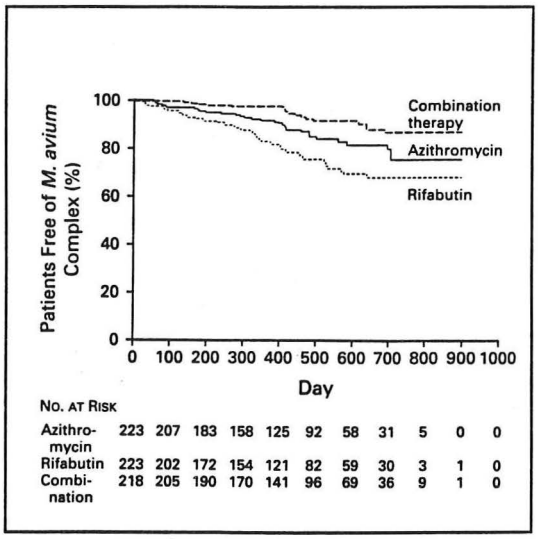

Figure 8

In patients failing azithromycin, only 11% of the isolates were resistant to azithromycin. The azithromycin was given as a dose of 1200 mg once weekly and drug limiting side effects were more common with the combination of azithromycin plus rifabutin. In atypical mycobacterial infections caused by *Mycobacterium fortuitum*, *Mycobacterium abscessus* or *Mycobacterium chelonae*, azithromycin and clarithromycin show excellent activity because of their capacity to achieve high concentrations in macrophages. *Mycobacterium chelonae* is the most resistant of the these rapid growers but is usually susceptible to clarithromycin. An additional drug always needs to be added to avoid the emergence of resistance when treating infections caused by these organisms.

Azithromycin and clarithromycin have been approved for use in upper, non-viral respiratory tract infections. Azithromycin has been approved for use in children with pharyngitis and acute otitis media. It has been an approved for use in pharyngitis in adults. It has been approved for use in acute bacterial exacerbations of chronic bronchitis in adults. It is now approved for community-acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* in patients considered appropriate for oral therapy. In the usual course, 500 mg of azithromycin is given on the first day and 250 mg of azithromycin are

given on days 2 through 5. The total course of therapy is 5 days. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors which would make them less than ideal hosts. These factors include elderly patients ($\geq$ 60), debilitated patients, and persons with significant underlying health problems that might compromise their ability to respond to illness. Bacteremia has been reported to have persisted after the institution of azithromycin. This drug has the efficacy of erythromycin against oral anaerobes and little activity against gram negative organisms exept *Hemophilus influenzae* and *Moraxella catarrhalis*.

Clarithromycin is metabolized to a 14-hydroxyclarithromycin which also has anti-bacterial properties. Clarithromycin has been approved for use in pharyngitis, sinusitis, lower respiratory tract infections, and skin and skin-structure infections caused by susceptible pathogens. Again, there is a need to utilize clarithromycin only in patients with mild to moderate pneumonia and who do not have underlying conditions which may predispose them to have unusual organisms as a cause of their disease or to have risk factors that might impair host defenses.

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CIDOFOVIR

Cidofovir (HPMPC) is the first clinically available acyclic nucleoside phosphonate. It has a broad spectrum of action that includes herpes simplex viruses type 1 and 2, acyclovir resistant herpes simplex virus, varicella zoster virus, cytomegalovirus, and adenovirus. Cidofovir bypasses the initial virally coded monophosphorylation step, necessary for acyclovir and ganciclovir activation and crosses the cell membrane as a phosphonate. It is subsequently diphosphorylated to HPMPCpp (Figure 9) (Lalezari et al.).

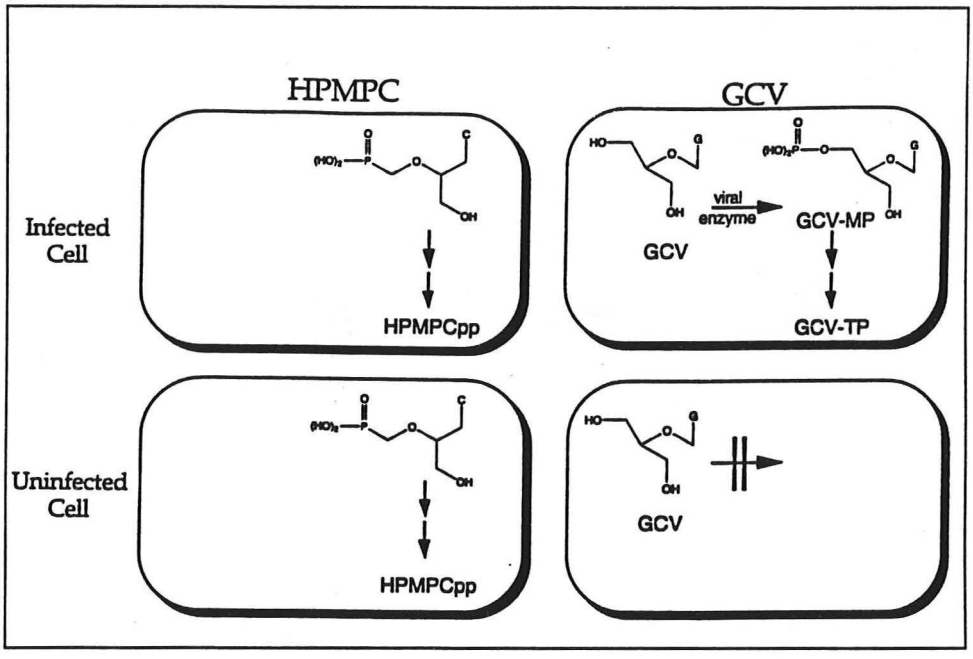

Figure 9

This compound can interact with viral DNA polymerase as a competitive inhibitor for dCTP, or it can serve as an alternative substrate and be incorporated into the growing DNA either internally or at the 3′-end where it acts as a chain terminator (Figure 10) (De Clercq). Compounds found in the cell include HPMPC, HPMPCp, HPMPCpp, and HPMPCp-choline. The HPMPCp-choline adduct is a compound with very long half life within the cell and acts as a repository form of the drug; it is subsequently converted back to HPMPCp and to HPMPCpp which then acts to inhibit viral replication. Cidofovir is the first compound of its class to be approved by the Food and Drug Administration for its use in cytomegalovirus infections. Adefovir, a compound with anti-HIV and CMV properties is presently being studied. Cidofovir can be given either locally by direct inoculation into the eye or systemically by intravenous infusion. When given systemically, the possibility of inducing severe nephrotoxicity exists. Cidofovir nephrotoxicity is characterized by tubulointerstitial disease and has been minimized by volume repletion and by giving probenecid before and after the infusion. Probenecid prevents the active tubular secretion of cidofovir. As a consequence of increased urine flow with volume repletion and the inhibited tubular secretion of cidofovir, the proximal

convoluted tubule cell is exposed to a lesser concentration of cidofovir. Cidofovir should not be given if there is 3+ proteinuria before the infusion or if the serum creatinine has risen by 0.5 mg/dL. The development of nephrotoxicity can be very rapid and some patients have had to go on permanent hemodialysis. When injected directly into the vitreous of the eye, cidofovir and its metabolites have a prolonged half-life and it can be accentuated by the use of liposomal cidofovir. Liposomal cidofovir, in experimental animals, after a single injection can be effective for eight months. Ocular hypotonia can be induced by cidofovir and probenecid is given to prevent this complication. When given intravenously, the induction period consists of one dose of intravenous cidofovir once a week (5 mg/kg) for two weeks, and then once every two weeks for the duration of therapy. The stabilization of CMV retinitis with cidofovir is approximately twice as long as that seen with ganciclovir or sodium phosphonoformate. Whether nephrotoxicity will preclude the widespread use of intravenous cidofovir is yet to be determined. It seems likely, however, that one of this new class of antiviral drugs with their broad spectrum of activity will find a role in clinical medicine.

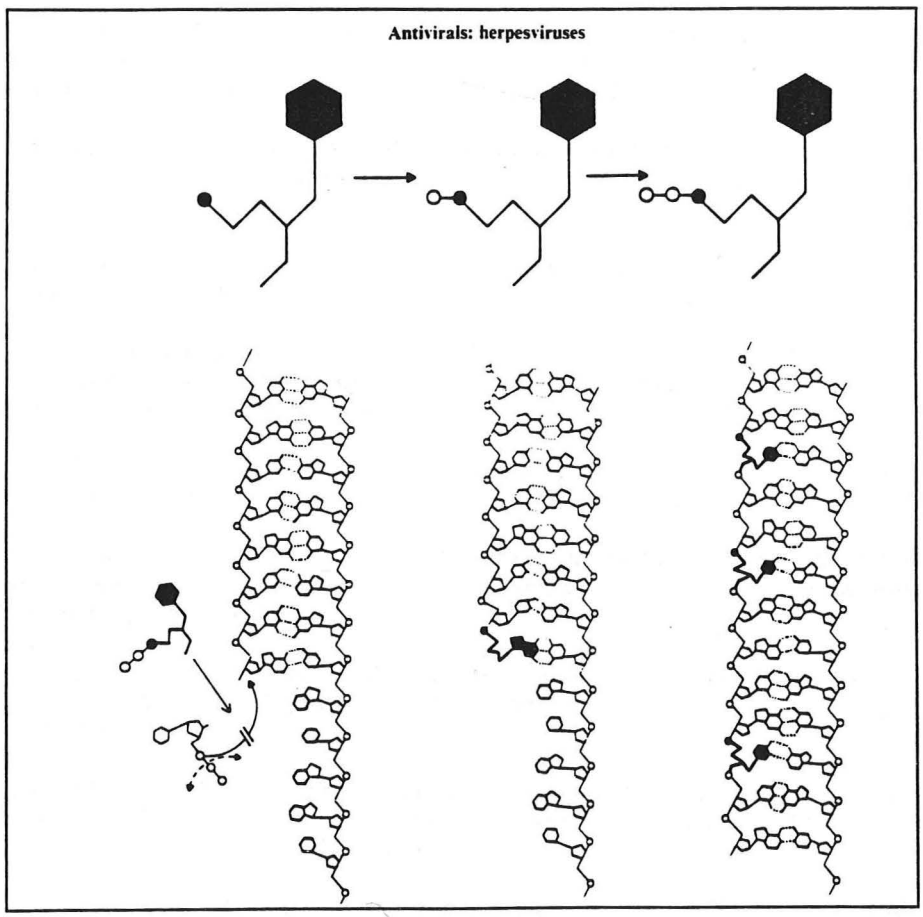

Figure 10

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SYNERCID

Synercid (RP 59500) is the combination of two antimicrobial substances, dalfopristin and quinupristin in a 30:70 ratio which when given together have a synergistic effect against gram positive cocci. Synercid constitutes an advance because with its use, *Enterococcus faecium* infections can be managed. Use of the combination of the two drugs also results in beneficial effects in MRSA infections in both man and in animal models. Synercid can be also utilized to treat penicillin resistant *Streptococcus pneumoniae* infections. Synercid merits attention because of the fact that it constitutes an approach toward vancomycin resistant gram positive coccal infections, which may be increasing if the vancomycin resistance problem is not controlled. Synercid has no effect against *Enterococcus faecalis* infections. Its effect on *Enterococcus faecium* infections is bacteriostatic one and it could not be used to treat endocarditis (Table 15) (Adapted from Chant et al.).

Table 15
SUMMARY OF IN VITRO ACTIVITIES OF RP 59500

Organism	MIC_{90} (mg/L)	Range (mg/L)
Staphylococcus aureus		
methicillin-sensitive	0.62	<0.10-2.0
methicillin-resistant	0.87	0.03-4.0
Staphylococcus epidermidis		
methicillin-sensitive	0.41	0.03-4.0
methicillin-resistant	0.40	0.03-4.0
Streptococcus pneumoniae	0.71	0.025-2.0
penicillin-resistant	1.0	<0.125-2
Enterococcus faecalis		
vancomycin-sensitive	7.1	0.25-32
vancomycin-resistant	32	4-32
Enterococcus faecium		
vancomycin-sensitive	2.8	0.25-8
vancomycin-resistant	4.7	0.06-32

Given its lack of bactericidal capacity against vancomycin resistant enterococci, the use of synercid may be severely limited, but the drug is mentioned because it constitutes a "state of the art" present potential answer to the problem. The problem of resistance in gram positive infections represents a severe threat to the practice of medicine as we know it today. Synercid is an approach to that problem, but the therapy of these infections lags behind that seen with gram negative bacillary infections.

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