



**PERITONEAL  
DIALYSIS**

**2004**

**A GUIDE TO MEDICATION USE**

**George R. Bailie**, PharmD, PhD  
**Curtis A. Johnson**, PharmD  
**Nancy A. Mason**, PharmD  
**Wendy L. St. Peter**, PharmD, BCPS

Nephrology Pharmacy Associates, Inc.  
Ann Arbor, Michigan

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## PREFACE

The average peritoneal dialysis (PD) patient takes 8 to 12 prescribed medications. Some of these drugs are used to treat the underlying diseases leading to chronic kidney disease, such as diabetes mellitus and hypertension. Others are used to control or treat the common complications of PD, such as peritonitis and exit-site infections, and the complications of ESRD, such as anemia, renal bone disease and lipid disorders.

The processes of dialysis in general, and of PD in particular, produce unique alterations in drug pharmacokinetics. There are few reference sources to provide guidance about drug dosing, and so the appropriate use of drugs in PD patients may be problematic. New dialysate solutions that offer certain advantages for the patient are becoming increasingly available. However, the chemical composition of dialysis solutions is complex, and may produce a variety of stability issues for drug additives to the dialysate.

Drugs are frequently administered by the intraperitoneal route for the treatment of peritoneal infections. Occasionally drugs may also be administered intraperitoneally to produce a systemic effect.

The accompanying text and tables have been prepared as a reference for pharmacokinetics in peritoneal dialysis, medication stability in PD solutions, intraperitoneal drug

administration, and dosing of antibiotics for infections. This information should be used as a general guideline only. Clinicians must use their best judgement when prescribing or assessing drug therapy in PD patients.

## PHARMACOKINETICS IN PERITONEAL DIALYSIS

PD may alter the pharmacokinetics of drugs. Drugs in PD may move in either direction across the peritoneal membrane under the influence of many factors including plasma protein binding, volume of distribution, dialysate flow rates, peritoneal membrane transport characteristics, molecular weight, residual renal function, type of PD, and continuous *versus* intermittent dosing. It is important to distinguish between the two directions of drug movement. The first is the passage of drugs from blood across the peritoneal membrane into the dialysate, a process commonly referred to as dialysis clearance. The second is the movement of intraperitoneally administered drugs from the dialysate, across the peritoneal membrane, into the circulatory system.

### **Clearance of drugs from blood into the dialysate**

Several factors influence the clearance of drugs from the systemic circulation into the dialysate.

#### **Plasma protein binding**

Many drugs in blood are complexed to some extent to plasma proteins, and therefore exist as bound and unbound (or free), drug. Ordinarily, only the free component of a drug may cross the peritoneal membrane. Therefore, if a drug

normally exists in a highly protein bound state (> 90%), such as anticonvulsants, warfarin and aspirin, very little of the drug will be available for passage across the peritoneal membrane. Few highly protein bound drugs are significantly cleared by PD, and PD would have a negligible effect on serum concentrations of these drugs.

Alternatively, many antimicrobial agents have a low degree of plasma protein binding (< 50%). Therefore, systemically administered antibiotics generally have a large component of the drug unbound and available to pass into the dialysate. Thus, many antibiotics may be administered orally or intravenously for the treatment of peritonitis.

### **Volume of distribution (Vd)**

A small volume of distribution (< 1 L/kg) suggests that a drug is highly water-soluble, and that most of it exists within body water as opposed to within tissue compartments. Therefore, more is present within the circulatory system. Many antimicrobial agents, such as vancomycin, cephalosporins and aminoglycosides, are highly water-soluble and have a small Vd. Together with a low degree of protein binding, this factor permits ready passage across the peritoneal membrane and clearance of these drugs from the systemic circulation by PD.

Conversely, a large Vd (> 5-10 L/kg) is commonly seen with lipid soluble drugs that distribute into other tissues. For example, antidepressants distribute widely into the

central nervous system, and digoxin distributes into the myocardium. These medications have only a very small percent of the drug within the systemic circulation, and therefore it is unlikely that dialysis would produce significant clearance of the drug.

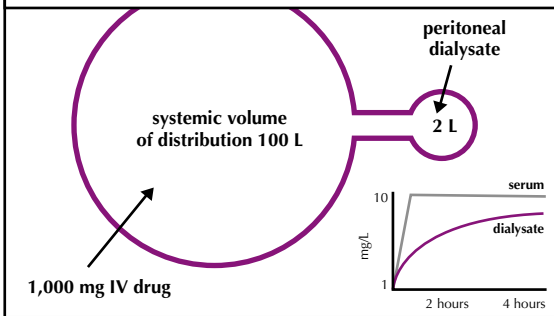
The ratio of systemic  $V_d$  to dialysate volume is a major factor that determines the rate and extent of dialysis clearance. For systemically administered drugs, the smaller this ratio, the greater is the concentration gradient from blood to dialysate, allowing easier drug diffusion into dialysate.

Figures 1a and 1b show a hypothetical situation of 1,000 mg of drug A (large  $V_d = 100$  L) and drug B (small  $V_d = 10$  L) administered IV into a patient. The patient is treated with a 2-L volume of dialysate. In the case of drug A with a large  $V_d$ , the resulting serum concentration is low (about 10 mg/L), and therefore there is a small concentration gradient between the serum and dialysate (Figure 1a). There will be a low tendency for drug to diffuse into the dialysate, and clearance will be low. After a typical 4-6 hour dwell, equilibration between serum and dialysate is usually incomplete, and the resulting dialysate concentration is unlikely to be much greater than 5-7 mg/L.

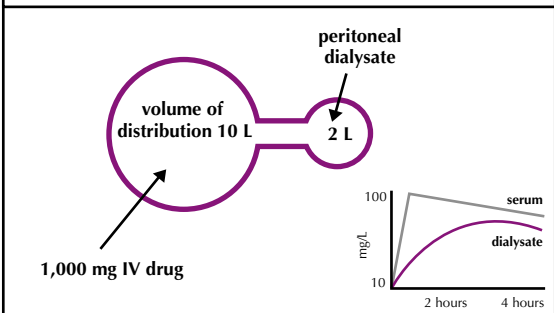
However, in the case of drug B with a small  $V_d$  (Figure 1b), the serum concentration after the dose will be high (about 100 mg/L). The resultant concentration gradient from serum to dialysate is large, and there will be a greater

transport of the drug across the peritoneal membrane into the dialysate. Again, in actual clinical practice, complete equilibration is unlikely after a dwell of only 4-6 hours, but in this case, dialysate concentrations are likely to be 50-70 mg/L, substantially greater than in the previous case.

**FIGURE 1a:** Effect of 1,000 mg of a drug with a large volume of distribution on serum and dialysate concentrations, after IV administration.



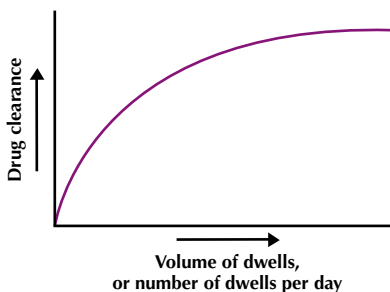
**FIGURE 1b:** Effect of 1,000 mg of a drug with a small volume of distribution on serum and dialysate concentrations, after IV administration.



## Dialysis fluid flow rates

Greater drug clearances tend to result from large versus small dialysate volumes and frequent versus few exchanges per day. This is because the concentration gradient between serum and dialysate is maximized. Therefore, as shown in Figure 2, the volume and the duration of the dwell will influence the extent of drug clearance. However, usual PD flow rates (8-12 L/d [5-8 mL/min]) lead to low drug clearance, even under ideal circumstances. The effect on clearance of very high dialysate flow rates, such as with continuous flow PD (100-200 mL/min), is unclear.

**FIGURE 2:** Relationship between increasing number of dwells per day, or volume of each dwell, and drug clearance by PD.

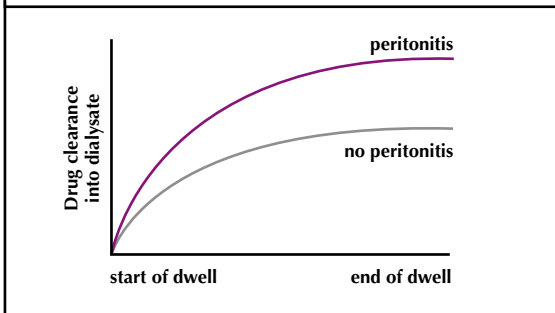


## Peritoneal membrane solute transport status

Infection and inflammation, as with peritonitis, may grossly increase peritoneal membrane porosity to small molecules (Figure 3). Apart from antibiotics, these changes in clearance

characteristics have not been adequately studied for most drugs. In the case of systemically administered antibiotics, this change in membrane porosity optimizes treatment. Early during an episode of peritonitis when the membrane is inflamed, more of the antibiotics will be cleared into the peritoneal cavity and enhance the antimicrobial activity against the peritonitis-producing organisms. As peritonitis resolves, there is less drug diffusion into the dialysate.

**FIGURE 3:** Influence of peritoneal membrane inflammation on drug clearance into dialysate from serum.



Peritoneal membrane transport status is often characterized by the peritoneal equilibration test (PET). Depending on the relative passage of creatinine and glucose across the membrane, patients are classified as being high, high-average, low-average, or low solute transporters. There are few data for drugs, but it appears that high solute transporters demonstrate relatively high drug clearances.

## Residual renal function

Most patients commence PD with significant residual renal function (RRF), with glomerular filtration rates  $>10$  mL/min. Available data suggest that patients with RRF have increased drug clearances compared to anuric patients. Clinicians must use caution to ensure that adequate doses of drugs are administered to patients who retain significant RRF and renal drug clearance. The International Society of Peritoneal Dialysis recommendations for peritonitis management make dosing suggestions based on RRF. Note that the ISPD is reviewing the guidelines during 2004, although it is unclear when the new guidelines will be published.

## Molecular weight

The peritoneal membrane generally favors passage of smaller, rather than larger, molecules. Most antibiotics have molecular weights in the range of 100-1,000 daltons, which are small enough to pass readily through the membrane. Larger molecules, such as proteins with molecular weights of 10,000-100,000, will not usually cross the peritoneal membrane.

## Intraperitoneal administration of drugs

Many medications are administered directly into the peritoneal cavity, usually to produce a local effect, such as antibiotics used to treat peritonitis. However, intraperitoneal (IP) administration may be used as a matter of convenience for drugs intended to have a systemic effect, such as insulin. To exert a systemic effect, IP drugs must first traverse the

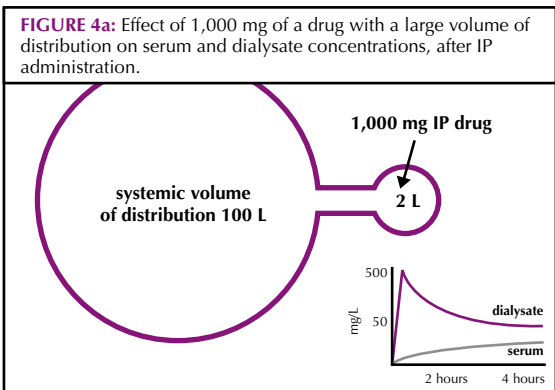
peritoneal membrane from the dialysate into the blood. This process is also considered “clearance”, only in this circumstance, the clearance is of drug *from dialysate into* blood.

Several drug- and dialysis-related factors influence the movement of drug molecules after IP administration.

### Volume of distribution

The effect of volume of distribution ( $V_d$ ) on IP drug administration is the opposite of that for intravenous administration. The larger the systemic  $V_d$  of an intraperitoneally administered drug, the more rapid will be its movement from dialysate into blood. This is the result of the dialysate to serum concentration gradient being maximized for a more prolonged period.

Figures 4a and 4b demonstrate the effect of IP administration of 1,000-mg doses of drugs A and B into 2 L of dialysate. Drug A exhibits



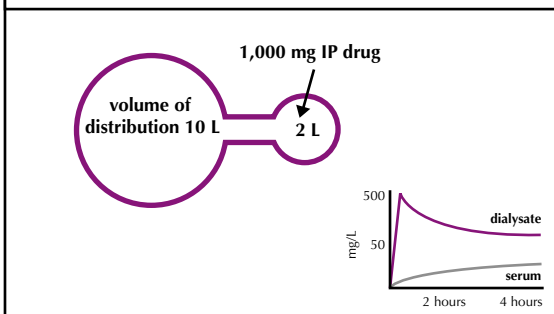
a large  $V_d$  of 100 L after administration, while drug B exhibits a small  $V_d$  of 10 L. Initially, the dialysate drug concentrations in the patient are the same for each drug (about 500 mg/L). The dialysate concentration of drug A will decrease more rapidly than for drug B because of the large concentration gradient.

As drug gets absorbed from the dialysate into the systemic circulation, the rise in serum concentration is greater for drug B than drug A, because the systemic  $V_d$  is smaller. Therefore, for intraperitoneally administered drugs, the larger the ratio of systemic  $V_d$  to dialysate volume, the more favorable conditions become for diffusion from the dialysate into the blood.

### Molecular weight

Generally, the same principles apply as previously discussed. The peritoneal membrane will preferentially permit passage of smaller, as opposed to larger molecules.

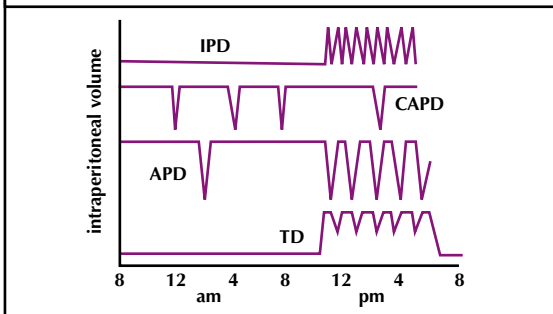
**FIGURE 4b:** Effect of 1,000 mg of a drug with a small volume of distribution on serum and dialysate concentrations, after IP administration.



## Type of PD process

Most pharmacokinetic data have been generated from continuous ambulatory PD (CAPD) patients, using a standardized dialysis of four 2-liter exchanges per day. Fewer studies have examined the influence of other variants of PD, such as automated, cycler-assisted systems (APD), which typically use large volumes with short dwells at night, followed by one or more longer daytime dwells. Tidal PD uses smaller volumes with short dwells at night (Figure 5).

**FIGURE 5:** Variants of PD; IPD = intermittent PD; CAPD = continuous ambulatory PD; APD = automated PD; TD = tidal PD.



There are significantly increased antibiotic clearances by APD because of the increased concentration gradient produced. Table 8 shows some dosing recommendations for peritonitis treatment in APD.

## Continuous versus intermittent therapy

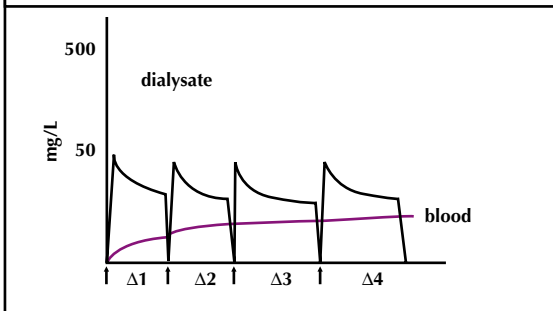
Continuous IP administration describes the process whereby medications are added to each exchange, with or without a loading dose. Intermittent use is the administration of one large dose of drug into just one of the exchanges each day. Principles of intermittent and continuous IP therapy are particularly of interest in antibiotic therapy, since there is increasing use of intermittent antibiotic therapy. The serum and dialysate concentrations following continuous (Figure 6) and intermittent (Figure 7) dosing are very different, and clinicians are advised to become familiar with these regimens.

The pharmacokinetics relating to the intermittent use of antimicrobials are complex. As seen in Figure 7, a high dialysate antibiotic concentration results from the initial IP administration of antibiotic. This permits ready diffusion of the antibiotic across a steep concentration gradient into the systemic circulation. For most antibiotics, this diffusion of antibiotic into the systemic circulation continues throughout the entire duration of that dwell, and generally results in about 75% of the drug being absorbed into the blood stream over a 4 to 6 hour dwell. If the initial antibiotic dose is adequate, then enough of it will be absorbed to produce a systemic depot of the drug. After the initial dialysate is drained and replaced with fresh dialysate to which no additional antibiotic has been added, then a reverse diffusion occurs. At this point, there

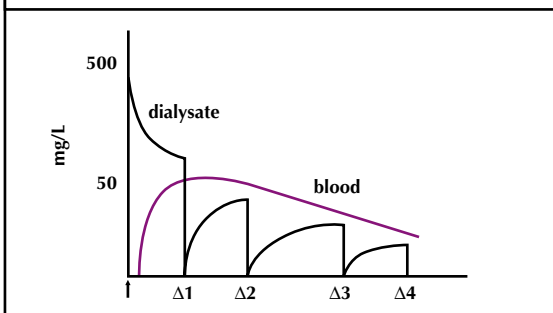
is now a concentration gradient between the antibiotic in the blood and the new dialysate, and antibiotic will travel across the peritoneal membrane into the dialysate.

**Key:** ↑ = IP dose  
Δ = dialysate exchange

**FIGURE 6:** Blood and dialysate concentrations following continuous IP dosing into all four exchanges in a 24 hour period for CAPD.



**FIGURE 7:** Effect of a single, intermittent IP dose of a drug on blood and dialysate concentrations over a 24 hour period for CAPD.

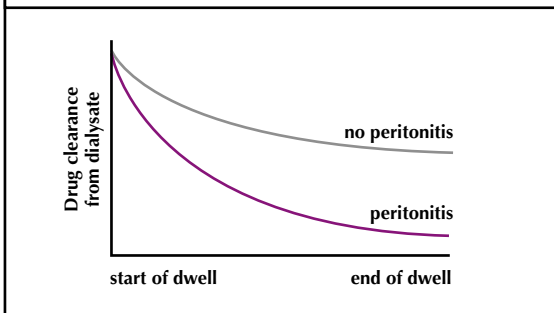


With intermittent IP dosing, subsequent dialysate drug concentrations are dependent upon the various factors discussed above. However, it is critical that there is high enough antibiotic concentration in the systemic circulation to permit an adequate amount to be absorbed back into each exchange of fresh dialysate administered during the 24-hour period. Unless adequate dialysate concentrations are achieved with each dwell, inadequate antimicrobial control will result.

## Peritonitis

An inflamed peritoneal membrane permits more drug movement from dialysate to blood, as shown in Figure 8. The percentage of the IP administered antibiotic dose that is absorbed from dialysate into blood is usually increased during an episode of peritonitis.

**FIGURE 8:** Influence of an inflamed peritoneal membrane on the clearance of a drug from dialysate to blood.



## PERITONEAL DIALYSIS SOLUTIONS

Two osmotic agents are currently used as the basis for peritoneal dialysis solutions in the U.S, dextrose and icodextrin (approved for use in the U.S. in late 2002). Icodextrin is a mixture of high molecular weight, water-soluble glucose polymers that, by virtue of their size, have limited diffusive transport across the peritoneal membrane, and thus provide sustained ultrafiltration during long dialysis dwells. In contrast to dextrose, icodextrin does not cause hyperglycemia or hyperinsulinemia. Both icodextrin- and dextrose-based solutions contain other anionic and cationic ingredients in various concentrations to allow for individualization of the dialysis prescription. Table 1 provides information on the current formulations.

In addition, an amino acid dialysate solution and a bicarbonate-containing solution are available in other countries (Table 2). Amino acid solutions are used to enhance nutritional status through peritoneal absorption of these nutrients. Solutions containing bicarbonate as the buffer have a more physiological pH than lactate-based solutions (pH 7.0-7.6 vs pH 5.5-6.5) and may have several advantages, including less pain on instillation and fewer detrimental effects on peritoneal macrophages and mesothelial cells. These solutions require a double-bag system to avoid interactions and

decomposition during storage, one containing sodium bicarbonate and the other containing calcium and glucose.

**Table 1. Composition of commercial peritoneal dialysis solutions in the U.S.**

Brand Name	Dextrose-Based Solutions			Icodextrin-Based Solution
	Standard Calcium and Magnesium	Standard Calcium, Low Magnesium	Low Calcium, Low Magnesium	Standard Calcium, Low Magnesium
	Delflex <sup>®a</sup>	Delflex <sup>®a</sup> Dianeal PD-2 <sup>®b</sup>	Delflex <sup>®a</sup> Dianeal <sup>®b</sup>	Extraneal <sup>®b</sup>
<b>Electrolytes</b>				
Na (mEq/L)	132	132	132	132
Ca (mEq/L)	3.5	3.5	2.5	3.5
Mg (mEq/L)	1.5	0.5	0.5	0.5
Cl (mEq/L)	102	96	95	96
Lactate (mEq/L)	35	40	40	40
Dextrose (%) <sup>c</sup>	1.5, 2.5, 4.25	1.5, 2.5, 4.25	1.5, 2.5, 4.25	
Icodextrin (%)				7.5

**Key:**

a = Registered Trademark of Fresenius Medical Care, North America

b = Registered Trademark of Baxter Healthcare Corporation

c = The corresponding anhydrous glucose content is as follows:  
1.36%, 2.27%, 3.86%.

**Table 2. Composition of additional PD solutions available outside the U.S. (in addition to those listed in Table 1).**

Amino Acid 1.1% Solution		Bicarbonate-Based Solutions	
Nutrineal <sup>®b</sup> (Baxter)		Physioneal <sup>®b</sup> (Baxter)	Stay-Safe <sup>®a</sup> (Fresenius)
<b>Essential Amino Acids</b>	<b>g/L</b>		
Valine	1.39		
Leucine	1.02		
Isoleucine	0.85		
Methionine	0.85		
Lysine	0.76		
Threonine	0.65		
Phenylalanine	0.57		
Tryptophan	0.27		
Histidine	0.71		
<b>Non-Essential Amino Acids</b>			
Arginine	1.07		
Alanine	0.95		
Proline	0.60		
Glycine	0.51		
Serine	0.51		
Tyrosine	0.30		
<b>Electrolytes (mEq/L)</b>			
Sodium	132	132	134
Calcium	2.5	2.5	3.5
Magnesium	0.50	0.50	1.0
Chloride	105	95	104.5
Lactate	40	15	0
Bicarbonate		25	34
Glucose (%) <sup>c</sup>		1.5 – 4.25	1.5 – 4.25

**Key:**

a = Registered Trademark of Fresenius Medical Care, North America

b = Registered Trademark of Baxter Healthcare Corporation

c = The corresponding anhydrous glucose content is as follows:  
1.36% – 3.86%.

## STABILITY OF DRUG ADDITIVES IN PERITONEAL DIALYSIS SOLUTIONS

Medications are frequently added to peritoneal dialysis solutions to produce local or systemic effects. These drugs must be stable and compatible in dialysate. Stability refers to a lack of degradation of the parent drug after addition to the dialysate. Instability of a drug additive may be the result of degradation of the drug by chemical, thermal or ultraviolet mechanisms. A drug that is termed unstable generally means that the pharmacological effect of the parent compound is lessened by one of these processes. Usually, when the drug has degraded to less than 90% of its initial activity or concentration, it is classified as unstable and unacceptable for use. Compatibility refers to the physical or chemical interaction of a drug additive with the constituents of the dialysate.

Assays that are used to examine the stability of drugs in dialysate can be those that determine the concentration of the drug over time after addition to the dialysate, or those that determine the pharmacological activity of the additive. In the first type, the assay used for any particular drug must be able to differentiate between the parent drug and its degradation products which may be pharmacologically active or inactive. An assay that is able to distinguish between the drug and its degradation products

is termed a stability-indicating assay, and is the preferred type. Similarly, an assay which does not measure concentration of the drug or its degradation products, but which estimates biological activity, may be an appropriate assay to determine drug stability, providing that any degradation products have some of the biological activity of the parent drug. Table 3 shows the stability of some common additives in peritoneal dialysate, including antibiotic combinations.

Cycler-assisted PD poses some unique challenges when antibiotic combinations are used. One mixing procedure with some automated PD systems on the last fill is to 1) disconnect from the cycler, 2) inject antibiotics into an empty effluent bag and then, 3) connect effluent bag to PD catheter allowing it to fill with dialysate and mix with the antibiotics. This technique results in short-term contact with high concentrations of antibiotics, which has led in some cases to precipitation of the antibiotics involved. This problem can be circumvented by instructing the patient to connect the empty effluent bag to the PD catheter, allowing the bag to fill to an appropriate volume and then injecting the antibiotics into the bag.

**Table 3. Stability of drug additives to peritoneal dialysis solutions**

Drug	Dialysate dextrose conc. (%)	Drug conc. (mg/L)	Storage temp (°C)	Duration of observation in hours (h) or days (d)	Duration of stability in hours (h) or days (d)
Amphotericin B	1.5	1, 2	37	2d	6h
	1.5	5	37	2d	1d
Ampicillin <sup>a</sup>	4.25	50	25	2d	2d
Azlocillin <sup>a</sup>	4.25	200	25	2d	2d
Cefamandole	1.5	8	RT	1d	1d
Cefazolin	1.5, 4.25	500	4	14d	14d
	1.5, 4.25	500	25	11d	8d
	1.5, 4.25	500	37	1d	1d
±heparin (666 U/L) <sup>b</sup>	1.5	333	4	25d	20d
±heparin (666 U/L) <sup>b</sup>	1.5	333	25	14d	11d
±heparin (666 U/L) <sup>b</sup>	1.5	333	37	1d	1d
+heparin (1000 U/L) <sup>b</sup>	1.5	75	4, 26	2d	2d
+heparin (1000 U/L) <sup>b</sup>	1.5	75	37	2d	8h
+heparin (1000 U/L) <sup>b</sup>	1.5	150	4, 26	2d	2d
+heparin (1000 U/L) <sup>b</sup>	1.5	150	37	2d	1d
+gentamicin and heparin (1000 U/L) <sup>b</sup>	1.5	75 & 8	4, 26, 37	2d	2d <sup>d</sup>
+gentamicin and heparin (1000 U/L) <sup>b</sup>	1.5	150 & 8	4, 26	2d	2d <sup>d</sup>
+gentamicin and heparin (1000 U/L) <sup>b</sup>	1.5	150 & 8	37	2d	1d <sup>d</sup>
Cefepime	1.5	100	4	14d	14d
	1.5	100	25	7d	7d
	1.5	100	37	2d	2d
Cefmenoxime	1.5	4	RT	1d	1d
Cefoperazone	1.5	4	RT	1d	1d
Cefotaxime	1.5	4	RT	1d	1d
	1.5, 4.25	1000	25	8d	1d
	1.5, 4.25	1000	37	1d	6h
	4.25 <sup>a</sup>	125	25	2d	1d
Cefoxitin	1.5	8	RT	1d	1d

<b>Drug</b>	<b>Dialysate dextrose conc. (%)</b>	<b>Drug conc. (mg/L)</b>	<b>Storage temp (°C)</b>	<b>Duration of observation in hours (h) or days (d)</b>	<b>Duration of stability in hours (h) or days (d)</b>
Ceftazidime	1.5	8	RT	1d	1d
	1.5	2000	5	NR	10d
	1.5	2000	RT	NR	1d
	1.5	2000	37	NR	4h
	1.5	100	25	6d	4d
	1.5	100	25	24h	24h <sup>e</sup>
	1.5	100	37	8h	2h or 8h <sup>e</sup>
	1.5	100	4	7d	7d <sup>e</sup>
	1.5	100	37	8h	8h <sup>e</sup>
	2.5	125	4	14d	10d
	2.5	125	20	14d	3d
	+heparin (1000 U/L) <sup>b</sup>	1.5	100	4	6d
+heparin (1000 U/L) <sup>b</sup>	1.5	100	25	6d	4d
+heparin (1000 U/L) <sup>b</sup>	1.5	100	37	6d	<12h
+teicoplanin	1.5	100 & 25	37	8h	8h <sup>d,e</sup>
+teicoplanin	1.5	100 & 25	25	24h	<2h <sup>d,e</sup>
+teicoplanin	1.5	100 & 25	4	4d	4d <sup>d,e</sup>
+tobramycin	2.5	125 & 8	24	16h	16h <sup>d</sup>
+tobramycin	2.5	125 & 8	37	8h	8h <sup>d</sup>
+vancomycin	1.5	100 & 50	4	6d	6d <sup>d</sup>
+vancomycin	1.5	100 & 50	25	6d	2d <sup>d</sup>
+vancomycin	1.5	100 & 50	37	6d	12h <sup>d</sup>
+vancomycin and heparin (1000 U/L) <sup>b</sup>	1.5	100 & 50	4	6d	6d <sup>d</sup>
+vancomycin and heparin (1000 U/L) <sup>b</sup>	1.5	100 & 50	25	6d	3d <sup>d</sup>
+vancomycin and heparin (1000 U/L) <sup>b</sup>	1.5	100 & 50	37	6d	12h <sup>d</sup>
Ceftriaxone	1.5	4	RT	1d/1d	1d
	1.5, 4.25	1000	4	14d	14d
	1.5, 4.25	1000	23	5d	1d
	1.5, 4.25	1000	37	1d	6h

Drug	Dialysate dextrose conc. (%)	Drug conc. (mg/L)	Storage temp (°C)	Duration of observation in hours (h) or days (d)	Duration of stability in hours (h) or days (d)
Cephapirin	4.25 <sup>a</sup>	125	25	2d	2d
	4.25 <sup>a</sup>	500	35	1d	<1d
+tobramycin	4.25	500 & 65	25	1d	1d <sup>d</sup>
+tobramycin	4.25	500 & 65	35	1d	<1d <sup>d</sup>
Ciprofloxacin	1.5	25	4, 20, 37	42d	42d
	1.5	100	23	1d	1d
	1.5, 4.25	25	4	14d	<12h
	1.5, 4.25	25	25	7d	7d
	1.5, 4.25	25	37	2d	2d
Clindamycin <sup>a</sup>	4.25	10	25	2d	2d
Deferoxamine	1.5, 4.25	350	4	15d	15d
	1.5, 4.25	350	25	7d	7d
	1.5, 4.25	350	37	2d	2d
Dobutamine	1.5	2.5	4, 26, 37	1d	1d
	1.5	5, 7.5	4, 26, 37	1d	1d
	4.25	2.5, 5, 7.5	4, 26, 37	1d	1d
Erythromycin	1.5	150	4	14d	2d
	1.5	150	25	7d	3d
	1.5	150	37	2d	8h
	4.25	150	4	14d	14d
	4.25	150	25	7d	3d
	4.25	150	37	2d	2d
Fosfomycin	1.5	3200	23	1d	1d
Gentamicin	1.5, 4.25	10	25	1d	1d
	1.5	8	4, 25	2d	2d
	1.5	120	37	8h	8h
	2.5	8	4, 20	14d <sup>c</sup>	14d <sup>c</sup>
+heparin (1000U/L) <sup>b</sup>	1.5	8	4, 26, 37	2d/2d	2d
+heparin (500U/L) <sup>b</sup> & albumin (5%)	1.5	8	RT	3d	6h
+cefazolin & heparin (500 U/L) <sup>b</sup> & albumin (5%)	1.5	4 & 125	RT	3d	3d <sup>d</sup>

<b>Drug</b>	<b>Dialysate dextrose conc. (%)</b>	<b>Drug conc. (mg/L)</b>	<b>Storage temp (°C)</b>	<b>Duration of observation in hours (h) or days (d)</b>	<b>Duration of stability in hours (h) or days (d)</b>
+cefazolin & heparin (500 U/L) <sup>b</sup> & albumin (5%)	4.25	4 & 125	RT	3d	3d <sup>d</sup>
+vancomycin	1.5	8 & 30	4, 25	2d	<2h <sup>d</sup>
+vancomycin	1.5	120 & 1000	37	8h	8h <sup>d</sup>
+vancomycin	2.5	8 & 25	4, 20	14d	14d
Iron Dextran	1.5	2	RT	28d	28d
	1.5	10	37	24h	24h
	1.5, 4.25	0.05	4	14d	14d
	1.5, 4.25	0.25	25	14d	14d
	1.5, 4.25	0.5	37	3d	3d
Linezolid	1.5	150, 300, 600	4, 25	7d	7d
	1.5	150, 300, 600	37	1d	1d
	4.25	150, 300, 600	4, 25	7d	7d
	4.25	150, 300, 600	37	1d	1d
Mezlocillin <sup>a</sup>	4.25	200	25	2d	2d
Miconazole	4.25	20	20	9d	2h
Moxalactam	1.5	8	RT	1d	1d
Nafcillin	1.5, 4.25	100	25	1d	1d
	4.25 <sup>a</sup>	100	25	2d	1d
Ofloxacin	1.5	100	23	1d	1d
	1.5, 4.25	25	4	14d	14d
	1.5, 4.25	25	25	7d	7d
	1.5, 4.25	25	37	2d	2d
Pefloxacin	1.5	100	23	1d	1d
Penicillin	1.5, 4.25	6	25	1d	<1d
Piperacillin <sup>a</sup>	4.25	200	25	2d	2d
Sodium Bicarbonate <sup>f</sup>	1.5, 2.5, 4.25	21.8 mEq/L	32-38	5h	5h
	1.5, 2.5, 4.25	21.8 mEq/L	RT, then 32-38	24h, then 1h	25h

Drug	Dialysate dextrose conc. (%)	Drug conc. (mg/L)	Storage temp (°C)	Duration of observation in hours (h) or days (d)	Duration of stability in hours (h) or days (d)
Teicoplanin	1.5	25	4	42d	42d
	1.5	25	20	42d	25d <sup>g</sup>
	1.5	25	37	42d	7d
	1.5	25	25	24h	24h
Ticarcillin	1.5, 4.25	200	25	1d	1d
TMP/SMX	4.25	20 & 100	20	9d	12h
Tobramycin	1.5	8	4, 25	2d	2d
	1.5	120	37	8h	8h
	4.25 <sup>a</sup>	10	25	2d	2d
	4.25 <sup>a</sup>	65	35	1d	<1d
+vancomycin	1.5	8 & 30	4	2d	1d <sup>d</sup>
+vancomycin	1.5	8 & 30	25	2d	2d <sup>d</sup>
+vancomycin	1.5	120 & 1000	37	8h	8h <sup>d</sup>
Vancomycin	1.5, 4.25	15	25	1d	1d
	1.5	50	4, 25	6d	6d
	1.5	50	37	6d	5d
	1.5	30	4, 25	2d	2d
	1.5	1000	37	8h	8h
	1.5	25	4	42d	28d <sup>h</sup>
	1.5	25	20	42d	28d <sup>h</sup>
	1.5	25	37	42d	7d
	2.5	25	4, 20	14d	14d <sup>c</sup>
	4.25	25	4, 20	42d	28d
	4.25	25	37	42d	5d
	4.25 <sup>a</sup>	20	25	2d	1d
+heparin (1000U/L) <sup>b</sup>	1.5	50	4, 25	6d	6d
+heparin (1000U/L) <sup>b</sup>	1.5	50	37	6d	5d

This table was adapted and updated from: Bailie GR, Kane MP. Stability of drug additives to peritoneal dialysate. *Perit Dial Int* 1995; 15(8): 328-335.

**Key:**

U = Units

RT = Room temperature (not defined)

NR = Not reported

a = Results combined from dialysate with or without heparin 500 U/L.

b = The addition of heparin in concentrations usually recommended for treatment or prevention of fibrin clots will not alter the activity of most antibiotics.

c = Immunoassay results are shown. Bioassay also performed and suggested greater loss of activity over time, but results were not presented in table due to probable assay inaccuracy and/or operator error.

d = In studies where two drugs were combined in dialysate, the "Duration of stability" time noted in the last column of the table represents the period of time during which both drugs maintained 90% of their original activity or concentrations.

e = Study mimicked real life conditions.

Condition A = storage at 25°C for 24 hours, followed by 8 hours at 37°C; Condition B = storage at 4°C for 7 days followed by 16 hours at 25°C and 8 hours at 37°C.

Ceftazidime was less stable at 37°C under condition A.

An interaction with ceftazidime and teicoplanin was found at 25°C. Mixing this combination at any temperature not recommended because of variability in dialysate storage conditions.

f = Sodium bicarbonate was added to dialysate to increase solution pH and reduce potential for pH-related infusion pain. Calcium did not precipitate out of solution during duration of study. There is a risk of developing sodium overload with hypertension with addition of sodium bicarbonate to dialysate. Authors suggested using lower final sodium bicarbonate concentrations of 11 mEq/L to lessen this risk.

g = Data extrapolated from 21 days by original authors.

h = HPLC assay indicated stability for 42 days, while EMIT assay demonstrated stability for 28 days.

## INTRAPERITONEAL ADMINISTRATION FOR A SYSTEMIC EFFECT

The intraperitoneal (IP) route of drug administration can be successfully used to achieve systemic pharmacological activity. The peritoneal catheter provides a method of drug dosing that may be a suitable alternative to other routes of drug administration. Many medications achieve pharmacologically effective plasma concentrations following instillation into the peritoneum. This observation permits the use of IP administration for treating a systemic or distant medical problem. Most clinical experience has been gained with IP dosing of antibiotics for systemic infections (e.g. cellulitis, endocarditis, osteomyelitis), insulin for treatment of hyperglycemia, calcitriol for suppression of parathyroid activity, and erythropoietin for treatment of anemia.

The section of this guide dealing with the pharmacokinetics of IP dosing explains the rationale for using this route of drug dosing. The accompanying table (Table 4) summarizes relevant pharmacokinetic parameters of selected medications administered by the intraperitoneal route in CAPD patients. Most of the pharmacokinetic data presented in the table come from studies in which the subjects did not have peritonitis, the situation most closely mimicking the circumstances for which IP dosing for systemic effect might be considered. The advantage of IP drug administration is that

there is no need for an intravenous line or for subcutaneous or intramuscular injections.

**Table 4. Pharmacokinetics of selected medications given by intraperitoneal administration to CAPD patients**

Drug	Dose	Dwell Time (h)	Cmax (mg/L)	Bioavailability (%)	Mean $t_{1/2}$ (h)	
<b>ANTIBIOTICS</b>						
Amikacin	7.5 mg/kg	5	19.6	53	42	
<b>Comment:</b> PD patients at high risk for ototoxicity						
Ampicillin	2 g	6	48.0	60	9.6	
<b>Comment:</b> Often used in combination with sulbactam						
Ampicillin/ sulbactam	2 g/ 1 g	6 –	48.0 27.8	60 68	9.6 9.4	
	Aztreonam	2 g in 2 L 1 g	6 8	83 42.5	92 90.8	9.3 2.4
Cefazolin	10 mg/kg	4	30-40	73	33	
	15 mg/kg	6	~90	69.7	31.5	
	1 g	6	64.6	77.9	39.9	
	1 g in 2L x 1 and 500 mg in 2L	6	110.9	85	–	
Cefoxitin	50 mg/L 100 mg/L	6 –	7 15	71 –	20 –	
	Cefoperazone	1 g 2g	10 6	33 38	81 61	– –
Cefoperazone/ sulbactam		2 g plus 1 g	6 –	38.9 24.4	61 70	2.3 6.3
	Cefotaxime	500 mg 1 g 2 g	5 4 6	12 15 30	60 58 47	2 11 –
Cefpirome		1 g	6	33	84	17.5
Ceftazidime		50 mg/L 15 mg/kg 1 g	6 6 4	11 46.3 24.2	– 72 74.1	– 21.6 20.8
	Ceftriaxone	2 g	5	104	74	12.7
	Cefuroxime	0.5 g	5	12.1	70	14.4

Drug	Dose	Dwell Time (h)	Cmax (mg/L)	Bioavailability (%)	Mean t <sub>1/2</sub> (h)
Ciprofloxacin	50 mg/L	6	1.1	–	–
	5 mg/kg	4	1.9	84	5.6
	25 mg/L	4	0.5	66	–
Clindamycin	300 mg/L	4-6	5.8	–	–
Erythromycin	<b>Comment:</b> No published pharmacokinetic studies.				
Gentamicin	0.6 mg/kg	6	1.4	56	35.8
	1 mg/kg	6	3.5	84	27.9
	7.5 mg/L	6	1.5	69	–
<b>Comment:</b> PD patients at high risk for ototoxicity					
Imipenem/cilastatin	500 mg	6	10	79	–
Linezolid	<b>Comment:</b> No published pharmacokinetic studies.				
Metronidazole	<b>Comment:</b> No published pharmacokinetic studies.				
Nafcillin	<b>Comment:</b> No published pharmacokinetic studies.				
Netilmicin	100 mg	6	~3	–	–
<b>Comment:</b> PD patients at high risk for ototoxicity.					
Ofloxacin	200 mg	8	3.2	93.6	–
Pefloxacin	400 mg	6	3.5	–	19.7
Piperacillin	1 g	6	–	83	–
<b>Comment:</b> May cause in vitro inactivation of aminoglycosides.					
Piperacillin/tazobactam	4 g/0.5 g	6	25.6 (pip)	–	10.7 (pip)
<b>Comment:</b> May cause in vitro inactivation of aminoglycosides.					
Quinupristin/dalfopristin	<b>Comment:</b> No published pharmacokinetic studies.				
Ticarcillin	<b>Comment:</b> May cause in vitro inactivation of aminoglycosides.				
Tobramycin	2 mg/kg	6	5.6	73	31
	1.5 mg/kg	4	1.8	52	35
<b>Comment:</b> PD patients at high risk for ototoxicity.					
Trimethoprim/sulfamethoxazole	320 mg T	4	2.4	84	5.6
	1600 mg S	–	46	66	5.6
Vancomycin	10 mg/kg	4	6	65	66
	1 g LD and 50 mg per exchange	6	9.1	73	–

Drug	Dose	Dwell Time (h)	Cmax (mg/L)	Bioavailability (%)	Mean t <sub>1/2</sub> (h)
Vancomycin	1 g	6	23.7	54	66.9
	30 mg/kg	6	30.4	52	91

## ANTIFUNGALS

Amphotericin

**Comment:** No published pharmacokinetic studies.

Fluconazole	50 mg	6	0.9	87	72-85
	150 mg	6	2.2	88	72-85
	200 mg	12	3.5	96	71.6

Flucytosine

**Comment:** No published pharmacokinetic studies.

## MISCELLANEOUS

Calcitriol	11 ng/kg	8-9	50.4 ng/mL	–	19.2
	60 ng/kg	10	100 ng/mL	–	16.5
	120 ng/kg	10	260 ng/mL	–	16.5

**Comment:** Undergoes adsorption to dialysis system (35-40% of dose).

Erythropoietin	100 units per kg	4	99.8 U/L	11.4	7.4
	100 units per kg	8	208 U/L	–	8.0

**Comment:** Undergoes minimal adsorption to dialysis system (<10% of dose).

**Comment:** Administer in dry peritoneum for maximal absorption.

Heparin products

**Comment:** No published pharmacokinetic studies; IP administration of standard heparin causes negligible systemic anticoagulation. See text.

Insulin	20 units/ 2L exchange	3	20 µU/mL	–	–
	20 units/ 2L exchange	3	15.5 µU/mL	–	–
	20 units in 20 mL NS flush	3	55.6 µU/mL	–	–
	33 units/ 1L exchange	6	35 µU/mL	70	5

**Comment:** Undergoes adsorption to dialysis system (10-20% of dose).

**Comment:** Administer in dry peritoneum for maximal rate of absorption.

## Key:

LD = Loading dose

MD = Maintenance dose

NS = Normal saline

U = Units

Cmax = Maximum plasma concentration achieved following dosing

t<sub>1/2</sub> = Plasma elimination half-life

Bioavailability = Fraction of administered dose absorbed from the peritoneum

## Treatment of infections

There is little published literature describing the use of intraperitoneal antibiotics for treatment of cellulitis, endocarditis, or osteomyelitis. Therefore, no specific recommendations can be provided. However, there is substantial anecdotal, unpublished experience with this technique. Clinicians are encouraged to use appropriate clinical diagnostic and microbiologic testing methods to help guide antibiotic therapy.

Because endocarditis and osteomyelitis often require prolonged antibiotic therapy, IP dosing may provide a suitable method for providing antibiotic therapy in a relatively convenient manner in the home setting. Clinicians are urged to monitor treatment response carefully, due to the serious nature of these infections.

## Intraperitoneal insulin

Considerable published experience exists for IP insulin dosing in PD patients. Insulin administered by the IP route crosses the peritoneal membrane by passive diffusion, and is predominantly delivered to the liver via the portal circulation before reaching the systemic circulation. Following IP administration, the concentration of peripheral free insulin is lower when compared to the peripheral free insulin concentration achieved following subcutaneous dosing. A proposed advantage of IP insulin administration is that insulin is delivered to the liver without creating hyperinsulinemia, a situation thought to be

potentially atherogenic. IP insulin has been used successfully in treating hyperglycemia in diabetic patients receiving peritoneal dialysis.

Absorption of insulin from the peritoneal cavity is concentration dependent. Insulin administered into an empty peritoneal cavity will be absorbed more rapidly and completely than if the insulin is administered in a large volume of dialysis solution. Direct injection of multiple daily doses of insulin into the peritoneum may be impractical for most patients. Therefore IP insulin is usually administered via the routine dialysis fluid exchange.

Conversion from a stable subcutaneous insulin dose to IP insulin dosing at initiation of PD usually requires a 2.5 to 3.5-fold increase in the required insulin. This difference reflects incomplete absorption during the dialysate dwell period, an increased insulin requirement due to the hypertonic dextrose-containing dialysate, and possible adsorption (binding) of the insulin to the polyvinyl chloride surface of the dialysis system. Approximately 10 to 20% of the administered dose may bind to the surface of the PD bag and tubing. Regular (short-acting) insulin should be used for IP dosing.

For patients using CAPD, the total daily insulin dose should be divided among the exchanges according to anticipated caloric intake from food and dialysate dextrose. Additional amounts of insulin may need to be added to exchanges containing more hypertonic dextrose concentrations. Dose adjustment should

utilize frequent blood glucose testing. Dose stabilization may require several days. Insulin requirements often increase during episodes of peritonitis. Successful use of IP insulin requires the full participation of the patient or caregiver who understands the importance of home glucose monitoring and techniques for adding insulin to the dialysate. The addition of insulin to the dialysis solution, using appropriate aseptic techniques, has not been associated with an increased incidence of peritonitis.

IP insulin administration may be less well suited for patients using cyclic or automated PD methods. There is little published experience with successful dosing methods when more rapid dialysis exchanges are performed or if the patient has a dry peritoneum during any portion of the day. At present, there are no published recommendations for IP insulin administration when cyclic or automated dialysis methods are used.

### **Intraperitoneal vitamin D products**

Because of the difficulty of chronically administering intravenous (IV) vitamin D products to PD patients, there has been some interest in dosing calcitriol (Calcijex<sup>®</sup>, Abbott Laboratories) via the IP route. Intraperitoneal administration of calcitriol can achieve serum concentrations comparable to IV dosing (Table 4). The overall pharmacokinetic parameters of IP calcitriol doses are generally similar to comparable doses given orally or intravenously. Limited studies have demonstrated that IP

calcitriol administration is safe and effective in children and adults, however IP dosing offers no clear biologic advantage over oral dosing. A potential disadvantage of IP dosing is that calcitriol undergoes adsorption to the dialysis system, necessitating increased dose requirements to achieve desired therapeutic effect.

At the present time, there is little justification for the use of IP calcitriol. No studies have been published that examine IP paricalcitol (Zemplar<sup>®</sup>, Abbott Laboratories) or IP doxercalciferol (Hectorol<sup>®</sup>, Bone Care International).

### **Intraperitoneal erythropoietin**

Experience with IP erythropoietin is limited. Early pharmacokinetic studies demonstrated that a very small fraction of the dose reached the systemic circulation. More recent work has shown that absorption from the peritoneum can be enhanced considerably if the drug is administered into a dry peritoneal cavity. This “dry-dwell” technique employs the following steps:

1. Drain the peritoneal cavity of dialysis effluent.
2. Inject the erythropoietin dose into the peritoneal cavity via the peritoneal catheter.
3. Flush the catheter with 30 mL of normal saline.
4. Allow the dose to dwell in the peritoneal cavity for four to eight hours. A longer dwell time leads to enhanced drug absorption. This dry-dwell period may be best suited for the overnight hours.
5. Resume normal dialysis exchanges.

The use of the “dry-dwell” technique has been shown to be an effective and safe method of chronic erythropoietin administration for children and adults. While individual patient dosing requirements vary, the overall dose requirement may increase compared to subcutaneous dosing needs. Most patients can maintain a satisfactory and stable hemoglobin value with one to two doses of IP erythropoietin per week.

A recommended method for converting from subcutaneous dosing to IP dosing is to initiate IP dosing with the previous subcutaneous dose using the “dry-dwell” technique. Monitor the hemoglobin and adjust the IP dose according to the patient’s response. As with subcutaneous dosing, patients should be given adequate amounts of iron. Because the “dry-dwell” technique is required for optimal drug absorption, PD patients will lose a small amount of dialysis per week. This will have an adverse impact on dialysis adequacy. A single weekly IP dose (8-hour dry dwell) will result in an approximate 3% reduction in weekly dialysis adequacy. Monitoring is important because decreased dialysis adequacy has been associated with an increased risk of mortality.

Selected patient populations may be best suited for IP erythropoietin. Because of the importance of administering the drug into a dry peritoneal cavity, patients who have an empty peritoneum during any portion of the day may be ideal candidates for this

technique. In addition, adults and children who have needle phobia may welcome this method of dosing.

There are no data on the IP administration of darbepoetin alfa (ARANESP®).

### **Intraperitoneal iron**

Because the use of oral iron products is often associated with suboptimal iron maintenance, and because IV iron administration is inconvenient for PD patients, some investigators have explored the safety and efficacy of intraperitoneal iron administration. Anecdotal reports and studies with small numbers of patients suggest that iron dextran may be administered safely and effectively by the IP route. However, some animal studies have indicated that IP iron dextran may cause toxicity to the peritoneal membrane in a dose-dependent fashion. To date, there are no published reports of IP administration of iron sucrose or ferric gluconate to PD patients. Presently available parenteral iron products have not been approved for intraperitoneal use. Further safety and efficacy data are needed before IP iron administration can be recommended.

## **Intraperitoneal heparin products**

### *Standard (unfractionated) heparin*

Standard heparin is often added to PD solutions for prevention or treatment of fibrin formation. The instillation of usual doses of heparin (500-1000 units per liter) is associated with little systemic anticoagulant effect, perhaps due to limited absorption of the heparin into the systemic circulation.

Limited animal and *ex vivo* studies have suggested that heparin may have a dose-dependent adverse effect on peritoneal mesothelial cells. The use of the smallest effective dose is therefore recommended. Doses of 500 to 1000 units per liter of peritoneal dialysate do not appear to cause peritoneal toxicity.

### *Low-molecular-weight heparins (LMWH)*

Experience with IP administration of LMWH products is extremely limited. Preliminary evidence suggests that IP dosing of these products may result in systemic anticoagulant effects, however these effects appear to be dependent upon the dose of antifactor Xa administered. Due to the lack of clinical experience and lack of efficacy and safety data, IP dosing of LMWH cannot be recommended at present.

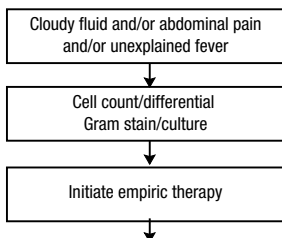
## TREATMENT OF PERITONEAL DIALYSIS INFECTIONS

Peritonitis continues to be a common complication of PD. Peritonitis is the cause of significant numbers of hospitalizations and is the leading cause of technique failure and catheter loss. The most common microorganisms causing peritonitis are *S. epidermidis* (coagulase-negative staphylococci) and *S. aureus* (coagulase-positive staphylococci), which together account for over one-half of all peritonitis cases in PD patients.

Exit-site and tunnel infections constitute the other major PD-related infections. *S. aureus* is the predominant cause of exit-site and tunnel infections, and is strongly associated with *S. aureus* on the skin and in the nares. *S. epidermidis*, gram-negative organisms, and others such as fungi, are also potential causative organisms.

Treatment recommendations for PD-related peritonitis were published in 2000 by the Advisory Committee on Peritonitis Management of the International Society for Peritoneal Dialysis (ISPD). The tables and figures on the following pages reflect these recommendations for peritonitis and exit-site infections (Tables 5-8 and Figures 9-12). For a more detailed discussion, the reader is referred to the full-text article cited in the References section. Note that the ISPD is working on updating the guidelines during 2004, but it is uncertain when they will be published.

**Figure 9. Empiric initial therapy for peritoneal dialysis-related peritonitis, stratified for residual urine volume**



	Residual urine output			
	<100 mL/day		>100 mL/day	
Agent	Continuous	Intermittent	Continuous	Intermittent
Cefazolin	500 mg/L load 125 mg/L MD	15 mg/kg q.d.	625 mg load 175 mg MD	20 mg/kg q.d.
Cephalothin	500 mg/L load 125 mg/L MD	15 mg/kg q.d.	625 mg load 175 mg MD	20 mg/kg q.d.
Ceftazidime	250 mg/L load 125 mg/L MD	1.0-1.5 g q.d.	300 mg/L load 150 mg/L MD	1.5-2.0 g q.d.
Gentamicin Netilmicin Tobramycin	8 mg/L load 4 mg/L MD	0.6 mg/kg q.d.	10 mg/L load 5 mg/L MD	0.75 g q.d. Dosing frequency should be individualized based on serum/dialysate levels
Amikacin	24 mg/L load 12 mg/L MD	2 mg/kg q.d.	30 mg/L load 15 mg/L MD	2.5 mg/kg q.d. Dosing frequency should be individualized based on serum/dialysate levels

Key: All doses are IP

MD = maintenance dose; q.d. = once per day

Despite the 2000 recommendations, treatment of PD-related infection continues to be the subject of great debate and variable clinical practice. The following discussion highlights the areas of clinical controversy or concern.

### **Empiric treatment in CAPD**

Initial gram-positive coverage should be effective against staphylococci (both coagulase-negative and -positive) and streptococci. Continuing concerns with the spread of vancomycin resistance and potential aminoglycoside toxicity have led to the current recommendation for cefazolin plus ceftazidime as the choice for initial empiric treatment of peritonitis. Cefazolin and ceftazidime dosing is dependent on residual renal function (RRF) because of increased drug clearances in patients with RRF.

The guidelines recommend against routine use of aminoglycosides in patients with RRF. This arises from a desire to preserve residual function for as long as possible, since RRF is an independent predictor of survival. Thus, empiric aminoglycosides are recommended only for anuric patients. Table 5 and Figure 9 suggest dosage regimens of antibiotics based upon the presence or absence of residual renal function.

**Table 5. Antibiotic dosing recommendations for CAPD (only) patients with and without residual renal function<sup>a</sup>**

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
<b>AMINOGLYCOSIDES</b>				All LD same as anuric
Amikacin	2 mg/kg	Increase all doses by 25%	LD 24 mg, MD 12 mg	Increase all MD by 25%
Gentamicin	0.6 mg/kg	Increase all doses by 25%	LD 8 mg, MD 4 mg	Increase all MD by 25%
Netilmicin	0.6 mg/kg	Increase all doses by 25%	LD 8 mg, MD 4 mg	Increase all MD by 25%
Tobramycin	0.6 mg/kg	Increase all doses by 25%	LD 8 mg, MD 4 mg	Increase all MD by 25%
<b>CEPHALOSPORINS</b>				All LD same as anuric
Cefazolin	15 mg/kg	20 mg/kg	LD 500 mg, MD 125 mg	MD increase by 25%
Cephalothin	15 mg/kg	ND	LD 500 mg, MD 125 mg	MD, ND
Cephradine	15 mg/kg	ND	LD 500 mg, MD 125 mg	MD, ND
Cephalexin	500 mg p.o., q.i.d.	ND	As intermittent	MD, ND
Cefuroxime	400 mg p.o./IV, q.d.	ND	LD 200 mg, MD 100-200 mg IV/po	MD, ND
Ceftazidime	1000-1500 mg	ND	LD 250 mg, MD 125 mg	MD, ND
Ceftizoxime	1000 mg	ND	LD 250 mg, MD 125 mg	MD, ND
<b>PENICILLINS</b>				All LD same as anuric
Piperacillin	4 g IV, b.i.d.	ND	LD 4 g IV, MD 250 mg IV	MD, ND
Ampicillin	250-500 mg p.o., b.i.d.	ND	MD 125, or 250-500 mg p.o., b.i.d.	MD, ND

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
Dicloxacillin	250-500 mg p.o., q.i.d.	ND	250-500 mg p.o., q.i.d.	MD, ND
Oxacillin	ND	ND	MD 125 mg	MD, ND
Nafcillin	ND	No change <sup>b</sup>	MD 125 mg	MD, no change <sup>b</sup>
Amoxicillin	ND	ND	LD 250-500 mg, MD 50 mg	MD, ND
Penicillin G	ND	ND	LD 50,000 U, MD 25,000 U	MD, ND
<b>QUINOLONES</b>				
Ciprofloxacin	500 mg p.o., b.i.d.	ND	LD 50 mg, MD 25 mg	ND
Ofloxacin	400 mg p.o., then 200 mg p.o., q.d.	ND	Same as intermittent	ND
<b>OTHERS</b>				
Vancomycin	15-30 mg/kg q.5-7 d	Increase doses by 25%	MD 30-50 mg/L	Increase MD by 25%
Teicoplanin	400 mg IP, b.i.d.	ND	LD 400 mg, MD 40 mg <sup>c</sup>	ND
Aztreonam	ND	ND	LD 1000 mg, MD 250 mg	ND
Clindamycin	ND	ND	LD 300 mg, MD 150 mg	ND
Metronidazole	250 mg p.o., b.i.d.	ND	Same as intermittent	ND
Rifampin	300 mg p.o., b.i.d.	ND	Same as intermittent	ND
<b>ANTIFUNGALS</b>				
				All LD same as anuric
Amphotericin	NA	NA	MD 1.5 mg	NA
Flucytosine	2 g LD, then 1 g q.d., p.o.	ND	Same as intermittent	ND
Fluconazole	200 mg q.d.	ND	Same as intermittent	ND
Itraconazole	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
<b>ANTITUBERCULARS</b>				
Isoniazid	300 mg p.o., q.d.	ND	Same as intermittent	ND
+ rifampin	600 mg p.o., q.d.			
+ pyrazinamide	1.5 g p.o., q.d.			
+ pyridoxine	100 mg/d			
<b>COMBINATIONS</b>				
All LD same as anuric				
Ampicillin/ sulbactam	2 g q.12 hr	ND	LD 1000 mg, MD 100 mg	ND
Trimethoprim/ sulfamethoxazole	320/1600 mg p.o., q.1-2 days	ND	LD 320/1600 mg p.o., MD 80/400 mg p.o. q. d.	ND

**Key:**

All doses are IP unless otherwise noted

MD = Maintenance dose

LD = Loading dose

ND = No data

p.o. = Oral

q.i.d. = Four times per day

IV = Intravenous

q.d. = Once per day

b.i.d. = Twice per day

IP = Intraperitoneal

ND = No data. These drugs are normally renally excreted, therefore an increase in dose by 25% is probably warranted. CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens.

NA = Not applicable, that is, drug is extensively metabolized and therefore there should be no difference in dosing between anuric and nonanuric patients.

Anuric = <100 mL urine/24 hours; nonanuric = >100 mL/24 hours.

<sup>a</sup> The route of administration is IP unless otherwise specified. These pharmacokinetic data and dosage regimens are based on published literature reviewed through June 2001, or established clinical practice.

<sup>b</sup> These penicillins are predominantly hepatically metabolized, or hepatically metabolized and renally excreted.

<sup>c</sup> Dosed as: in each bag x 7 days, then in 2 bags/day x 7 days, and then in 1 bag/day x 7 days.

## Modification of treatment regimen

Tables 6 and 7 and Figures 10 and 11 indicate how treatment regimens should be modified once culture and sensitivity results become known. When indicated by cultures and sensitivities and other factors, both aminoglycosides and vancomycin use may be appropriate for some patients.

**Table 6. Treatment strategies if peritoneal dialysis fluid cultures are negative at 24 to 48 hours or not performed**

Continue initial therapy		Duration of therapy
If clinical improvement	Discontinue ceftazidime or aminoglycoside	14 days
	Continue cephalosporin	
If no clinical improvement at 96 hours	Repeat cell count, Gram stain, and culture	14 days
If culture positive, adjust therapy accordingly		
If culture negative, continue antibiotics, consider infrequent pathogens and/or catheter removal		14 days

**Table 7. Treatment recommendations if yeast or other fungus identified on Gram stain or culture**

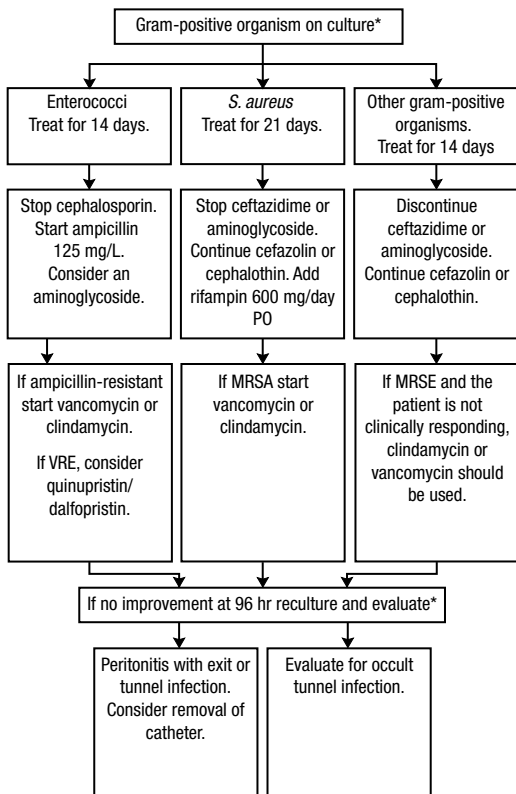
### AT 24 TO 48 HOURS

Flucytosine and Fluconazole	LD 2 g p.o.; MD 1 g p.o. 200 mg, p.o., or intraperitoneally, daily
If organism is resistant, consider itraconazole	

### AT 4 TO 7 DAYS

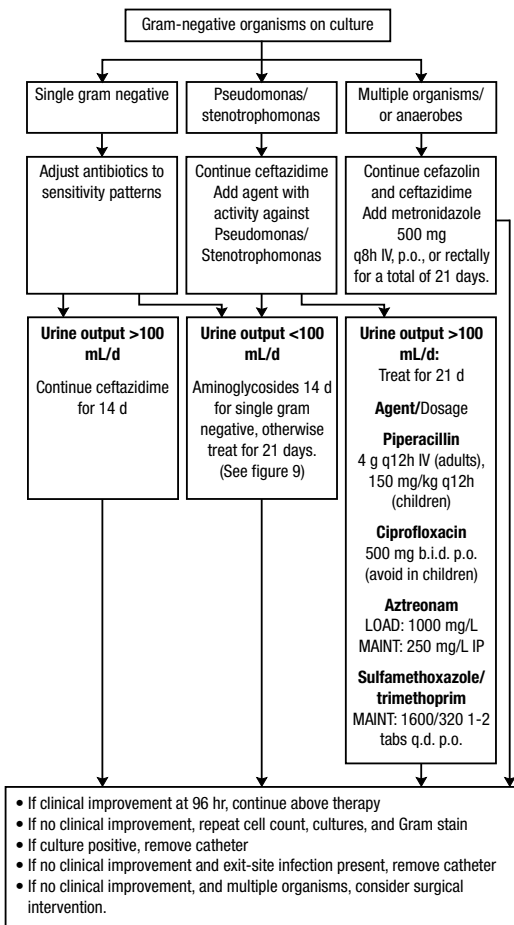
If clinical improvement, duration of therapy 4-6 weeks
If no clinical improvement, remove catheter and continue therapy for 7 days after catheter removal

**Figure 10. Treatment strategies after identification of gram-positive organism on culture**



\*Choice of therapy should always be guided by sensitivity patterns.

**Figure 11. Treatment recommendations if a gram-negative organism is identified on culture at 24-48 hours**



\*Choice of treatment should always be guided by sensitivity patterns.

**Table 8. Dosing of antibiotics, by IP intermittent route, in automated (cyclor-assisted) PD (These data for APD only)**

Drug	
Piperacillin	4 g IV, b.i.d.
Vancomycin	LD 35 mg/kg IP; MD 15 mg/kg q.d. Caution: see text
Cefazolin	20 mg/kg q.d., in first or second ambulatory dwell
Tobramycin	LD 1.5 mg/kg day 1; MD 0.5 mg/kg q.d., in first or second ambulatory dwell.
Fluconazole	200 mg IP, q.24-48 hr

Aminoglycoside use carries the risk of irreversible cochlear and vestibular ototoxicity. Aminoglycoside toxicity is associated with large cumulative doses, high or prolonged serum trough concentrations, frequent courses of therapy, and increasing age.

To avoid prolonged high aminoglycoside concentrations, an intermittent, once-daily IP aminoglycoside dosing regimen is recommended for treatment of infections caused by non-Pseudomonas/Xanthomonas gram-negative microorganisms. However, it is not known whether this regimen reduces the risk of toxicity as compared to continuous therapy.

### **Automated, cyclor-assisted PD (APD)**

APD produces higher drug clearances than CAPD. Table 8 indicates the dosage recommendations for some drugs in APD.

Of note are the large doses recommended for vancomycin. High intermittent IP doses are necessary to maintain adequate dialysate vancomycin concentrations over a 24 hour period. This regimen will produce high, sustained serum vancomycin concentrations, which may predispose some patients to toxicity.

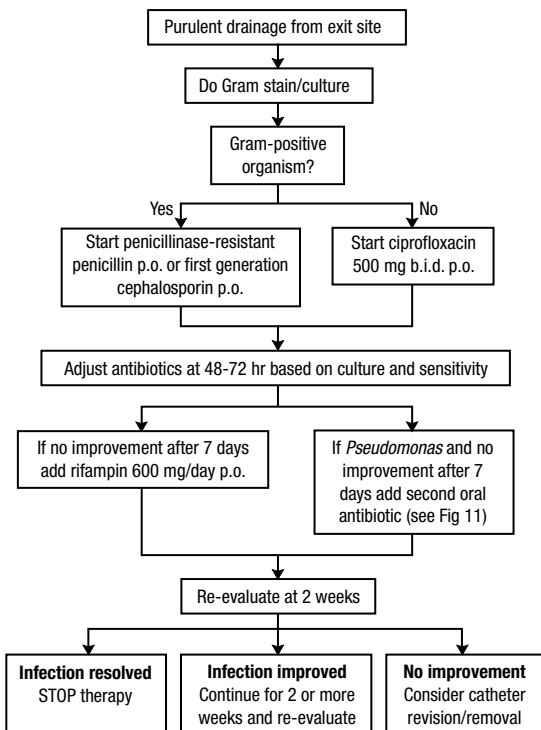
For APD patients that absolutely require vancomycin, health care professionals should consider switching patients to CAPD for the duration of treatment. An alternate, unstudied method may be to use a continuous dosing schedule for APD patients.

### **Prophylaxis and treatment of exit-site infections**

*S. aureus* is the leading cause of exit-site and tunnel infections, as well as catheter-related peritonitis. Several regimens for *S. aureus* prophylaxis have been shown to be effective, including intranasal mupirocin and mupirocin application to the exit-site, or cyclic oral rifampin. It is impractical to routinely screen all PD patients with nasal swabs to determine carrier status of *S. aureus*. Routine prophylaxis with daily mupirocin to the exit-site is recommended for PD patients at risk for the development of *S. aureus* exit-site infection. Patients at increased risk include diabetics, those that are immunocompromised, or those with previously documented nasal carriage of *S. aureus*. Mupirocin regimens include application of a small amount of ointment daily to the exit-site. Mupirocin is preferred to rifampin for prophylaxis because of its negligible toxicity.

Figure 12 shows recommendations for the treatment of exit-site infections.

**Figure 12. Flow chart for diagnosis and management of exit-site infections**



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## REFERENCES

1. Keane WF, Bailie GR, Boeschoten E, et al. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit Dial Int* 2000; 20:396-411.
2. Taylor CA, Abdel-Rahman E, Zimmerman SW, Johnson CA. Clinical pharmacokinetics during continuous ambulatory peritoneal dialysis. *Clin Pharmacokinet* 1996; 31:293-308.
3. Diaz-Buxo JA, Crawford TL, Bailie GR. Peritonitis in automated peritoneal dialysis: antibiotic therapy and pharmacokinetics. *Perit Dial Int* 2001; 21 (Suppl 3): S197-S201.
4. Yishak A, Bernardini J, Fried L, Piraino B. The outcome of peritonitis in patients on automated peritoneal dialysis. *Adv Perit Dial* 2001; 17: 205-208.
5. Piraino B. Peritonitis as a complication of peritoneal dialysis. *J Am Soc Nephrol* 1998; 9:1956-1964.
6. Bailie GR, Kane MP. Stability of drug additives to peritoneal dialysate. *Perit Dial Int* 1995; 15:328-335.
7. Vancomycin-Intermediate *Staphylococcus aureus* (VISA) Fact Sheet from the Centers for Disease Control and Prevention. <http://www.cdc.gov/ncidod/hip/vanco/VANCO.HTM>
8. Vancomycin-Resistant Enterococci (VRE) Fact Sheet from the Centers for Disease Control and Prevention. <http://www.cdc.gov/ncidod/hip/ARESIST/VRE.HTM>
9. Manley HJ, Bailie GR. Treatment of peritonitis in APD: pharmacokinetic principles. *Semin Dial* 2002; 15:418-421.