Harper Hospital
Detroit Medical Center/Wayne State University

10WS
Nephrology/Medicine

Table of Contents

Overview of the floor

10WS is a 25-bed unit comprised mostly of ESRD and kidney transplant patients. Internal Medicine overflow patients complete the census when extra beds are available. Currently, there are 4 internal medicine teaching services at HUH. "Medicine 4" is the only service dedicated solely to patients with chronic kidney disease (CKD) and end stage renal disease (ESRD). The service is always covered by an attending nephrologist as well as a nephrology fellow and 2-3 medical residents. However, evening and overnight admissions may be covered by residents/physicians who are not familiar with ESRD patients so careful patient profile review is important to ensure drugs are dosed appropriately. Patients will be listed as "NEP" service in MS MEDS or under one of the following admitting physicians: Kissner, Sondheimer, Migdal, Sillix, Haririan, El-Amm or Mohanty (Jena). The Nephrology census can be printed from CIS by adding the 'CARE TEAM', HA-Nephrology Inpatient to the patient list.

Who needs to be followed?

For Medicine 4 (nephrology) patients (print list from CIS..see above), the Fellow generally writes for vanco/aminoglycosides/cephalosporins on the HD order sheet and antibiotics are often given from floor stock in the HD unit. Initial notes and follow-up notes are appropriate when pharmacy is consulted to follow, but the Fellows oftentimes take care of ordering the antibiotics and levels in HD. Please be sure to look on the HD flowsheet to verify if antibiotics have already been given before ordering additional antibiotics. Note that the provision in the renal dosing policy and Pharmacokinetic policy states that orders written by Nephrology will NOT be automatically changed, please be sure to always contact the Fellow or resident on service (list posted on 10 WS) before giving additional doses of antibiotics or changing doses.

For all other ESRD patients on 10WS, pharmacy should follow the vanco/gent, write notes and order doses and levels as needed (see guidelines below).

All anticoagulation patients should be followed. If the patient is on iv heparin and we are not consulted, contact the resident or attending to confirm that we are not to follow. All anticoagulation service patients should have notes written every day, per protocol.

Basic Nephrology

End stage renal disease (ESRD) patients, by definition, have Clcr < 10 ml/min. These patients do not have a functional clearance of metabolic waste products through the kidneys. For most hemodialysis patients, clearance only occurs three times a week during their 3-4 hour hemodialysis session. Some patients may retain residual renal function and have a CLcr ~ 10 ml/min, check UOP records or ask the patient if they still make urine. In continuous ambulatory peritoneal dialysis (CAPD) patients, creatinine clearance occurs continuously at a reduced rate of <10ml/min. As such, dosing of medications needs to be adjusted accordingly.

HEMODIALYSIS

Gentamicin / Tobramycin

2 mg/kg loading dose (IBW or AdjBW if > 30% IBW)

LD = (Cmx) x (Vd) Cmx = LD / Vd

[Vd for aminoglycosides in ESRD ~ 0.3 – 0.4 L/kg ** (prefer .35 L/kg)]

- A 2mg/kg LD would be expected to provide a Cmx ~ 4-6 mg/L
- subsequent doses should be given **1 - 1.5 mg/kg after each HD session**
  - ****** (prefer 1 mg/kg) (IBW or adj. BW)
  - ** (use upper end of dosing for patients with residual renal function)
- in general, at Harper Hospital, HD removes 40-60% of aminoglycosides
- supplementing with 1 mg/kg after each HD would be expected to maintain a level of **4-6 mg/L**

** sustained levels > 6 mg/L increase risk of ototoxicity
**sustained levels > 8 mg/L are rarely, if ever needed

Amikacin

7.5 mg/kg loading dose (IBW or adjusted BW if > 30% IBW)

- A 7.5 mg/kg LD would be expected to provide a Cmx ~ 18 -25 mg/L
- subsequent doses should be given **3 - 5 mg/kg after each HD session**
  - ****** (prefer 3 mg/kg) (IBW or adj.BW)
  - ** (use upper end of dosing for patients with residual renal function)
- supplementing with 3 mg/kg each HD would be expected to maintain a level of **15 - 20 mg/L**

** sustained levels > 20 mg/L increase risk of ototoxicity
** sustained levels > 25 mg/L are rarely, if ever needed

Obtaining Levels

Theoretically, if dosed as above, it is unnecessary to “dose by levels”. A practical approach would be to order a random level before HD (labs routinely drawn pre-HD). Desired concentrations are 4-6 mg/L. (15-20 mg/L for amikacin). Assume ~ 50% will be removed by HD, and supplement post-HD (usually 1 mg/kg) or (3 mg/kg if amikacin) to maintain desired concentration.

Alternatively, a serum concentration may be obtained at the end of dialysis to verify ‘trough’ levels < 2-3 mg/L (<12 mg/L for amikacin). Note that rebound of levels occurs and post-HD levels should be increased by ~ 20-25% for aminoglycosides. ‘Peak’ levels may be ordered 1 hour after dose is given. In between dialysis sessions, most ESRD patients will only remove 5-10% / day of aminoglycosides.

Bottom Line

If dosed by above guidelines, 1-2 levels may be obtained to verify patient's Vd and HD clearance, then schedule subsequent doses for after each HD. Doses may get off schedule if the patient has a HD catheter pulled or HD is deferred. As a general rule, 1 - 1.5 mg/kg q72h (with initial loading dose) should provide adequate levels when no HD.

HEMODIALYSIS

Vancomycin

LD = (Cmx) x (Vd) Cmx = LD / Vd

1 g loading dose if 50-65 kg (Act. BW…AdjBW if > 30% IBW)
1.5 g loading dose if 66-80 kg
2 g loading dose if > 80 kg

- Vd for vancomycin in ESRD ~ 0.6 - 0.8 L/kg ** (prefer .75 L/kg)
- above LD expected to obtain a level 20-30 mg/L

- Most patients will only eliminate ~ 10% Vanco every 24 hours
  - therefore; no need for levels until ~ day #4
- A random level should be ordered to be drawn pre-HD
- Redose with same Vanco dose as given previously when **level ~ < 12mg/L**

Note that at Harper Hospital, a HD session removes < 10% vancomycin. Post-HD levels are rarely useful because of the significant rebound in concentration that occurs. In general, post-HD levels should be increased by ~ 40-50% for vancomycin. Outpatient HD units may use high-efficiency/high-flux dialysis membranes and therefore, remove a greater % of vancomycin (up to 50%). Patients receiving vancomycin as an outpatient may require dosing more frequently than 1-2 g / week.

Other Antibiotics:

Oftentimes, dialysis patients have poor vascular access making administering IV antibiotics a challenge. Creative dosage regimens utilizing the prolonged half-life of antibiotics in ESRD are often prescribed. These regimens are most effective for medications that are highly (>80%) excreted renally. Some examples include:

- Cefazolin 2g iv after qHD
- Cefepime 2g iv after qHD
- Ceftazidime 2g iv after qHD
- Fluconazole (twice the normal dose) after qHD
- Ganciclovir iv 0.625-1.25 mg/kg iv after qHD

**After qHD is generally <u>after</u> (schedule @ 1800..do not want to remove the drug during the dialysis) the session on MWF or TTHSa. Harper Hospital des not perform routine hemodialysis on Sundays.

NOTE: Pharmacokinetic properties preclude the use of the following renally eliminated antibiotics on a qHD basis

- Ampicillin, amp/sulbactam, aztreonam, cefoxitin,cefuroxme, ciprofloxacin, levofloxacin, imipenem, penicillin, piperacillin, pip/tazo

PERITONEAL DIALYSIS

** An excellent reference for the treatment guidelines for CAPD-related peritonitis can be found on line at *http://www.ispd.org/guidelines/articles/update/ispdperitonitis.pdf*

Aminoglycosides

If the patient is a continuous ambulatory peritoneal dialysis (CAPD) patient and receiving 4 exchanges / day, ideal dosing is as follows:

Gent / Tobra **0.6 mg / kg IP q HS** in the bedtime exchange (LD not needed)
(average dose is 40 mg IP qHS) (IBW… AdjBW if > 30% IBW)

Amikacin 2mg / kg IP qHS

*** Alternatively, may give Gent / Tobra 16 mg/ 2L bag **intraperitoneally (IP)** x's 1 dose
(Amikacin 50 mg / 2L bag)

Subsequent doses may be given IP **8**-12 mg / 2 L bag each exchange
(Amikacin **24**-30 mg / 2L bag)

Since we are giving IP antibiotics to locally treat the infection, systemic toxicity is usually minimal. It may be prudent to check a PRE- exchange level ("trough") before the 3rd bedtime dose if q HS (or before the 3rd or 4th exchange if every exchange dosing)

As we are not treating a systemic infection, we do not need "therapeutic" systemic levels.
Desire systemic level < 2 - 3 mg/L (Amikacin < 8-10 mg/L)

(dose-adjust directly : ie: if on 40mg IP Gent q HS and pre HS level = 4.0 mg/L)
Change dose to 20mg IP q HS

Vancomycin

Vancomycin dose **IP** q 5-7 days using bolus doses

15-30 mg/kg IP loading dose (Act. BW…AdjBW if > 30% IBW)
** (generally all patients receive a **2 g** loading dose)

Subsequent doses may be given as **1-2 g IP** when systemic levels are < 10mg/L

****Alternatively:

LD of 1g given **IP** X's 1 dose (Act. BW…AdjBW if > 30% IBW)

Subsequent doses should be 50mg / 2L bag q exchange IP

Obtaining levels

If dosing IP q 5-7 days, check a random level in 4-5 days, if systemic level < 10 mg/L may redose with 1-2g IP. Vancomycin clearance across the peritoneal membrane is limited, therefore, if dosing IP Vancomycin with each exchange, NO NEED for levels...will rarely be > 20 mg/L

Stability of drugs alone/combination in PD bag

The pharmacist may receive questions pertaining to stability of drugs in the PD bag (antibiotics alone or in combination with/without heparin). An excellent reference for this information is located at www.nephrologypharmacist.com, under "publications – peritoneal dialyisis guide". This guide is adapted from *Perit Dial Int 1995;15:328-335*. It is also found in *Appendix B*.

Anticoagulation Tips for ESRD Patients

Please consider the following when following ESRD patients on the anticoagulation service:

- ESRD patients have a tendency to bleed from a uremic platelet dysfunction.
  Do not be overly aggressive with bolusing heparin in these patients. Always use AdjBW when calculating heparin doses.

- Initiate warfarin conservatively (patients have a tendency to bleed). Most ESRD patients have low albumin and decreased warfarin binding… INR may rise rapidly.

- Try to minimize blood draws. Patients are anemic at baseline, unless absolutely necessary, try to keep PT / PTT's at QD.

- CBC's are routinely drawn with each hemodialysis session, no need to order additional CBC unless a specific problem arises.

- On hemodialysis days, please order PT / PTT to be drawn in HD (no need for 2 blood draws)
  ** note that PTT's drawn in HD are often high because the patients are given heparin to flush the catheters…PTT's should be drawn AFTER hemodialysis

- ESRD patients often have arteriovenous grafts in one of their arms…no blood draws are allowed from this arm. If iv heparin is running into the other arm, chances are that this is also from where the blood draw has come. Consider this when PTT is unexpectedly high.

- ESRD patients are usually vascular access nightmares! Most patients are Lab to Draw.

- ESRD patients are usually vascular access nightmares! If starting a peripheral line or obtaining PTT values become a problem, consider LMWH (enoxaparin). Please refer to the DMC Guidelines for Enoxaparin Use (special section for dosing in ESRD)

- If the decision is made to use enoxaparin, consider 1 mg/kg q24h regimen. Enoxaparin was recently approved to be used in patients with CrCl < 30 ml/min. Enoxaparin may accumulate after >3 doses in ESRD patients. If patients are to remain on LMWH, be sure to order aXa levels (low molecular weight heparin assay) 4 hrs AFTER the dose is given. Please refer to the DMC Guidelines for Enoxaparin Use

Detroit Medical Center
Wayne State University

DMC Guidelines for the Use of Low-Molecular-Weight Heparin (Enoxaparin) in Adults with CrCl < 30mL/min

June 2004

Renal Dysfunction: In patients with renal impairment, there is a decrease clearance of enoxaparin. Accumulation of the drug may occur with prolonged use and a dosage adjustment is recommended. All patients should be observed carefully for signs and symptoms of bleeding. Clinicians are encouraged to weigh the risks vs. benefits of prescribing LMWH in this patient population on a case-by-case basis

Anti-Xa monitoring: There is limited evidence to support the clinical significance of anti-Xa levels in association with efficacy and safety of LMWH. Clinicians are encouraged to weigh the risks vs. benefits of prescribing LMWHs in these patient populations on a case-by-case basis.

Consider consulting Pharmacy to follow dosing if therapy is expected to last > 48 hours

Indication	DMC Criteria	Recommended Dose CrCl <30 mL/min	Duration of Therapy
DVT Prophylaxis	Joint Replacement Surgery Knee and hip replacement	Enoxaparin 30 mg subQ q 24hr	At least 10 days Consider extended prophylaxis up to 4 weeks.
	Orthopedic Trauma (SCD in all) Pelvic and complex lower extremity fractures	Enoxaparin 30 mg subQ q 24hr	At least 10 days 4 Weeks for hip fracture
	Spinal Cord Injury a. For patients with no other injuries that put them at high risk for bleeding b. Exclude head-injured patients with intracranial bleeding	Enoxaparin 30 mg subQ q 24hr	Continue until rehab phase (up to 3 months)
	Bariatric surgery	No data	At least 7-10 days.
	Medically Ill patients a. For high risk patients b. For patients who refuse or unable to receive heparin TID	Enoxaparin 30 mg subQ q 24hr	Until ambulation
MONITORING		If anticipated to continue >7 days, anti-Xa level should be obtained 4 hrs after the 7th dose Target: <0.5 units/mL	

Indication	DMC Criteria	Recommended Dose CrCl <30 mL/min	Duration of Therapy
DVT/PE Treatment	**LMWH is 1st line agent for candidates for outpt therapy** LMWH is NOT recommended if any of the following apply: • Use of thrombolytic is indicated • Invasive procedure is planned • History of HIT • Recent history/ high risk of bleeding	1 mg/kg subQ q 24hr Use total body weight Max initial dose: 150mg subQ q 24hr	When transition patient to warfarin, give LMWH and warfarin for at least 4-5 days, then LMWH can be discontinued when therapeutic INR is achieved.
Unstable Angina & NSTEMI	Must meet one of the following criteria: 1. Meet DMC ACS Guidelines: Intermediate or high risk patients with TIMI Score ≥3 2. No IV access for heparin 3. Poor access for PTT draw 4. Non-compliant to IV therapy	1 mg/kg subQ q 24hr Use total body weight Max initial dose: 150mg subQ q 24hr	Continue for at least 48 hours Discontinue based on clinical assessment
Bridge Therapy and Miscellaneous Indications	LMWH may be used if patient meets one of the followings: 1. Bridge therapy to warfarin for outpatient treatment 2. No IV access for heparin 3. Poor access for PTT draw 4. Non-compliant to IV therapy 5. Contraindication to warfarin 6. Warfarin failure (recurrent thrombosis with therapeutic INR)	1 mg/kg subQ q 24hr Use total body weight Max initial dose: 150mg subQ q 24hr	When transition patient to warfarin, give LMWH and warfarin for at least 4-5 days, then LMWH can be discontinued when therapeutic INR is achieved.
MONITORING		If anticipated to continue >5 days, anti-Xa level should be obtained 4 hrs after the 3rd AM dose Target: 0.5-1.5 units/mL	

Calculation Guide

Creatinine Clearance (mL/min)	Male: $\frac{[140 - \text{age (yr)}] \times \text{Ideal body weight (kg)}}{72 \times \text{serum creatinine}}$ Female: $\frac{[140 - \text{age (yr)}] \times \text{Ideal body weight (kg)}}{72 \times \text{serum creatinine}} \times 0.85$ Use serum creatinine of ≥1 mg/dL for patients older than 60 years of age
Ideal body weight (kg)	Male: 50 kg + [2.3 x (inches > 5 feet)] Female: 45.5 kg + [2.3 x (inches > 5 feet)]
Adjusted body weight (kg)	[(Total body weight - Ideal body weight) x 0.4] + Ideal body weight
Body Mass Index (kg/m^2)	Total body weight (kg) / Height ^{2} (m^2)

Instruction on Ordering and Obtaining Low Molecular Heparin Assay (Anti-Factor Xa level):

Ordering Process:

- Write an order as: Heparin: Low Molecular Heparin Assay- send sample as STAT to the lab.
- Obtain peak level 4 hours after Lovenox administration
- Test is performed at MOTT laboratory (M-F @ 9 - 16:30pm. Phone: 313-577-0432)
- To inquire about results, call Core Laboratory at DRH (30714).
- Note that STAT order is completed in 2 - 5 hours, while routine order is completed in 24 hours.

Sample Collection:

- Collect sample in Blue Top test tube, 4 hours after Lovenox administration.

Reviewed by Cardiovascular and Thrombosis P & T Subcommittee, June 2004

Peritoneal Dialysis International, Vol. 25, pp. 107–131
Printed in Canada.

0896-8608/05 $3.00 + .00

ISPD GUIDELINES/RECOMMENDATIONS

PERITONEAL DIALYSIS-RELATED INFECTIONS RECOMMENDATIONS: 2005 UPDATE

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Peritonitis remains a leading complication of peritoneal dialysis (PD). It contributes to technique failure and hospitalization, and sometimes is associated with death of the patient. Severe and prolonged peritonitis can lead to peritoneal membrane failure. Therefore, the PD community continues to focus attention on prevention and treatment of PD-related infections (1–8).

Guidelines under the auspices of the International Society for Peritoneal Dialysis (ISPD) were first published in 1983 and revised in 1989, 1993, 1996, and 2000 (9–11). The initial focus was on the treatment of peritonitis, but the more recent guidelines included sections on preventing peritonitis. In the present guidelines, the Committee has expanded the section on prevention since prevention of peritonitis is one of the keys to success with PD.

The present recommendations are organized into five sections:

1. Prevention of PD-related infections
2. Exit-site and tunnel infections
3. Initial presentation and management of peritonitis
4. Subsequent management of peritonitis (organism specific)
5. Future research

These guidelines are evidence based where such evidence exists. The bibliography is not intended to be comprehensive as there have been over 9000 references to peritonitis in PD patients published since 1966. The Committee has chosen to include articles that are considered

The authors are the members of the ISPD Ad Hoc Advisory Committee on Peritoneal Dialysis Related Infections. The guidelines have been approved by the ISPD Committee on Standards and Education, chaired by Isaac Teitelbaum.

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Received 10 November 2004; accepted 17 January 2005.

key references. Guidelines are not based solely on randomized controlled trials, as such studies in PD patients are limited. If there is no definitive evidence but the group feels there is sufficient experience to suggest a certain approach, this is indicated as "opinion based." The guidelines are not meant to be implemented in every situation but are recommendations only. Each center should examine its own pattern of infection, causative organisms, and sensitivities, and adapt the protocols as necessary for local conditions.

The members of the Advisory Committee were carefully selected. First, nephrologists widely published on PD infections were chosen from around the world, with particular attention to including nephrologists from Asia, where the use of PD is growing very rapidly. Second, members were appointed with expertise in microbiology (Kuijper), pharmacotherapy (Bailie), infectious diseases (Paterson), and immunology (Holmes). The current guidelines are for adults only, as pediatric guidelines are published separately but, for coordination, a pediatrician was added to the work group (Schaefer). Third, two nurses (Bernardini and Uttley) represent the very important role of the nurse in the prevention of PD infections and care for PD patients with infections.

PREVENTION OF PD-RELATED INFECTIONS

- Every effort should be made in each PD program to prevent peritonitis to optimize outcomes on PD. Every program should monitor infection rates, at a minimum, on a yearly basis (*Opinion*) (12–14).

Programs should carefully monitor all PD-related infections, both exit-site infections and peritonitis, including the presumed cause and cultured organisms, as part of a continuous quality improvement program. The frequency of relapsing peritonitis also must be examined. For each peritonitis episode, a root cause analysis should be done to determine the etiology, and, whenever possible, an intervention made to prevent another episode. This may involve review of the patient's technique. If necessary, retraining should be performed; this should be done only by an experienced PD nurse. Causative organisms and presumed etiology must be reviewed in a regular fashion by the PD team, including both the home nurses and the physician(s), and, if appropriate, the physician assistant or nurse practitioner. In this way, interventions can be implemented if infection rates are rising or unacceptably high. Table 1 provides an easy method to calculate infection rates. Infection rates for individual organisms should also be calculated and compared to the literature. The center's peritonitis rate should be no more than 1 episode every 18 months (0.67 per year at risk), although the rate achieved will depend to some extent on the patient population. However, overall rates as low as 0.29 to 0.23/year have been reported, a goal that centers should strive to achieve (15,16).

TABLE 1
Methods for Examining Peritoneal Dialysis-Related Infections (Peritonitis, Exit-Site Infections) Ref. (14)

1. As rates (calculated for all infections and each organism):
   a. Number of infections by organism for a time period, divided by dialysis-years' time at risk, and expressed as episodes per year
   b. Months of peritoneal dialysis at risk, divided by number of episodes, and expressed as interval in months between episodes
2. As percentage of patients per period of time who are peritonitis free
3. As median peritonitis rate for the program:
   a. Calculate peritonitis rate for each patient
   b. Obtain the median of these rates

The type of PD used may have an impact on the frequency of infection. Patients on nightly PD (cycler at night with a dry day) may have a decreased risk of infection compared to continuous cycling peritoneal dialysis (CCPD; cycler at night plus day fill), perhaps because the empty abdomen for part of the day enhances immune function (17). The literature describing the relative risks of peritonitis with CCPD versus continuous ambulatory peritoneal dialysis (CAPD) is conflicting. Several studies have shown that CCPD patients have significantly lower peritonitis rates than CAPD patients (18–22). However, use of a cycler that requires spiking may lead to high rates of peritonitis due to contamination if an assist device is not used. The Committee recommends the use of an assist device for all spiking procedures. Some cyclers require a cassette; if reused, there is a high risk of peritonitis with water-borne organisms. Cassettes should not be reused (23,24). More research is needed comparing peritonitis risk with dry day, CCPD, and CAPD.

CATHETER PLACEMENT

- No particular catheter has been definitively shown to be better than the standard silicon Tenckhoff catheter for prevention of peritonitis (*Evidence*) (25–35).
- Prophylactic antibiotics administered at the time of insertion decrease infection risk (*Evidence*) (36–39).

Ideally, the patient should see the surgeon and/or training nurse prior to catheter placement, and the ideal location for the exit site determined. In addition, the

patient should be free of constipation. A single dose of intravenous (IV) antibiotic given at the time of catheter placement decreases the risk of subsequent infection. A first-generation cephalosporin has been most frequently used in this context. However, a recent randomized trial found that vancomycin (1 g IV, single dose) at the time of catheter placement is superior to cephalosporin (1 g IV, single dose) in preventing early peritonitis (37). The odds ratio of peritonitis without any antibiotic was 11.6, and for cefazolin (vs vancomycin) 6.45. Therefore, each program must consider using vancomycin for prophylaxis for catheter placement, carefully weighing the potential benefit versus the risk of use of vancomycin in hastening resistant organisms.

The double-cuff catheter had superior survival compared to the single-cuff catheter in patients participating in the National CAPD Registry, and was less likely to result in catheter removal for exit-site infection (33). This benefit was not confirmed in a single-center randomized trial with much smaller numbers (30). The role of the superficial cuff in preventing infection is primarily to anchor the catheter (40). The most superficial cuff (if a double-cuffed catheter is used) should be 2 – 3 cm from the exit site.

A downward directed tunnel may decrease the risk of catheter-related peritonitis (32). However, randomized trials have not confirmed the benefit of the swan neck configuration on reducing PD-related infections (28,29, 41). Nor has burying the catheter proved effective in reducing the risk of infection (25).

Every effort should be made to avoid trauma and hematoma during catheter placement. The exit site should be round and the tissue should fit snugly around the catheter. Sutures increase the risk of infection and are contraindicated. Some programs obtain nose cultures prior to placement of the catheter and treat *Staphylococcus aureus* nasal carriage with a 5-day course of intranasal mupirocin if positive. No data exist on the effectiveness of this approach.

EXIT-SITE CARE

- Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care. Antibiotic protocols against *S. aureus* are effective in reducing the risk of *S. aureus* catheter infections (*Evidence*) (25, 42–59).

Once the catheter is placed, and until healing is completed, the dressing changes should be done by a dialysis nurse using sterile technique. The exit site should be kept dry until well healed, which precludes showers or tub baths for this period, which can take up to 2 weeks. Once the exit site is well healed, the patient should be taught how to do routine exit-site care. Antibacterial soap and water are recommended by many centers. Use of an antiseptic to clean the exit site is preferred in some programs. Povidone iodine or chlorhexidine for cleansing are reasonable options (60). Hydrogen peroxide is drying and should be avoided for routine care. The catheter should always be kept immobile to prevent pulling and trauma to the exit site, which may lead to infection.

Staphylococcus aureus nasal carriage is associated with an increased risk of *S. aureus* exit-site infections, tunnel infections, peritonitis, and catheter loss. A single culture may yield a false negative result since many patients have intermittent nasal carriage. Colonization with *S. aureus*, and subsequently, infection, may come from partners as well as from health care workers (49). Therefore, excellent hand hygiene is very important prior to any examination of the patient's exit site by the patient, family members, and members of the health care team. Diabetic patients and those on immunosuppressive therapy are at increased risk for *S. aureus* catheter infections.

A number of protocols for prevention of *S. aureus* PD-related infections have been examined (Table 2). Prophylaxis with daily application of mupirocin cream or ointment to the skin around the exit site has been effective in reducing *S. aureus* exit-site infection and peritonitis in a number of reports. (Mupirocin ointment at the exit site, in contrast to mupirocin cream, should be avoided in patients with polyurethane catheters, as structural damage to the catheter has been reported.)

Mupirocin resistance has been reported, particularly with intermittent use (50,51,61). Resistance to mupirocin can be classified as low if the minimal inhibitory concentration (MIC) (62) is greater than or equal to 8 µg/mL, or high if the MIC is greater than or equal to 512 µg/mL. It is expected that high-level resistance will eventually result in clinical failure or a high relapse rate.

TABLE 2
Antibiotic Protocol Options for Preventing Exit-Site Infections

1. Exit site mupirocin:
   a. Daily after cleansing in all patients
   b. Daily after cleansing in carriers only
   c. In response to a positive exit-site culture for *Staphylococcus aureus* denoting carriage
2. Intranasal mupirocin twice per day for 5–7 days:
   a. Every month, once patient identified as a nasal carrier
   b. Only in response to positive nose culture
3. Exit-site gentamicin cream daily in all patients after cleansing

Resistance to mupirocin does not yet appear to have eliminated its efficacy, but this may occur eventually.

With the reduction in *S. aureus* infections using mupirocin, *Pseudomonas aeruginosa* becomes the most troublesome organism at the exit site (58). Recently, in a double-blinded randomized trial, gentamicin cream applied daily to the exit site was shown to be as effective as exit-site mupirocin in reducing *S. aureus* exit-site infections, and highly effective in reducing *P. aeruginosa* exit-site infections as well (48). This protocol had the added advantage of reducing peritonitis risk compared to the mupirocin approach. Ciprofloxacin otologic solution applied daily to the exit site as part of routine care was also effective in reducing both *S. aureus* and *P. aeruginosa* compared to historic controls using soap and water only (63).

To summarize, comparisons of different methods of exit-site care in randomized trials are limited, making it difficult to recommend a specific protocol. Each program should evaluate the organisms causing exit-site infections and institute a protocol to diminish such risk as seems appropriate for the program.

CONNECTION METHODS

- Spiking of dialysis bags is a high-risk procedure for contamination of the system. "Flush before fill" reduces the risk of contamination (*Evidence*) (15, 64–68).

Abundant data exist to show that spiking leads to peritonitis. Furthermore, flushing with dialysate before filling the abdomen has been shown to decrease peritonitis risk from contamination for both CAPD and automated peritoneal dialysis (APD). Therefore, for CAPD, a double-bag system should be used and manual spiking should be avoided as much as possible; if spiking is required, assist devices may be employed. Close attention must be paid to the connection methodology. For programs that switch vendors and, therefore, connection method, careful attention should be paid to subsequent infection rates. For APD, if spiking is part of the system, consideration should be given to training patients with the use of an assist device to prevent contamination.

TRAINING METHODS

- Training methods influence the risk of PD infections (*Evidence*) (69–71).

A recently published study in the United States documents the success of training and retraining to reduce peritonitis rates (71). Centers were randomly assigned to provide patients enhanced training ($n = 246$) or standard training ($n = 374$), with follow-up for 418 patient-years. Patients having enhanced training had significantly fewer exit-site infections (1 every 31.8 months) compared to patients having standard training (1 every 18 months). Peritonitis was also reduced with enhanced training compared to standard training: 1 every 36.7 months versus 1 every 28.2 months respectively. Thus, training is an effective tool in reducing PD infections.

In general, patients must be taught aseptic technique, with emphasis on proper hand washing techniques. If the water the patient uses is thought to have a high bacterial count, then use of an alcohol hand wash should be encouraged (*Opinion*). The hands must be completely dried using a clean towel after washing, before initiating the exchange. Location for exchanges must be clean, with avoidance of animal hair, dust-laden air, and fans.

All patients must be taught what contamination is and the proper response to contamination (presentation to the center for a tubing change if the end of the tubing is contaminated). Prophylactic antibiotics should be prescribed if dialysis solution was infused after contamination or if the catheter administration set was open and exposed to bacteria for an extended period of time. After a known break in technique, most nephrologists give a 2-day course of antibiotics (*Opinion*). There is no standard regimen. A culture of the effluent, if positive, is helpful in determining subsequent therapy.

The PD nurses are central to a successful PD program with low infection rates. Unfortunately, there are few if any studies on nurse-to-patient ratios that lead to the best outcomes. Overburdening the nurse with excessive numbers of patients will result in shortened training times and difficulty in retraining as needed. The Committee recommends home visits. These may be very useful in detecting problems with exchange technique, but can be carried out only if the nurses have sufficient time to do such visits.

ANTIBIOTIC PROPHYLAXIS FOR PROCEDURES

- Invasive procedures may infrequently cause peritonitis in PD patients (*Evidence*) (1,72).

A single oral dose of amoxicillin (2 g) 2 hours before extensive dental procedures is reasonable, although there are no studies to support this approach (*Opinion*). Patients undergoing colonoscopy with polypectomy are at risk for enteric peritonitis, presumably from movement of bacteria across the bowel wall into the peri-

toneal cavity. Ampicillin (1 g) plus a single dose of an aminoglycoside, with or without metronidazole, given IV just prior to the procedure may decrease the risk of peritonitis (*Opinion*). The work group recommends that the abdomen be emptied of fluid prior to all procedures involving the abdomen or pelvis (such as colonoscopy, renal transplantation, and endometrial biopsy) (*Opinion*).

PREVENTION OF BOWEL SOURCE OF INFECTION

- There is an association between both severe constipation and enteritis and peritonitis due to enteric organisms (*Evidence*) (73,74).

Possibly, peritonitis results from transmigration of micro-organisms across the bowel wall. Dialysis patients may have hypomotility disorders, may be more prone to gastrointestinal ulcerations and bleeds, and tend to be on drugs contributing to constipation (*e.g.*, oral iron, oral calcium, some analgesics), which is, therefore, quite common and sometimes not recognized by the patient. All PD patients should be instructed during training on the importance of regular bowel movements and avoidance of constipation. Hypokalemia, which can worsen bowel immotility, should be treated.

Colitis and diarrhea may be followed by peritonitis. The mode of entry of infection in such cases is unclear. Transmural migration of organisms is possible, as is touch contamination. Again, the importance of hand washing should be emphasized to the patient and, if need be, in areas where the water is contaminated the use of alcohol hand wash considered. Active inflammatory bowel disease is considered by many of the work group members to be a contraindication to PD.

PREVENTION OF FUNGAL PERITONITIS

- The majority of fungal peritonitis episodes are preceded by courses of antibiotics (*Evidence*) (75–77).
- Fungal prophylaxis during antibiotic therapy may prevent some cases of Candida peritonitis in programs that have high rates of fungal peritonitis (78–83).

Patients with prolonged or repeated courses of antibiotics are at increased risk of fungal peritonitis. A number of studies have examined the use of prophylaxis, either oral nystatin or a drug such a fluconazole, given during antibiotic therapy to prevent fungal peritonitis, with mixed results. Programs with high baseline rates of fungal peritonitis found such an approach to be beneficial, while those with low baseline rates did not detect a benefit. The work group is unable to render a definitive recommendation and, therefore, each PD program must examine their history of fungal peritonitis and decide whether such a protocol might be beneficial.

EXIT-SITE AND TUNNEL INFECTIONS

DEFINITIONS

- Purulent drainage from the exit site indicates the presence of infection. Erythema may or may not represent infection (*Evidence*) (84–86).

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter–epidermal interface. Pericatheter erythema without purulent drainage is sometimes an early indication of infection but can also be a simple skin reaction, particularly in a recently placed catheter or after trauma to the catheter. Clinical judgment is required to decide whether to initiate therapy or to follow carefully. A scoring system developed by pediatricians, while not examined critically in adults, may be a useful method of monitoring exit sites (Table 3). A positive culture in the absence of an abnormal appearance is indicative of colonization rather than infection. Intensifying exit-site cleaning with antiseptics is advised (*Opinion*).

A tunnel infection may present as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult, as shown by sonographic studies (88). A tunnel infection usually occurs in the presence of an exit-site infection but rarely occurs alone. In the present article, exit-site and tunnel infections are collectively referred to as catheter infections. *Staphylococcus aureus* and *P. aeruginosa* exit-site infections are very often associated with concomitant tunnel infections and are the organisms that most often result in catheter-

TABLE 3
Exit-Site Scoring System Ref. (87)

	0 points	1 point	2 points
Swelling	No	Exit only; <0.5 cm	>0.5 and/or tunnel
Crust	No	<0.5 cm	>0.5 cm
Redness	No	<0.5 cm	>0.5 cm
Pain	No	Slight	Severe
Drainage	No	Serous	Purulent

Infection should be assumed with exit-site score of 4 or greater. Purulent drainage, even if alone, is sufficient to indicate infection. A score of less than 4 may or may not represent infection.

infection-related peritonitis; aggressive management is always indicated for these organisms.

THERAPY OF EXIT-SITE AND TUNNEL INFECTIONS

- The most serious and common exit-site pathogens are *S. aureus* and *P. aeruginosa*, as these organisms frequently lead to peritonitis (*Evidence*). Therefore, such infections must be treated aggressively (7,8,84, 89–94).
- Oral antibiotic therapy is as effective as intraperitoneal (IP) therapy, with the exception of methicillin-resistant *S. aureus* (MRSA) (86).

Exit-site and tunnel infections may be caused by a variety of micro-organisms. Although *S. aureus* and *P. aeruginosa* are responsible for the majority of infections, other bacteria (diphtheroids, anaerobic organisms, non-fermenting bacteria, streptococci, Legionella, yeasts, and fungi) can also be involved. Empiric antibiotic therapy may be initiated immediately. Alternatively, the health care team may decide to defer therapy until the results of the exit-site culture can direct the choice of antibiotic. A Gram stain of exit-site drainage can guide initial therapy. Cultures should be taken to the laboratory using appropriate transport materials also allowing anaerobic bacteria to survive. Oral antibiotic therapy has been shown to be as effective as IP antibiotic therapy.

Empiric therapy should always cover *S. aureus*. If the patient has a history of *P. aeruginosa* exit-site infections, empiric therapy should be with an antibiotic that will cover this organism (*Opinion*). In some cases, intensified local care or a local antibiotic cream may be felt to be sufficient in the absence of purulence, tenderness, and edema (*Opinion*). Especially severe exit-site infections may be treated by hypertonic saline dressings twice daily, as well as oral antibiotic therapy. This procedure involves adding 1 tablespoon of salt to 1 pint (500 mL) of sterile water; this solution is then applied to gauze and wrapped around the catheter exit site for 15 minutes, once or twice daily (*Opinion*).

Gram-positive organisms are treated with oral penicillinase-resistant penicillin or a first-generation cephalosporin such as cephalexin. Dosing recommendations for frequently used oral antibiotics are shown in Table 4. To prevent unnecessary exposure to vancomycin, and thus emergence of resistant organisms, vancomycin should be avoided in the routine treatment of gram-positive exit-site and tunnel infections, but will be required for MRSA infections. In slowly resolving or particularly severe-appearing *S. aureus* exit-site infections, rifampin 600 mg daily may be added, although this drug should be held in reserve in areas where tuberculosis is endemic. Rifampin should never be given as monotherapy.

TABLE 4
Oral Antibiotics Used in Exit-Site and Tunnel Infections

Amoxicillin	250–500 mg b.i.d.
Cephalexin	500 mg b.i.d.
Ciprofloxacin	250–500 mg b.i.d.
Clarithromycin	250–500 mg b.i.d.
Dicloxacillin	250–500 mg b.i.d.
Fluconazole	200 mg q.d.
Flucloxacillin	500 mg b.i.d.
Flucytosine	2 g load, then 1 g p.o., q.d.
Isoniazid	300 mg q.d.
Linezolid	600 mg b.i.d.
Metronidazole	400 mg b.i.d. for <50 kg 400–500 t.i.d. for >50 kg
Ofloxacin	400 mg first day, then 200 mg q.d.
Pyrazinamide	35 mg/kg q.d. (given as b.i.d. or once daily)
Rifampin	450 mg q.d. for <50 kg 600 mg q.d. for >50 kg
Trimethoprim/sulfamethoxazole	80/400 mg q.d.

b.i.d. = two times per day; q.d. = every day; p.o. = orally; t.i.d. = three times per day.

Pseudomonas aeruginosa exit-site infections are particularly difficult to treat and often require prolonged therapy with two antibiotics. Oral quinolones are recommended as the first choice. If quinolones are given concomitantly with sevelamer, multivalent cations such as calcium, oral iron, zinc preparations, sucralfate, magnesium–aluminum antacids, or milk, chelation interactions may occur that reduce quinolone absorption. Administration of the quinolone should, therefore, be separated from these drugs by at least 2 hours (with the quinolone administered first). If resolution of the infection is slow or if there is recurrence, a second anti-pseudomonal drug, such as IP ceftazidime, should be added.

Many organisms can cause exit-site and tunnel infections, including corynebacteria (7,95). Therefore, culture with sensitivity testing is important in determining antibiotic therapy. Close follow-up is necessary to determine the response to therapy and relapse. Unfortunately, both *S. aureus* and *P. aeruginosa* catheter infections tend to recur.

Antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time (*Opinion*), and longer may be necessary. If prolonged therapy with appropriate antibiotics fails to resolve the infection, the catheter can be replaced as a single procedure under antibiotic cover-

age (96–99). Revision of the tunnel may be performed if the inner cuff is not involved, in conjunction with continued antibiotic therapy. This procedure, however, may result in peritonitis, in which case the catheter should be removed. Sonography of the tunnel has been shown to be useful in evaluating the extent of infection along the tunnel and the response to therapy, and may be used to decide on tunnel revision, replacement of the catheter, or continued antibiotic therapy (*Opinion*) (100). Although there are scant data on the efficacy of exit-site cuff shaving in treating refractory infections, centers familiar with this technique and achieving good results may try cuff shaving before catheter exchange. Antibiotics must be continued during and after cuff shaving.

A patient with an exit-site infection that progresses to peritonitis, or who presents with an exit-site infection in conjunction with peritonitis with the same organism, will usually require catheter removal. Catheter removal should be done promptly rather than submitting the patient to prolonged peritonitis or relapsing peritonitis. The exception is peritonitis due to coagulase-negative staphylococcus (CoNS), which is generally readily treated.

INITIAL PRESENTATION AND MANAGEMENT OF PERITONITIS

CLINICAL PRESENTATION OF PERITONITIS

- Peritoneal dialysis patients presenting with cloudy effluent should be presumed to have peritonitis. This is confirmed by obtaining effluent cell count, differential, and culture (*Evidence*) (101–105).

Patients with peritonitis usually present with cloudy fluid and abdominal pain. However, peritonitis should always be included in the differential diagnosis of the PD patient with abdominal pain, even if the effluent is clear, as a small percentage of patients present in this fashion. However, in the PD patient with abdominal pain and clear fluid, other causes such as pancreatitis should be investigated as well. Conversely, while patients with peritonitis most often have severe pain, some episodes are associated with mild or even no pain. The degree of pain is somewhat organism specific (*e.g.*, generally less with CoNS and greater with streptococcus, gram-negative rods, *S. aureus*) and can help guide the clinician regarding the decision to admit or treat as an outpatient. Patients with minimal pain can often be treated on an outpatient basis with IP therapy and oral pain medication. Those requiring IV narcotics always require admission for management.

Cloudy effluent will almost always represent infectious peritonitis but there are other causes (106). The differential diagnosis is shown in Table 5. Case reports of sterile peritonitis associated with icodextrin-based dialysis solutions have been reported from Europe (107). Randomized trials comparing icodextrin to glucose-based dialysis solution show similar peritonitis risk with the two solutions (108–110).

The abdomen should be drained and the effluent carefully inspected and sent for cell count with differential, Gram stain, and culture. An effluent cell count with white blood cells (WBC) more than 100/μL, with at least 50% polymorphonuclear neutrophil cells, indicates the presence of inflammation, with peritonitis being the most likely cause. To prevent delay in treatment, antibiotic therapy should be initiated as soon as cloudy effluent is seen, without waiting for confirmation of the cell count from the laboratory. Patients with extremely cloudy effluent may benefit from the addition of heparin, 500 units/L, to the dialysate to prevent occlusion of the catheter by fibrin. Heparin is also usually added in cases of hemoperitoneum (*Opinion*). An experienced observer can differentiate hemoperitoneum from cloudy effluent due to peritonitis. If there is a question, a cell count with differential should be performed.

The number of cells in the effluent will depend in part on the length of the dwell. For patients on APD who present during their nighttime treatment, the dwell time is much shorter than with CAPD; in this case, the clinician should use the percentage of polymorphonuclear cells rather than the absolute number of white cells to diagnose peritonitis. The normal peritoneum has very few polymorphonuclear cells; therefore, a proportion above 50% is strong evidence of peritonitis, even if the absolute white cell count does not reach 100/μL. Patients on APD with a day dwell who present during the day generally have cell counts similar to those of CAPD patients and are not difficult to interpret. However, APD patients without a daytime exchange who present with abdominal pain may have no fluid to withdraw. In this case, 1 L of dialysate

TABLE 5
Differential Diagnosis of Cloudy Effluent

Culture-positive infectious peritonitis
Infectious peritonitis with sterile cultures
Chemical peritonitis
Eosinophilia of the effluent
Hemoperitoneum
Malignancy (rare)
Chylous effluent (rare)
Specimen taken from "dry" abdomen

should be infused and permitted to dwell a minimum of 1 to 2 hours, and then drained and examined for turbidity and sent for cell count and differential and culture. The differential (with a shortened dwell time) may be more useful than the absolute WBC count. In equivocal cases, or in patients with systemic or abdominal symptoms in whom the effluent appears clear, a second exchange is performed with a dwell time of at least 2 hours. Clinical judgment should guide initiation of therapy.

Even though the Gram stain is often negative in the presence of peritonitis, this test should be performed as the Gram stain may indicate the presence of yeast, thus allowing for prompt initiation of antifungal therapy and permitting timely arrangement of catheter removal. With this exception, empiric therapy should not be based on the Gram stain, but should cover the usual pathogens as discussed below.

The patient should always be questioned in a non-threatening manner about a break in technique and in particular whether contamination occurred recently. Information about recent exit-site infections and the last (if any) episode of peritonitis should be obtained. The patient should also be questioned about the presence of either constipation or diarrhea.

In peritonitis, abdominal tenderness is typically generalized and is often associated with rebound. The physical examination of the patient presenting with peritonitis should always include a careful inspection of the exit site and tunnel of the catheter. Any drainage from the exit site should be cultured, along with the effluent. If the exit site grows the same organism as the effluent (with the exception of CoNS), then it is very likely that the origin of the peritonitis is the catheter.

Although an abdominal film is generally not necessary, if there is any suspicion of a bowel source, an abdominal film should be obtained. The presence of a large amount of free air is suggestive of perforation (although this may be due to inadvertent infusion of air by the patient). Routine peripheral blood cultures are unnecessary since they are usually negative, but they should be obtained if the patient appears septic.

Some PD patients reside in locations that are remote from medical facilities and thus cannot be seen expeditiously after the onset of symptoms. These patients also may not have immediately available microbial and laboratory diagnostic services. Since prompt initiation of therapy for peritonitis is critical, this necessitates reliance on immediate patient reporting of symptoms to the center, and then initiating IP antibiotics in the home setting. Such an approach requires that the patients be trained in this technique and that antibiotics be kept in the home. A delay in treatment of even a few hours is sometimes dangerous. Whenever possible, cultures should be obtained prior to starting antibiotic, either at a local facility or by having the patient keep blood-culture bottles at home for use. Alternatively, the patient may place the cloudy effluent bag in the refrigerator to slow bacterial multiplication and white cell killing until they are able to bring in the sample.

SPECIMEN PROCESSING

- Culture-negative peritonitis should not be greater than 20% of episodes. Standard culture technique is the use of blood-culture bottles, but culturing the sediment after centrifuging 50 mL of effluent is ideal for low culture-negative results (*Evidence*) (111–113).

The correct microbiological culturing of peritoneal effluent is of utmost importance to establish the microorganism responsible. Identification of the organism and subsequent antibiotic sensitivities will not only help guide antibiotic selection but, in addition, the type of organism can indicate the possible source of infection. Centrifugation of 50 mL of peritoneal effluent at 3000g for 15 minutes, followed by resuspension of the sediment in 3 – 5 mL of sterile saline and inoculation of this material both on solid culture media and into a standard blood-culture medium, is the method most likely to identify the causative organisms. With this method, less than 5% will be culture negative. The solid media should be incubated in aerobic, microaerophilic, and anaerobic environments. The Committee considers this the optimum culture technique. Blood-culture bottles can be directly injected with 5 – 10 mL of effluent if equipment for centrifuging large amounts of fluid is not available; this method generally results in a culture-negative rate of 20%. The removal of antibiotics present in the specimen may increase the isolation rate if the patient is already on antibiotics. The speed with which bacteriological diagnosis can be established is very important. Concentration methods not only facilitate correct microbial identification, but also reduce the time necessary for bacteriological cultures. Rapid blood-culture techniques (*e.g.*, BACTEC, Septi-Chek, BacT/Alert; Becton Dickinson) may further speed up isolation and identification and are probably the best approach. The majority of cultures will become positive after the first 24 hours and, in over 75% of cases, diagnosis can be established in less than 3 days.

EMPIRIC ANTIBIOTIC SELECTION

- Empiric antibiotics must cover both gram-positive and gram-negative organisms. The Committee recom-

mends center-specific selection of empiric therapy, dependent on the history of sensitivities of organisms causing peritonitis (*Opinion*). Gram-positive organisms may be covered by vancomycin or a cephalosporin, and gram-negative organisms by a third-generation cephalosporin or aminoglycoside (*Evidence*) (87,114–134).

Therapy is initiated prior to knowledge of the causative organism. The selection of empiric antibiotics must be made in light of both the patient's and the program's history of micro-organisms and sensitivities. It is important that the protocol cover all serious pathogens that are likely to be present. For many programs, a first-generation cephalosporin, such as cefazolin or cephalothin, with a second drug for broader gram-negative coverage (including coverage for Pseudomonas) will prove suitable. This protocol has been shown to have equivalent results to vancomycin plus a second drug for gram-negative coverage (125,135). However, many programs have a high rate of methicillin-resistant organisms and thus should use vancomycin for gram-positive coverage with a second drug for gram-negative coverage (136).

Gram-negative coverage can be provided with an aminoglycoside, ceftazidime, cefepime, or carbapenem. Quinolones should be used for empiric coverage of gram-negative organisms only if local sensitivities support such use. For the cephalosporin-allergic patient, aztreonam is an alternative to ceftazidime or cefepime for gram-negative coverage if aminoglycosides are not used. Antibiotic resistance may develop with empiric use of extended-spectrum cephalosporins and quinolones. Resistance should be monitored, especially for gram-negative organisms such as *Pseudomonas* species, *Escherichia coli*, *Proteus* species, *Providencia* species, *Serratia* species, *Klebsiella* species, and *Enterobacter* species.

While an extended course of aminoglycoside therapy may increase the risk for both vestibular and ototoxicity, short-term use appears to be safe and inexpensive and provides good gram-negative coverage. Once-daily dosing (40 mg IP in 2 L) is as effective as dosing in each exchange (10 mg/2 L, IP, in 4 exchanges per day) for CAPD peritonitis (137,138). There does not appear to be convincing evidence that short courses of aminoglycosides harm residual renal function (87,139). Repeated or prolonged courses of aminoglycoside therapy are probably not advisable if an alternative approach is possible (*Opinion*).

Either ceftazidime or cefepime is an appropriate alternative for gram-negative coverage. Cefepime is not broken down by many of the beta-lactamases that are currently produced by gram-negative bacilli worldwide, so it has better *in vitro* coverage than ceftazidime. If an aminoglycoside is used for the initial gram-negative coverage, intermittent dosing is strongly encouraged and prolonged courses should be avoided.

Monotherapy is also possible. In a randomized trial, imipenem/cilastatin (500 mg IP with a dwell of 6 hours, followed by IP 100 mg per each 2 L dialysis solution) was as effective in curing peritonitis as was cefazolin plus ceftazidime in CAPD patients (140). Cefepime (2 g IP load with a dwell time of >6 hours, followed by 1 g/day IP for 9 consecutive days) was as effective as vancomycin plus netilmicin in another randomized trial of CAPD-related peritonitis (117).

Quinolones (oral levofloxacin 300 mg daily or oral pefloxacin 400 mg daily) appear to be an acceptable alternative to aminoglycosides for gram-negative coverage (141–143) and do reach adequate levels within the peritoneum, even with cycler PD (144). In another study, oral ofloxacin alone (400 mg followed by 300 mg daily) was equivalent to cephalothin 250 mg/L for all CAPD exchanges, in combination with tobramycin 8 mg/L (145). However, resolution of *S. aureus* may prove to be slow with use of ciprofloxacin alone and it is not the ideal drug (146).

In the early days of PD, mild cases of peritonitis, such as those caused by *S. epidermidis*, were treated effectively with oral cephalosporin therapy (147). If the organism is sensitive to first-generation cephalosporin and the patient relatively asymptomatic, then this approach is still possible if for some reason IP or IV antibiotic therapy is not feasible. Oral therapy is not suitable for more severe cases of peritonitis.

DRUG DELIVERY AND STABILITY

Vancomycin, aminoglycosides, and cephalosporins can be mixed in the same dialysis solution bag without loss of bioactivity. However, aminoglycosides should not be added to the same exchange with penicillins because of chemical incompatibility. For any antibiotics that are to be admixed, separate syringes must be used for adding the antibiotics; although vancomycin and ceftazidime are compatible when added to dialysis solutions (1 L or higher), they are incompatible if combined in the same syringe or added to an empty dialysate bag for reinfusion into the patient. This approach is not recommended.

Antibiotics should be added using sterile technique (placing povidone iodine on the medication port for 5 minutes prior to insertion of the needle through the port). Dwell time of the exchange must be a minimum of 6 hours.

Data suggest that some antibiotics are stable for variable times when added to dextrose-containing dialysis solution. Vancomycin (25 mg/L) is stable for 28 days in dialysis solution stored at room temperature, although high ambient temperatures will reduce the duration of stability. Gentamicin (8 mg/L) is stable for 14 days, but the duration of stability is reduced by admixture of heparin. Cefazolin (500 mg/L) is stable for at least 8 days at room temperature or for 14 days if refrigerated; addition of heparin has no adverse influence. Ceftazidime is less stable: concentrations of 125 mg/L are stable for 4 days at room temperature or 7 days refrigerated, and 200 mg/L is stable for 10 days if refrigerated. Cefepime is stable in dialysis solution for 14 days if the solution is refrigerated (148).

These data are derived from duration of stability studies. It is possible that the agents are stable for longer periods, and more research is needed to identify the optimal stability conditions for antibiotic additives to dialysis solutions. Icodextrin-containing dialysis solutions are compatible with vancomycin, cefazolin, ampicillin, cloxacillin, ceftazidime, gentamicin, or amphotericin (149).

INTERMITTENT OR CONTINUOUS DOSING OF ANTIBIOTICS: SPECIAL CONSIDERATIONS FOR APD PATIENTS

Little is known about intermittent dosing requirements in patients treated with APD. The Committee agrees that IP dosing of antibiotics for peritonitis is preferable to IV dosing in CAPD, since IP dosing results in very high local levels of antibiotics. For example, 20 mg/L IP gentamicin is well above the MIC of sensitive organisms. The equivalent dose of gentamicin given IV would result in much lower IP levels. The IP route has the added advantage that it can be done by the patient at home, after appropriate training, and avoids venipuncture. Monitoring drug levels for aminoglycosides and vancomycin is recommended.

Intraperitoneal antibiotics can be given in each exchange (*i.e.*, continuous dosing) or once daily (intermittent dosing) (150–155). In intermittent dosing, the antibiotic-containing dialysis solution must be allowed to dwell for at least 6 hours to allow adequate absorption of the antibiotic into the systemic circulation. Most antibiotics have significantly enhanced absorption during peritonitis (*e.g.*, IP vancomycin is about 50% absorbed in the absence of peritonitis, but closer to 90% in the presence of peritonitis), which permits subsequent reentry into the peritoneal cavity during subsequent fresh dialysis solution exchanges. Table 6 provides doses for both continuous and intermittent administration for CAPD, where there is information available.

There are insufficient data on whether continuous dosing is more efficacious than intermittent for first-generation cephalosporins. A once-daily IP cefazolin dose of 500 mg/L results in acceptable 24-hour levels in the dialysis fluid in CAPD patients (152). An extensive body of evidence exists for the efficacy of intermittent dosing of aminoglycosides and vancomycin in CAPD, but less for APD. Table 7 provides dosing guidelines for APD, where such data exist or sufficient experience can allow a recommendation to be made. A randomized trial in children that included both CAPD and APD patients found that intermittent dosing of vancomycin/teicoplanin is as efficacious as continuous dosing (87). Intraperitoneal vancomycin is well absorbed when given in a long dwell and subsequently crosses again from the blood into the dialysate with fresh exchanges.

Rapid exchanges in APD, however, may lead to inadequate time to achieve IP levels. There are fewer data concerning efficacy of first-generation cephalosporins given intermittently for peritonitis, particularly for the patient on the cycler. For patients given a daytime exchange of a cephalosporin only, the nighttime IP levels are below the MIC of most organisms. This raises a concern that biofilm-associated organisms may survive and result in subsequent relapsing peritonitis. Until a randomized trial with large numbers is done, adding first-generation cephalosporin to each exchange would appear to be the safest approach (*Opinion*).

The Committee agrees that vancomycin can be given intermittently for patients on APD, even though there are few studies. However, the randomized European trial in children showed that intermittent dosing of vancomycin or teicoplanin (and many of the children were on APD) was as effective as continuous dosing. Generally, a dosing interval of every 4 – 5 days will keep serum trough levels above 15 µg/mL but, in view of the variability of losses due to residual renal function and peritoneal permeability, it is best to obtain levels. Intraperitoneal levels of vancomycin after the initial dose will always be lower than serum levels of vancomycin; therefore, the serum levels need to be kept higher than would be otherwise indicated (123). Re-dosing is appropriate once serum vancomycin levels reach 15 µg/mL.

Whether or not patients on a cycler need to convert temporarily to CAPD or to lengthen the dwell time on the cycler is at present unclear. It is not always practical to switch patients from APD to CAPD, especially if the patient is treated as an outpatient, since the patient may not have supplies for CAPD and may not be familiar with the technique. Resetting the cycler in such cases to per-

TABLE 6
Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients. Dosing of Drugs with Renal Clearance in Patients with Residual Renal Function (defined as >100 mL/day urine output): Dose Should Be Empirically Increased by 25%

	Intermittent (per exchange, once daily)	Continuous (mg/L, all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin	0.6 mg/kg	LD 8, MD 4
Netilmicin	0.6 mg/kg	LD 8, MD 4
Tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin	15 mg/kg	LD 500, MD 125
Cefepime	1 g	LD 500, MD 125
Cephalothin	15 mg/kg	LD 500, MD 125
Cephradine	15 mg/kg	LD 500, MD 125
Ceftazidime	1000–1500 mg	LD 500, MD 125
Ceftizoxime	1000 mg	LD 250, MD 125
Penicillins		
Azlocillin	ND	LD 500, MD 250
Ampicillin	ND	MD 125
Oxacillin	ND	MD 125
Nafcillin	ND	MD 125
Amoxicillin	ND	LD 250–500, MD 50
Penicillin G	ND	LD 50000 units, MD 25000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Vancomycin	15–30 mg/kg every 5–7 days	LD 1000, MD 25
Aztreonam	ND	LD 1000, MD 250
Antifungals		
Amphotericin	NA	1.5
Combinations		
Ampicillin/sulbactam	2 g every 12 hours	LD 1000, MD 100
Imipenem/cilistatin	1 g b.i.d.	LD 500, MD 200
Quinupristin/dalfopristin	25 mg/L in alternate bags[a]	

ND = no data; b.i.d. = two times per day; NA = not applicable; LD = loading dose, in mg; MD = maintenance dose, in mg.
[a] Given in conjunction with 500 mg intravenous twice daily.

TABLE 7
Intermittent Dosing of Antibiotics in Automated Peritoneal Dialysis

Drug	IP dose
Vancomycin	Loading dose 30 mg/kg IP in long dwell, repeat dosing 15 mg/kg IP in long dwell every 3–5 days, following levels (*Opinion*)
Cefazolin	20 mg/kg IP every day, in long day dwell [Ref. (153)]
Tobramycin	Loading dose 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP each day in long day dwell [Ref. (153)]
Fluconazole	200 mg IP in one exchange per day every 24–48 hours
Cefepime	1 g IP in one exchange per day (*Evidence* from unpublished data)

IP = intraperitoneal.

mit a longer exchange time is an alternative approach, which, however, has not been well studied. Further research is needed in this area.

SUBSEQUENT MANAGEMENT OF PERITONITIS

- Once culture results and sensitivities are known, antibiotic therapy should be adjusted as appropriate. Antibiotic dosing for anuric CAPD patients — defined as daily urine output of less than 100 mL — is shown in Table 6. For patients with residual renal function, the dose should be increased by 25% for those antibiotics that have renal excretion (*Evidence and Opinion*). Patients who are high transporters and those with high dialysate clearances may have a more rapid removal of some antibiotics. Adjustments in dosing for such patients are not yet known, but the clinician should err on the side of higher dosing.

Few data exist that provide dosing recommendations for patients treated with APD. Extrapolation of data from CAPD to APD may result in significant underdosing of APD patients for two reasons. First, intermittent administration to any exchange other than a prolonged daytime exchange would prevent an adequate proportion of the dose from being absorbed into the systemic circulation, but this problem can be avoided by ensuring a minimum of 6-hours' dwell during the daytime. Second, data exist suggesting that APD may result in higher peritoneal clearances of antibiotics than is the case in CAPD. This would result in reduced dialysate concentrations, reduced serum concentrations, and the possibility of prolonged intervals during a 24-hour period when dialysate concentrations are less than the MIC for susceptible organisms. Table 7 lists the most commonly used antibiotics that have been studied in APD and provides dosing recommendations.

Within 48 hours of initiating therapy, most patients with PD-related peritonitis will show considerable clinical improvement. The effluent should be visually inspected daily to determine if clearing is occurring. If there is no improvement after 48 hours, cell counts and repeat cultures should be done. Antibiotic removal techniques may be used by the laboratory on the effluent in an attempt to maximize culture yield.

REFRACTORY PERITONITIS

- Refractory peritonitis, defined as failure to respond to appropriate antibiotics within 5 days, should be managed by removal of the catheter to protect the peritoneal membrane for future use (*Evidence*) (3,156,157).

Refractory peritonitis is the term used for peritonitis treated with appropriate antibiotics without resolution after 5 days (see Table 8 for terminology). Catheter removal is indicated to prevent morbidity and mortality due to refractory peritonitis and to preserve the peritoneum for future PD (Table 9). If the organism is the same as that of the preceding episode, strong consideration should be given to replacing the catheter. The primary goal in managing peritonitis should always be the optimal treatment of the patient and protection of the peritoneum, and not saving the catheter. Prolonged attempts to treat refractory peritonitis are associated with extended hospital stay, peritoneal membrane damage, and, in some cases, death. Death related to peritonitis, defined as death of a patient with active peritonitis, or admitted with peritonitis, or within 2 weeks of a peritonitis episode, should be a very infrequent event. The risk of death is highest with peritonitis due to gram-negative bacilli and fungus.

COAGULASE-NEGATIVE STAPHYLOCOCCUS

- Coagulase-negative staphylococcus peritonitis, including *S. epidermidis*, is due primarily to touch contamination, is generally a mild form of peritonitis, responds readily to antibiotic therapy, but can sometimes lead to relapsing peritonitis due to biofilm involvement. In such circumstances catheter replacement is advised (*Evidence*) (99,158–160).

Coagulase-negative staphylococcus, especially *S. epidermidis*, is still a very common organism in many programs, usually denotes touch contamination, generally responds well to antibiotic therapy, and is seldom related to a catheter infection. Most patients with *S. epidermidis* peritonitis have mild pain and can often be managed as an outpatient. In some programs, there is a very high rate of methicillin resistance (>50%), and, therefore, these programs may wish to use vancomycin as empiric therapy. The PD program should inquire of the laboratory the definition of "resistance" based on MIC levels. Methicillin resistance indicates that the organism is considered to be resistant to all beta-lactam-related antibiotics, including penicillins, cephalosporins, and carbapenems. Every effort should be made to avoid inadequate levels that may lead to relapsing peritonitis. The Committee feels the existing data is inadequate to recommend intermittent dosing of first-generation cephalosporins and, until more data are available, continuous dosing may be preferable. Ideally, repeated cell counts and cultures of the effluent should guide the therapy, but 2 weeks of therapy is gen-

TABLE 8
Terminology for Peritonitis

Recurrent	An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
Relapsing	An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode
Repeat	An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
Refractory	Failure of the effluent to clear after 5 days of appropriate antibiotics
Catheter-related peritonitis	Peritonitis in conjunction with an exit-site or tunnel infection with the same organism or one site sterile

TABLE 9
Indications for Catheter Removal for Peritoneal Dialysis-Related Infections

Refractory peritonitis
Relapsing peritonitis
Refractory exit-site and tunnel infection
Fungal peritonitis

Consider catheter removal if not responding to therapy
- Mycobacterial peritonitis
- Multiple enteric organisms

erally sufficient. The patient's technique should be reviewed to prevent recurrence.

Relapsing *S. epidermidis* peritonitis suggests colonization of the intra-abdominal portion of the catheter with biofilm and is best treated with replacement of the catheter. This can be done under antibiotic coverage as a single procedure, once the effluent clears with antibiotic therapy. Often, hemodialysis can be avoided by using either supine PD or low volumes for a short period of time.

STREPTOCOCCUS AND ENTEROCOCCUS

- Streptococcal and enterococcal peritonitis tend to be severe and are best treated with IP ampicillin (*Opinion*) (161).
- Vancomycin-resistant *Enterococcus faecium* (VREF) has been reported but remains uncommon in PD patients; limited data are available on proper management (162–165).

Streptococcal and enterococcal peritonitis generally cause severe pain. Ampicillin 125 mg/L in each exchange is the preferred antibiotic (*Evidence*). An aminoglycoside (given once daily IP as 20 mg/L) may be added for synergy for enterococcal peritonitis. Addition of gentamicin is potentially useful only if there is no laboratory evidence of high-level resistance to the antibiotic. Since enterococci are frequently derived from the gastrointestinal tract, intra-abdominal pathology must be considered, but touch contamination as a source is also possible. Therefore, the patient's technique should be reviewed. Peritonitis with enterococci or streptococci may also derive from infection of the exit site and tunnel, which should be carefully inspected.

Vancomycin-resistant enterococcus (VRE) has been reported and is seen most often in conjunction with recent hospitalization and prior antibiotic therapy. If VRE are ampicillin susceptible, ampicillin remains the drug of choice for enterococcal peritonitis. Linezolid or quinupristin/dalfopristin should be used to treat VRE peritonitis (*Opinion*). Quinupristin/dalfopristin is not active against *E. faecalis* isolates. Bone marrow suppression usually occurs after 10 – 14 days of linezolid therapy, and more prolonged therapy can also result in neurotoxicity. It is unclear if the catheter must be removed for VREF peritonitis, but certainly if the peritonitis does not resolve readily, this should be done.

STAPHYLOCOCCUS AUREUS

- *Staphylococcus aureus* causes severe peritonitis; although it may be due to touch contamination, it is often due to catheter infection. Catheter-related peritonitis is unlikely to respond to antibiotic therapy without catheter removal (*Evidence*) (5,45,89).

If the organism is *S. aureus*, very careful attention must be paid to the exit site and tunnel of the catheter, as the mode of entrance of this organism is often via the catheter, although touch contamination is another source. If the episode occurs in conjunction with an exit-site infection with the same organism, then often the infection will prove to be refractory and the catheter must be removed. After a rest period off PD (generally a minimum of 2 weeks; *Opinion*), PD can be tried again.

If the strain of *S. aureus* cultured is methicillin resistant, then the patient must be treated with vancomycin. Such infections are more difficult to resolve. Rifampin 600 mg/day orally (in single or split dose) can be added to the IP antibiotics, but therapy with this adjunctive antibiotic should be limited to 1 week, as resistance often develops with longer courses. In areas where tuberculosis is endemic, use of rifampin to treat *S. aureus* probably should be avoided to preserve this drug for treatment of tuberculosis.

Vancomycin may be administered as 15 – 30 mg/kg body weight IP, with a maximum dose of 2 – 3 g. A typical protocol for a patient 50 – 60 kg is vancomycin IP 1 g every 5 days (*Opinion*). Ideally, the timing of repetitive dosing should be based on trough levels and is likely to be every 3 – 5 days (*Evidence and Opinion*). Dosing interval is dependent on residual renal function and patients should receive another dose once trough serum levels reach 15 µg/mL. Teicoplanin, where available, can be used in a dose of 15 mg/kg body weight every 5 –7 days (*Opinion*). Data from children suggest that this approach is successful for both CAPD and APD. Treatment should be for 3 weeks.

Unfortunately, the first infection with vancomycin-resistant *S. aureus* has been reported in a dialysis patient. Prolonged therapy with vancomycin is thought to predispose to such infections and should be avoided whenever possible. If vancomycin-resistant *S. aureus* peritonitis develops, linezolid, daptomycin, or quinupristin/dalfopristin must be used.

CULTURE-NEGATIVE PERITONITIS

- If a program has a rate of culture-negative peritonitis greater than 20%, then the culture methods should be reviewed and improved (*Opinion*) (166).

Cultures may be negative for a variety of technical or clinical reasons. The patient should always be queried on presentation about use of antibiotics for any reason, as this is a known cause of culture-negative peritonitis. If there is no growth by 3 days, repeat cell count with differential should be obtained. If the repeat cell count indicates that the infection has not resolved, special culture techniques should be used for the isolation of potential unusual causes of peritonitis, including lipid-dependent yeast, mycobacteria, Legionella, slow growing bacteria, Campylobacter, fungi, Ureaplasma, Mycoplasma, and enteroviruses. This will require coordination with the microbiology laboratory.

If the patient is improving clinically, the initial therapy can be continued, although the Committee would advise against continuing aminoglycoside therapy for culture-negative peritonitis, as this is generally not necessary. Duration of therapy should be 2 weeks if the effluent clears rapidly. If, on the other hand, improvement is inadequate by 5 days, catheter removal should be strongly considered.

PSEUDOMONAS AERUGINOSA PERITONITIS

- *Pseudomonas aeruginosa* peritonitis, similar to *S. aureus* peritonitis, is often related to a catheter infection and in such cases catheter removal will be required. Two antibiotics should always be used to treat *P. aeruginosa* peritonitis (*Evidence*) (91,167).

Pseudomonas aeruginosa peritonitis is generally severe and often associated with infection of the catheter. If catheter infection is present or has preceded peritonitis, catheter removal is necessary. Antibiotics must be continued while the patient is on hemodialysis for 2 weeks.

Occasionally, *P. aeruginosa* peritonitis occurs in the absence of a catheter infection. In this case, two antibiotics with differing mechanisms of activity against pseudomonades may be necessary for cure. An oral quinolone can be given as one of the antibiotics for *P. aeruginosa* peritonitis. Alternative drugs include ceftazidime, cefepime, tobramycin, or piperacillin. Should piperacillin be preferred, its dose is 4 g every 12 hours IV in adults. Piperacillin cannot be added to the dialysis solution in conjunction with aminoglycosides.

Every effort to avoid *P. aeruginosa* peritonitis should be made by replacing the catheter for recurrent, relapsing, or refractory exit-site infections with *P. aeruginosa*, prior to the development of peritonitis. In such cases, the catheter can be replaced as a single procedure; whereas, if peritonitis develops, the catheter must be removed and the patient taken off PD for a period of time. In many such cases, permanent peritoneal membrane damage may have occurred.

OTHER SINGLE GRAM-NEGATIVE MICRO-ORGANISMS CULTURED

- Single-organism gram-negative peritonitis may be due to touch contamination, exit-site infection, or transmural migration from constipation or colitis (*Evidence*) (6,168–172).

If a single gram-negative organism, such as *E. coli*, Klebsiella, or Proteus, is isolated, the antibiotic to be used can be chosen based on sensitivities, safety, and

convenience. A cephalosporin, ceftazidime, or cefepime may be indicated based on *in vitro* sensitivity testing. Unfortunately, organisms in the biofilm state may be considerably less sensitive than the laboratory indicates (170), which may account for the high proportion of treatment failures, even when the organism appears to be sensitive to the antibiotic used (171). Outcomes of these infections are worse than gram-positive outcomes and are more often associated with catheter loss and death. Single-organism gram-negative peritonitis may be due to touch contamination, exit-site infection, or possibly a bowel source, such as constipation, colitis, or transmural migration. Often the etiology is unclear.

The isolation of a Stenotrophomonas organism, while infrequent, requires special attention since it displays sensitivity only to a few antimicrobial agents (168,173). Infection with this organism is generally not as severe as with Pseudomonas and is usually not associated with an exit-site infection. Therapy for Stenotrophomonas peritonitis is recommended for 3 – 4 weeks if the patient is clinically improving. Treatment with two drugs (chosen based on the sensitivities) is recommended.

POLYMICROBIAL PERITONITIS

- If multiple enteric organisms are grown, particularly in association with anaerobic bacteria, the risk of death is increased and a surgical evaluation should be obtained (*Evidence*) (174–177).
- Peritonitis due to multiple gram-positive organisms will generally respond to antibiotic therapy (*Evidence*) (4,66,178–180).

In cases of multiple enteric organisms, there is a possibility of intra-abdominal pathology such as gangrenous cholecystitis, ischemic bowel, appendicitis, or diverticular disease. In this setting where the intestines are felt to be the source, the therapy of choice is metronidazole in combination with ampicillin and ceftazidime or an aminoglycoside in the recommended doses. The catheter may need to be removed, particularly if laparotomy indicates intra-abdominal pathology, and, in that case, antibiotics should be continued via the IV route. Antibiotics can be tried, however, and in some cases the catheter may not need to be removed. Computed tomographic (CT) scan may help identify intra-abdominal pathology, but a normal CT scan does not eliminate the possibility of intra-abdominal pathology as a source.

Polymicrobial peritonitis due to multiple gram-positive organisms, more common than that due to enteric organisms, has a much better prognosis. The source is most likely contamination or catheter infection; the patient's technique should be reviewed and the exit site carefully examined. Polymicrobial peritonitis due to contamination generally resolves with antibiotics without catheter removal, unless the catheter is the source of the infection.

FUNGAL PERITONITIS

- Catheter removal is indicated immediately after fungi are identified by microscopy or culture (*Evidence*) (75–77).

Prolonged treatment with antifungal agents to determine response and to attempt clearance is not encouraged. Fungal peritonitis is serious, leading to death of the patient in approximately 25% or more of episodes. Some evidence suggests that prompt catheter removal poses a lesser risk of death. Initial therapy may be a combination of amphotericin B and flucytosine until the culture results are available with susceptibilities. Caspofungin, fluconazole, or voriconazole may replace amphotericin B, based on species identification and MIC values. Intraperitoneal use of amphotericin causes chemical peritonitis and pain; IV use leads to poor peritoneal administration. Voriconazole is an alternative for amphotericin B when filamentous fungi have been cultured and can be used alone for Candida peritonitis (with catheter removal) (*Evidence*). If flucytosine is used, regular monitoring of serum concentrations is necessary to avoid bone marrow toxicity. Emergence of resistance to the imidazoles has occurred, thus indicating the importance of sensitivities, where available. Therapy with these agents should be continued after catheter removal, orally with flucytosine 1000 mg and fluconazole 100 – 200 mg daily for an additional 10 days. The withdrawal of oral flucytosine from some markets (*e.g.*, in Canada) will influence local protocols.

PERITONITIS DUE TO MYCOBACTERIA

- Mycobacteria are an infrequent cause of peritonitis but can be difficult to diagnose. When under consideration, special attention must be paid to culture techniques. Treatment requires multiple drugs (*Evidence*) (62,89,181–188).

Mycobacterial peritonitis can be caused by *Mycobacterium tuberculosis* or non-tuberculosis mycobacteria. The incidence of mycobacterial peritonitis is higher in Asia than elsewhere. While the classic symptoms of fever, abdominal pain, and cloudy effluent may occur with mycobacterial peritonitis, the diagnosis should be considered

in any patient with prolonged failure to thrive, prolonged symptoms despite antibiotic therapy, and relapsing peritonitis with negative bacterial cultures.

The cell count cannot be used to differentiate mycobacterial peritonitis from other forms. Most cases of mycobacterial peritonitis have a predominance of polymorphonuclear WBC, similar to bacterial peritonitis. Smears of the peritoneal effluent should be examined with the Ziehl–Neelsen stain, but "smear negative" disease is common. The sensitivity of the smear examination by the Ziehl–Neelsen technique can be enhanced by centrifuging 100 – 150 mL of the dialysate sample and the smear prepared from the pellet. A specific diagnosis can be made by culturing the sediment, after centrifugation of a large volume of effluent (50 – 100 mL), using a solid medium (such as Löwenstein–Jensen agar) and a fluid medium [Septi-Chek, BACTEC; Becton Dickinson; *etc.*). The time of detection for growth of mycobacteria is decreased considerably in fluid medium. Repeat microscopic smear examination and culture of dialysis effluent is mandatory for better yield in suspected cases of mycobacterial peritonitis. Exploratory laparotomy or laparoscopy with biopsy of the peritoneum or omentum should be considered in patients in whom the diagnosis is being considered.

The treatment protocol for *M. tuberculosis* peritonitis is based on the experience of treatment of extrapulmonary tuberculosis in end-stage renal disease. Since streptomycin, even in reduced doses, may cause ototoxicity after prolonged use, it should generally be avoided. Similarly, ethambutol is not recommended because of the high risk of optic neuritis in end-stage renal disease. Treatment is started with four drugs: rifampin, isoniazid, pyrazinamide, and ofloxacin. However, a recent study showed that rifampin dialysis fluid levels are quite low due to its high molecular weight, high protein-binding capacity, and lipid solubility. Therefore, for treatment of tuberculous peritonitis, rifampin may need to be given via the IP route. Treatment with pyrazinamide and ofloxacin is stopped after 3 months; rifampicin and isoniazid are continued for a total of 12 months. Pyridoxine (50 – 100 mg/day) should be given to avoid isoniazid-induced neurotoxicity. The treatment protocol for non-tuberculous mycobacterial peritonitis is not well established and requires individualized protocols based on susceptibility testing.

Removal of the catheter is still a contentious issue. While many people would remove the PD catheter in a patient with tuberculous peritonitis and consider reinsertion after 6 weeks of antitubercular treatment, there are some case series of successful treatment without catheter removal. Long-term continuation of CAPD is possible, especially if the diagnosis is made early and appropriate therapy initiated promptly.

LENGTH OF THERAPY FOR PERITONITIS

- The Committee feels that the minimum therapy for peritonitis is 2 weeks, although for more severe infections, 3 weeks is recommended (*Opinion*).

In clinical practice, the length of treatment is determined mainly by the clinical response. After initiation of antibiotic treatment, clinical improvement should be present in the first 72 hours. Patients having cloudy effluent on appropriate antibiotics after 4 – 5 days have refractory peritonitis and should have their catheter removed.

In patients with CoNS peritonitis and in patients with culture-negative peritonitis, antibiotic treatment should be continued for at least 1 week after the effluent clears, and for no less than 14 days total. This means that 14 days is usually adequate for treatment of peritonitis in uncomplicated episodes due to CoNS. In patients with *S. aureus*, gram-negative, or enterococcal peritonitis, the infection is usually more severe than in other gram-positive episodes. Therefore, a 3-week treatment is recommended for these episodes (whether the catheter is removed or not).

CATHETER REMOVAL AND REINSERTION FOR PERITONEAL INFECTION

- The Committee recommends removing the catheter for relapsing peritonitis, refractory peritonitis, fungal peritonitis, and refractory catheter infections. The focus should always be on preservation of the peritoneum rather than saving the peritoneal catheter (*Opinion*) (3,96–99,158,189,190).

It is the impression of the Committee that catheter removal is not done often enough in managing peritoneal infections. Indications for catheter removal for infections are shown in Table 9. Timely replacement of the catheter for refractory exit-site infections can prevent peritonitis, a far better approach than waiting until the patient has the more serious infection. This approach has the added advantage of permitting simultaneous replacement, thus avoiding prolonged periods on hemodialysis. Some patients, especially those using a cycler, can avoid hemodialysis altogether by dialyzing only in the supine position for several days to avoid leaks and hernias, with subsequent addition of the daytime exchange. Catheter replacement as a single procedure can

also be done for relapsing peritonitis, if the effluent can first be cleared. This procedure should be done under antibiotic coverage.

For refractory peritonitis and fungal peritonitis, simultaneous catheter replacement is not possible. The optimal time period between catheter removal for infection and reinsertion of a new catheter is not known. Empirically, a minimum period of 2 – 3 weeks between catheter removal and reinsertion of a new catheter is recommended (*Opinion*). After severe episodes of peritonitis, some patients are able to return to PD. In other patients, adhesions may prevent reinsertion of the catheter, or continuation on PD is not possible due to permanent membrane failure. Unfortunately, it is difficult to predict who will have many adhesions and who will not.

FUTURE RESEARCH

Further clinical trials in PD patients are required, particularly, double-blinded randomized trials assessing different treatment strategies, powered to detect meaningful differences using appropriate numbers of patients, and with sufficient follow-up. Although some pharmacokinetic data are available, randomized clinical trials comparing the efficacy of intermittent cephalosporin dosing versus continuous dosing in both CAPD and APD are needed, with long-term follow-up. Further studies on the pharmacokinetics of intermittent dosing, particularly with APD, during peritonitis episodes are also needed. Such studies require large enough patient numbers to evaluate significant differences in outcomes, and such studies may need to be multicenter in design. Outcomes to be examined should include not only resolution without catheter removal, but also days of inflammation and relapse of peritonitis. Follow-up should be sufficient to evaluate repeat episodes of peritonitis, that is, further episodes of peritonitis due to the same organism as the original organism, but more than 4 weeks from the completion of therapy. Investigations into the role of biofilm in repeat episodes are needed.

Many of the antibiotic stability data are old and need to be repeated with extended study durations in an effort to determine if pre-administration of antibiotics for patients is a reasonable approach. Over the past decade, pharmacodynamic research has advanced the management of infectious disease by characterizing complex antibiotic–pathogen–host interactions. Such investigations specific to dialysis-related peritonitis are scarce. Therapeutic decisions in the management of peritonitis are guided largely by the standard MIC, even though it does not account for unique factors such as high IP antibiotic concentration, commonly used antibiotic combinations, and altered antibiotic activity in the peritoneal environment.

Further outcome data on rapid catheter removal versus delayed catheter removal as a randomized trial would also be helpful, as well as the safe interval for catheter replacement. The impact of peritonitis and treatment approaches on both residual renal function and long-term outcomes are other important areas in which more data are needed.

More information is needed on modifiable risk factors for peritonitis. Preliminary data indicate that both a low serum albumin and depressive symptoms are risk factors for subsequent peritonitis, but it is not known if intervening for either of these problems modifies that risk (191,192). More epidemiological studies comparing peritonitis risk between APD, with and without dry day, and CAPD are needed. Conventional dialysis solutions inhibit peritoneal immune function, decreasing the ability of the patient to fight infection. More studies are needed on the newer dialysis solutions, which are more biocompatible and may possibly impact on peritonitis risk.

Additional insights into catheter management should be developed, particularly as they pertain to preventing and managing exit and tunnel infections. In this respect, further randomized trials regarding the safest and most effective antibiotic for prophylaxis at time of catheter replacement would be useful. A randomized double-blinded multicenter trial comparing exit-site antibiotic cream to exit-site care with an antiseptic solution should be performed to more definitively answer this question. Confirmatory studies of the effectiveness of prophylactic use of gentamicin cream at the exit site are needed, particularly with respect to possible effects on gram-negative peritonitis. Further research on exit-site appearance scoring systems is needed to validate the usefulness of such approaches for both clinical care and research purposes.

The development of antibiotic resistance in PD patients requires further study (193). Early data suggested a clandestine use of antibiotics by patients that had access to them at home. It is unclear how this might relate to the development of resistance and outcomes of therapy. Further research is needed to clarify the extent of this problem. The impact of the use of vancomycin as opposed to cephalosporins to treat PD-related infections on the development of vancomycin-resistant organisms should be examined in a large multicenter trial.

All manuscripts relating to PD infections should be standardized to include sufficient data for interpretation and reproducibility. Information that reviewers and editors should look for is included in Table 10. Methods must include data on training methods and connection

TABLE 10
Guidelines for Research in Peritoneal Dialysis-Related Infections

Manuscripts should include the following information
Description of population
Connection methodology (spike, Luer lock, *etc.*)
Type of peritoneal dialysis (CAPD with number of exchanges, CCPD, APD with dry day)
Exit-site infection definition
Exit-site care protocol
Staphylococcus aureus prevention protocol if there is one
Training protocol
Proportion of patients requiring a helper
Proportion of patients who are carriers, for all studies of *S. aureus*
Outcome of peritonitis
Power calculations for determining the number of patients required to evaluate an outcome
Detailed antimicrobial regimen description to include agents, doses, frequency of administration, duration, route, concomitant serum and dialysate levels (specify peak, trough, mean, other)

CAPD = continuous ambulatory peritoneal dialysis; CCPD = continuous cycling PD; APD = automated PD.

used to perform PD. Results should be presented as not only an over all rate, but also as individual rates rather than percentages of infections due to specific organisms. Terminology for relapsing and refractory peritonitis as well as "primary cure" should be kept constant. Multicenter studies will probably be needed to enable recruitment of the number of patients required to answer most of these questions.

ACKNOWLEDGMENTS

The ISPD has formally reviewed and endorsed these guidelines. The reviewers were carefully chosen to complement the expertise of the Committee members.

The Committee thanks the reviewers for providing thoughtful and careful commentary and suggestions that allowed the manuscript to be improved. The reviewers were J. Bargman, E. Brown, S. Davies, F. Finkelstein, T. Golper, D.S. Han, Y. Kawaguchi, H. Manley, G. Matzke, C. Pollock, B. Prowant, M. Riella, R. Selgas, S. Vas, T. Wang, and S. Zelenitsky.

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Peritoneal Dialysis International, Vol. 15, pp. 328-335
Printed in Canada

0896-8608/95 $300 + 00

STABILITY OF DRUG ADDITIVES TO PERITONEAL DIAL YSA TE

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.*Objective:* The primary literature was reviewed to determine the stability of drug additives in peritoneal dialysis solutions.
.*Data Sources:* A MEDLINE search and retrieval, covering the period 1981 to 1994, was undertaken to identify relevant original literature. Additional references were identified from citations within the original literature. Non-English literature was excluded unless an English abstract was provided.
.*Study Selection:* Forty-nine studies were identified. Of these, 24 were directly related to drug stability, 13 were related to the clinical use of the drug additives but included no stability data, and 12 examined other, nonstability aspects *ofin* vitroactivity of antibiotics, additives, or drug adsorption in peritoneal dialysis bags and tubing. .*Data Extraction:* Data included concentrations of drug additives and dialysate solutions, duration and temperatures of storage conditions, types of assay, and whether they were stability-indicating.
.*Results:* Stability was defined as the duration of time that the drug concentration remained at 90% or more of the original concentration. Stability was examined under a large variety of conditions. Thirty-one drugs were identified from 20 manuscripts as single-drug additives. Most beta-Iactams were stable for 1 -2 weeks in a refrigerator and for several days at room temperature. Aminoglycosides were stable for 1 -2 days at room temperature. Glycopeptides were stable for several weeks refrigerated or at room temperature. Prolonged storage at room temperature resulted in instability of cefotaxime, ceftazidime, ceftriaxone, and miconazole. Eleven drugs were identified from seven manuscripts as drug combination studies and showed similar stability as single agents. Dialysate concentration appeared to have minimal effect on stability.
.*Conclusions:* Drug additives in peritoneal dialysate, singly or combined, should be avoided unless data are available to support their stability. Additives should be made as close as possible to the time of the exchange. Alternatively, additives should be stored refrigerated, then warmed prior to use. The practice of preparing numerous bags at one time should be avoided. Finally, stability data do not indicate sterile integrity of the dialysate.

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Received 30 September 1994; accepted 4 January 1995.

KEY WORDS: Dialysis solutions; drug stability; drug administration, intraperitoneal; chemical degradation.

Peritoneal dialysis (PD) as a treatment modality for end-stage renal disease is growing rapidly worldwide. It is estimated that the global growth of PD is about 12% per year, compared to about 8% for hemodialysis, and that there were some 86300 PD patients at the end of 1993 (1). Peritonitis remains the most common source of morbidity for these patients (2) and is a leading cause of transfer from PD to hemodialysis.

The intraperitoneal (IP) route has now become the route of choice for the administration of antibiotics for the treatment of peritonitis; this demonstrates a move away from historical use of the intravenous route (3). Most antibiotics, which are commercially available in a parenteral formulation, have been administered IP. Because of the mechanics of PD exchanges, many IP additives may be stored for significant periods of time prior to instillation into the peritoneal cavity. Such procedures demand a knowledge of drug stability in the PD fluid. In addition, other nonantibiotic drugs have been administered IP for the treatment of a variety of conditions, but relatively few stability studies have been conducted to verify this as an acceptable practice.

Stability issues for drugs in PD fluid cannot be extrapolated from the extensive literature available for the same drugs as intravenous additives. PD fluid has a different constitution, contains a relatively large number of different cations and anions, has a high dextrose content, and has a low pH of about4 -6.

This paper will review the results of studies that have examined the stability of drugs in PD. In addition, reference will be made to papers where the IP administration of drugs has resulted in clinical efficacy of the drugs, but where no stability studies have been undertaken.

METHODS

A MEDLINE search and retrieval, covering the period 1981-1994, was used to identify relevant literature. Search terms included these MESH headings: peritoneal dialysis; dialysis solutions; drug stability; drug administration - intraperitoneal; chemical degradation. Non-English language literature was excluded unless an English abstract was provided. Additional manuscripts were obtained from citations within the original literature.

In each case, the information was extracted and tabulated according to the type of dialysate used, storage conditions, concentration of drug studied, and duration of study. The type of assay used to determine the drug concentration was noted, including the use of a bioassay or some other *in vitra* assay. Few studies reported whether the assays were specific for the parent drug compound and if they were able to distinguish the parent from a degradation product, that is, whether the assay was stability indicating. This issue may or may not be an important factor, depending on the drug and its indication, and the reader should consider this in the interpretation of the presented data. In addition, the reader should realize that although many of these studies evaluated the duration of drug stability for periods of days or weeks, sterility of the solutions was not evaluated.

In each case, we defined stability as the duration of time that the drug concentration remained 90% or more of the original concentration (4).

RESULTS

Table 1 lists those studies for which drug stability has been studied as single-drug additives (5-24). In each entry, the dialysate solution is referred to as its dextrose content. Some studies were reported in terms of glucose, and these have been converted in the following results. In general, most beta-Iactam antibiotics are stable for 1 -2 weeks when stored in a refrigerator and for several days at room temperature. The aminoglycosides are generally stable for 1 -2 days at room temperature. Vancomycin and teicoplanin are stable for several weeks at refrigerated and room temperatures. Higher temperatures for storage are generally associated with decreased drug stability.

Table 2 lists those drugs that have been studied as combinations (6,11,20,25-28). Drug combinations have been studied for shorter periods than individual drugs. The addition of heparin to the combination of drugs had minimal effect on stability.

Most of the data regarding drug stability in PD involve antimicrobial agents, which is not unexpected since peritonitis is the major cause of IP drug administration. However, other drugs have been administered by the IP route to produce extraperitoneal effects despite limited stability data. Table 3 lists drugs for which no stability data were reported, but for which information was presented concerning the IP use of the drug for a specific therapeutic effect (29-41).

For the sake of completeness, reference is made to drug stability in concentrated (e.g., 30%, 50% dextrose) PD solutions (42,43), to studies examining other aspects of the *in vitra* activity of antibiotics in PD fluid, PD effluent, buffered PD fluid, the influence of pH, altered media and osmolality of PD fluid (27,44-50), and to studies evaluating drug loss from PD as a result of drug adsorption to the PD bag and administration tubing, rather than as a result of drug instability (51-53). The results of these will not be discussed further because concentrated solutions are rarely used, or the studies are not true stability studies.

DISCUSSION

The entire issue of drug stability has important practical considerations. Many centers use the latest treatment recommendations of the Ad Hoc Advisory Committee on Peritonitis Management (3) and others (54,55), which suggest the administration of IP antibiotics and the coadministration of combination antibiotics for empiric treatment or for the treatment of complicated peritonitis. The exact practices of each center remain undocumented and they are probably varied. Thus it is possible that patients are taught to perform the additions and to store the antibiotic-containing dialysates under a variety of conditions. Clearly, the practice of prolonged storage, particularly at room temperature or warmer, is inappropriate for certain drugs such as cefotaxime, ceftazidime, ceftriaxone, and miconazole as single additives. Many other single-agent additives were only stored and studied at these temperatures for short periods of time; thus their intermediate-term stability (i.e., longer than one day) remains unclear , for example, most cephalosporins, penicillins, aminoglycosides, dobutamine, and fosfomycin. In addition, the combination of two or more agents has been studied for only a few cephalosporins and aminoglycosides, usually over period of 2 days or less.

In the absence of definitive data, what conclusions and recommendations can be made? First, combinations of drugs should be avoided unless there are adequate data to support their stability. Second,
stability data do not indicate the sterile integrity of the admixture. Third, since most instabilities are time-dependent, the admixture should be carried out

TABLE 1
Stability Studies of Single Drugs in CAPD

Drug	Dialysate Dextrose Conc.	Drug Conc. (mg/L)	Storage Temp (°C)	Duration of Evaluation hours (h) or days (d)	Duration of Stability hours (h) or days (d)	Assay	Reference No.
Amphotericin B	1.5%	1,2	37	2 d	6 h	H	5
		5	37	2 d	1 d		
Ampicillin[a]	4.25%	50	25	2 d	2 d	M	6
Azlocillin[a]	4.25%	200	25	2 d	2 d	M	6
Cefamandole	1.5%	8	RT[b]	1 d	1 d	M	7
Cefazolin	1.5%,4.25%	500	4	14 d	14 d	H[c]	8
	1.5%,4.25%	500	25	11 d	8 d		
	1.5%, 4.25%	500	37	1 d	1 d		
Cefmenoxime	1.5%	4	RT[b]	1 d	1 d	M	7
Cefoperazone	1.5%	4	RT[b]	1 d	1 d	M	7
Cefotaxime	1.5%	4	RT[b]	1 d	1 d	M	7
Cefotaxime	1.5%,4.25%[e]	1000	25	3 d	1 d	H[c]	9
	1.5%,4.25%	1000	37	1 d	6 h		
Cefotaxime[a]	4.25%	125	25	2 d	1 d	M	6
Cefoxitin	1.5%	8	RT[b]	1 d	1 d	M	7
Ceftazidime	1.5%	8	RT[b]	1 d	1 d	M	7
Ceftazidime	1.5%	2000	5	NR[d]	10 d	NR[d]	10
		2000	RTb	NR[d]	1 d		
		2000	37	NR[d]	4 h		
Ceftazidime	1.5%	100	4	6 d	6 d	H[c]	11
		100	25	6 d	4 d		
		100	37	6 d	<12 h		
Ceftriaxone	1.5%	4	RT[b]	1 d	1 d	M	7
Ceftriaxone	1.5%,4.25%	1000	4	14 d	14 d	H[c]	12
	1.5%,4.25%	1000	23	5 d	1 d		
	1.5%,4.25%	1000	37	1 d	6 h		
Cephapirin	1.5%/4.25%[e]	125	25	1 d	1 d	M	13
Cephapirin[a]	4.25%	125	25	2 d	2 d	M	6
		500	35	1 d	<1 d		
Ciprofloxacin	1.5%	25	4,20,37	42 d	42 d	H	14
	1.5%	100	23	1 d	1 d	M	15
	1.5%,4.25%	25	4	14 d	<12 h	H[c]	16
	1.5%,4.25%	25	25	7 d	7 d		
	1.5%,4.25%	25	37	2 d	2 d		
Clindamycin[a]	4.25%	10	25	2 d	2 d	M	6
Deferoxamine	1.5%,4.25%	350	4	15 d	15 d	H[c]	17
		350	25	7 d	7 d		
		350	37	2 d	2 d		
Dobutamine	1.5%	2.5	4,37	1 d	1 d	H[c]	18
		2.5	26	1 d	1 d[g]		
		5.0,7.5	4,26,37	1 d	1 d		
	4.25%	2.5,5.0,7.5	4,26,37	1 d	1 d		
Erythromycin	1.5%	150	4	14 d	2 d	H	19
		150	25	7 d	3 d		
		150	37	2 d	8 h		
	4.25%	150	4	14 d	14 d		
		150	25	7 d	3 d		
		150	37	2 d	2 d		

continued on next page

TABLE 1 continued

Drug	Dialysate Dextrose Conc.	Drug Conc. (mg/L)	Storage Temp (°C)	Duration of Evaluation hours (h) or days (d)	Duration of Stability hours (h) or days (d)	Assay	Reference No.
Fosfomycin	1.5%	3200	23	1 d	1 d	M	15
Gentamicin	1.5%,4.25%[e]	10	25	1 d	1 d	M	13
Gentamicin	1.5%	8	4,25	2 d	2 d	M	20
		120	37	8 h	8 h		
Mezlocillin[a]	4.25%	200	25	2 d	2 d	M	6
Miconazole	4.25%	20	20	9 d	2 h[f]	H[c]	21
Moxalactam	1.5%	8	RT[b]	1 d	1 d	M	7
Nafcillin	1.5%,4.25%[e]	100	25	1 d	1 d	M	13
Nafcillin[a]	4.25%	100	25	2 d	1 d	M	6
Ofloxacin	1.5%	100	23	1 d	1 d	M	15
Ofloxacin	1.5%,4.25%	25	4	14 d	14 d	H	22
	1.5%,4.25%	25	25	7 d	7 d		
	1.5%,4.25%	25	37	2 d	2 d		
Pefloxacin	1.5%	100	23	1 d	1 d	M	15
Penicillin	1.5%,4.25%[e]	6	25	1 d	<1 d	M	13
Piperacillin[a]	4.25%	200	25	2 d	2 d	M	6
Teicoplanin	1.5%	25	4	42 d	42 d	M[c]	23
		25	20	42 d	25 d[h]		
		25	37	42 d	7 d		
Ticarcillin	1.5%,4.25%[e]	200	25	1 d	1 d	M	13
Tobramycin	1.5%	8	4,25	2 d	2 d	M	20
		120	37	8 h	8 h		
Tobramycin[a]	4.25%	10	25	2 d	2 d	M	6
		65	35	1 d	<1 d		
Vancomycin	1.5%,4.25%[e]	15	25	1 d	1 d	M	13
Vancomycin	1.5%	50	4,25	6 d	6 d	H[c]	11
			37	6 d	5 d		
Vancomycin	1.5%	30	4,25	2 d	2 d	M	20
		1000	37	8 h	8 h		
Vancomycin	1.5%	25	4	42 d	28 d[i]	H[c]	24
		25	20	42 d	28 d[i]	E	
		25	37	42 d	7 d		
	4.25%	25	4,20	42 d	28 d		
		25	37	42 d	5 d		
Vancomycin[a]	4.25%	20	25	2 d	1 d	M	6

H = high-performance liquid chromatography; M = microbiological assay; E = enzyme-multiplied immunoassay.

[a] Results combined from dialysates with or without heparin 500 U/L.

[b] Room temperature (undefined).

[c] Stability-indicating nature of assay noted by author.

[d] Not reported.

[e] Reported as combined results from dialysates containing 1.5% and 4.25% dextrose.

[f] Reported stability of drug stored in PVC bags (vs glass ampules).

[g] Stated as unstable by original authors because only 91.5±4% remaining, but included here as stable since over 90% remaining.

[h] Data extrapolated from 21 days by original authors.

[i] HPLC indicated stability for 42 days, while EMIT demonstrated stability for 28 days.

TABLE 2
Stability of Drug Combinations in CAPD

Drug	Dialysate Dextrose Conc.	Drug Conc. (mg/L)	Storage Temp (°C)	Duration of Evaluation hours (h) or days (d)	Duration of Stability[a] hours (h) or days (d)	Assay	Reference No.
Cefazolin	1.5%	75	4,26	2 d	2 d	H	25
(1000 U/L)		75	37	2 d	8 h		
		150	4,26	2 d	2 d		
		150	37	2 d	1 d		
Cefazolin	1.5%	75 & 8	4,26,37	2 d	2 d	H,F	25
& Gentamicin		150 & 8	4,26	2 d	2 d		
& Heparin[b]		150 & 8	37	2 d	1 d		
(1000 U/L)							
Ceftazidime	1.5%	100	4	6 d	6 d	H[c]	11
& Heparin[b]		100	25	6 d	4 d		
(1000 U/L)		100	37	6 d	<12 h		
Ceftazidime	2.5%	125 & 8	24	16 h	16 h	H[c]	26
& Tobramycin		125 & 8	37	8 h	8 h	F[c]	
Ceftazidime	1.5%	100 & 50	4	6 d	6 d	H[c]	11
& Vancomycin		100 & 50	25	6 d	2 d	H[c]	
		100 & 50	37	6 d	12 h		
Ceftazidime	1.5%	100 & 50	4	6 d	6 d	H[c]	11
& Vancomycin		100 & 50	25	6 d	3 d	H[c]	
& Heparin[b]		100 & 50	37	6 d	12 h		
(1000 U/L)							
Cephapirin	4.25%	500 & 65	25	1 d	1 d	M	6
& Tobramycin[d]		500 & 65	35	1 d	<1 d		
Gentamicin	1.5%	8	4,26,37	2 d	2 d	F	25
& Heparin[b]							
(1000 U/L)							
Gentamicin	1.5%	8	RT[e]	3 d	6 h	M	27
& Heparin[b]							
(500 U/L)							
& Albumin[b] (5%)							
Gentamicin	1.5%	4 & 125	RT[e]	3 d	3 d	M	27
& Cefazolin[b]	4.25%	4 & 125	RT[e]	3 d	3 d		
& Heparin[b]							
(500 U/L)							
& Albumin[b] (5%)							
Gentamicin	1.5%	8 & 30	4,25	2 d	<12 h	M	20
& Vancomycin		120 & 1000	37	8 h	8 h		
Trimethoprim	4.25%	20 & 100	20	9 d	12 h[f]	H[c]	28
& Sulfamethoxazole						H[c]	
Tobramycin	1.5%	8 & 30	4	2 d	1 d	M	20
& Vancomycin		8 & 30	25	2 d	2 d		
		120 & 1000	37	8 h	8 h		
Vancomycin	1.5%	50	4,25	6 d	6 d	H[c]	11
& Heparin[b]			37	6 d	5 d		
(1000 U/L)							

H = high-performance liquid chromatography; F = fluorescence immunoassay; M = microbiological assay.
[a] Represents duration of stability of the shorter of the two drugs.
[b] Drug stability not assessed.
[c] Stability-indicating nature of assay noted by author.
[d] Results combined from dialysates with or without heparin 500 U/L.
[e] Room temperature (undefined).
[f] Reported stability of drug stored in PVC bags (vs glass ampules).

TABLE 3
Reports of IP Drug Administration

Drug	Indication	Drug Concentration	Dextrose Concentration	Comment	Reference No.
Calcitriol	Secondary hyperparathyroidism in CRF	60 ng/kg in 1.5 L	1.5%	Pharmacokinetic study. 67% bioavailability. Side effect & efficacy data not reported.	29
	Secondary hyperparathyroidism in CRF	0.5–4 µg/d	1.5%/4.25%	Caused a marked suppression of PTH levels via increasing ionized calcium levels.	30
Cisapride	Diabetic gastroparesis	5 mg/L	NR	Condition improved. Serum & dialysate levels recorded.	31
Deferoxamine	Iron overload	250 mg/L	1.5%/4.25%	Effective in reducing serum iron, reported no adverse effects.	32
Deferoxamine	Aluminum intoxication	200 mg/L	1.5%	Reversed osteomalacia and microcytic anemia, and improved encephalopathy. Reported no adverse effects.	33
Erythromycin	Diabetic gastroparesis	50 mg/L	NR	Improved symptoms. Reported no adverse effects.	34,35
Erythropoietin	Anemia of CRF	400 U/kg	Diluted in 1.5% vs undiluted	Bioavailability study. Ninefold increase in serum EPO with undiluted. Efficacy not reported	36
Heparin	Intraperitoneal fibrin formation	1000 U/L 2000 U/L	1.5%	Can prevent fibrin 37 formation. Reported no adverse effects.	
Insulin	Diabetes mellitus	8–25 U/L	0.5%,1.5%, 2.5%,4.25%	Offers an alternative treatment for diabetic patients with ESRD.	38
Lithium chloride	Bipolar affective disorder	38 mg/L	2.5%	Target serum lithium level of 1 mEq/L. Manic symptoms improved.	39
Metoclopramide	Diabetic gastroparesis	7.5 mg/L	1.5%	Pharmacokinetic study. Bioavailability of 97%. Efficacy not reported. No side effects documented.	40
	Diabetic gastroparesis	5 mg/L	NR	Improved symptoms. No side effects documented.	41

CRF = chronic renal failure; NR = not reported; ESRD = end-stage renal disease.

as close to the time of the exchange as possible. Fourth, any admixtures should be stored refrigerated until ready for use, then warmed and instilled as soon as possible. Finally, the practice of injecting the additive to many bags or several days' supply of bags at one time should be avoided.

CONCLUSION

Relatively few stability studies have been undertaken for drugs added to PD fluids. In addition, it may not be possible to extrapolate published data to other storage conditions or concentrations of additives. Many studies do not cite assay precision and sensitivity and some give little detail pertaining to whether the assay is stability-indicating or otherwise. More studies are required to address these issues.

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