

Management of peritoneal dialysis-associated peritonitis in adults and children

Date written: November 2010

Final submission: January 2013

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GUIDELINE

- a. In peritoneal dialysis patients with a provisional diagnosis of peritonitis, treatment should commence with a combination of intraperitoneal antibiotics that will adequately cover Gram-positive and Gram-negative organisms. Once bacterial diagnosis is made then a change to appropriate antibiotic should be made. Treatment should be of adequate duration to reduce recurrence (Level II evidence).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Where local or international guidelines are available they should be used to guide therapy.
- Peritoneal dialysate effluent should be collected and processed in an appropriate manner to ensure culture-negative episodes account for < 20% of all PD-associated peritonitis.
- While there is no good evidence to support specific antibiotic choice, empiric intraperitoneal therapy should consider local microbiological resistance profiles and cover Gram-positive and Gram-negative bacteria. Gram-positive organisms may be covered by vancomycin or a cephalosporin and Gram-negative organisms by a third generation cephalosporin or aminoglycoside.
- When there is a suitable alternative, aminoglycoside use should be limited to avoid their adverse effects of nephrotoxicity and ototoxicity.
- Dual antibiotic therapy is indicated for *Pseudomonas* spp. peritonitis.

IMPLEMENTATION AND AUDIT

1. Continuation of ANZDATA peritonitis registry, with incorporation of data from New Zealand Peritoneal Dialysis Registry.
2. Commencement of new Renal Unit key performance indicators for peritonitis episodes from 1 Jan 2011 collected from all units with benchmarking across identified Australian units.
3. All units should review their treatment protocol to ensure that they adhere to published clinical guidelines.
4. Audit local treatment protocols to ensure they adhere to published clinical guidelines.

BACKGROUND

Peritonitis remains one of the most important complications of peritoneal dialysis (PD), resulting in significant morbidity and mortality as well as being a major contributor to technique failure and permanent haemodialysis transfer. A significant proportion of peritoneal dialysis units in Australia and New Zealand (ANZ) fail to meet the internationally accepted minimum standard for episodes of peritonitis in PD patients (1 episode per 18 patient-months) [1] and the median technique survival of PD is lower in ANZ than in other parts of the world. Even the success rate for treatment of

peritonitis in PD patients is poor in Australia, with an overall cure rate of only 68% as reported recently to the ANZDATA Peritonitis Registry.

Variations in practice with respect to peritonitis treatment in PD are known to be widespread in ANZ despite guidelines being available to clinicians. The ANZDATA Registry reveals that peritonitis rates vary across ANZ PD units from 1 in 2 patient-months to 1 in 48 patient-months, a figure which cannot be solely due to differences in patient characteristics. The variance is likely to be due to the lack of consistency in PD program management and guideline implementation, two areas where improvement would be likely to result in better outcomes for PD patients.

One of the reasons for variations in practice with regard to treatment of PD peritonitis is local differences in patterns of antibiotic-resistant organisms, for example multi-resistant staphylococcus aureus (MRSA), which leads to variations in local protocols for initial antibiotic treatment of peritonitis. However, there is evidence of inappropriate antibiotic use even when resistant organisms are identified, which is associated with poor peritonitis outcomes.

Better awareness of the current published evidence with regards to PD-associated peritonitis outcomes, as is presented in this updated guideline, should enable individual PD units to embark on standardisation of PD programs and implementation of these guidelines to enable improved outcomes for PD patients up to, or even above, the minimal accepted International Society for Peritoneal Dialysis (ISPD) standard.

Definitions and diagnosis of peritonitis

For the purposes of this guideline, the standard definition of peritonitis is used. This is the presence of two or more clinical signs and symptoms of abdominal pain, nausea, vomiting, diarrhoea or fever with cloudy dialysate in a patient receiving PD. Microscopy of the peritoneal dialysate should demonstrate $WCC > 100/mm^3$ with at least 50% polymorphonuclear neutrophils (PMN). Often there is also demonstration of bacteria on Gram stain or culture although this is not required to make the diagnosis. The absolute number of cells will vary according to dwell duration. For patients using automated peritoneal dialysis $> 50\%$ PMN is a strong indicator of peritonitis, even if total WCC is below $100/mm^3$ [1].

Other definitions are listed in Appendix 1.

Management of peritonitis

Empiric therapy

Empiric therapy for PD-associated peritonitis should cover common Gram-positive and -negative organisms. Knowledge of local microbiology and resistance profiles are important in making appropriate empiric antibiotic choices. When this is not available, ISPD guidelines are appropriate to guide initial therapy. These state that Gram-positive organisms may be covered by vancomycin or a cephalosporin and Gram-negative organisms by a third generation cephalosporin or aminoglycoside.

Adjunctive initial therapy

Investigators have proposed the use of various adjunctive therapies to assist in the prevention and control of PD peritonitis. These have included the instillation of urokinase into the peritoneal cavity, and endoluminal brushing of peritoneal dialysis catheters. Persuasive evidence does not exist to support the use of endoluminal brushing, while the subsequent rate of peritonitis suggested that urokinase treatment produced inferior results when compared with catheter removal.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for peritoneal dialysis were combined with MeSH terms and text words for adult and paediatric and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1950 – November Week 3, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 8 December 2009; update search 14 October 2010.

WHAT IS THE EVIDENCE?

Systematic reviews

Wiggins et al performed a Cochrane systematic review of treatment of PD-associated peritonitis in 2008 [2], which included 36 studies of 2089 patients with interventions including antimicrobial agents, urokinase, peritoneal lavage, and intraperitoneal (IP) immunoglobulin. Of note, there were no randomised trials which examined the question of duration of antibiotic treatment or timing of PD catheter removal. The main finding of the review was that based on one study, IP antibiotics are superior to intravenous (IV) antibiotics in reducing treatment failure (75 patients, RR 3.52, 95% CI 1.26 to 9.81). The other three treatment strategies were not helpful, but none of the treatments were associated with significant harm.

Randomized controlled studies

Only one RCT has been reported since the last CARI Guideline review in 2004. This was an open label quasi-RCT (randomised by date of presentation) from a single dialysis unit in Hong Kong [3]. It compared IP therapy of imipenem/ cilastin (500 mg 6 hour load then 100 mg/2L continuous) monotherapy with cefazolin and ceftazidime (1 g each 6 hour load then 250 mg/2L of each as continuous therapy) in adults with PD peritonitis. There were similar outcomes of 51 patients in each treatment group. Treatment was adjusted on clinical response and culture results. Outcomes from this study were then compared to historical controls of the previous 96 consecutive peritonitis episodes.

The primary response rate to the assigned antibiotics was 49.0% for imipenem/cilastin monotherapy, 51.0% for treatment with cefazolin with ceftazidime and 49.0% for the historical group of 96 consecutive cases who had been treated with cefazolin and netilmycin. Overall primary response rates, which included patients whose antibiotics were modified during treatment was 82.4%, 90.2% and 82.3%, respectively (P = 0.41) [3].

The remaining studies examined were observational in nature. These mostly single unit reports, examined the epidemiology and microbiology of PD-associated peritonitis.

ANZDATA registry publications form the bulk of this guideline as they provide details of local epidemiology and treatment strategies. They report our current practices and do not provide evidence for superiority of specific treatment strategies. The ISPD treatment guidelines should be used where there is no specific Australian evidence available.

Registry reports: Australia and New Zealand Dialysis and Transplant Registry

The ANZDATA Registry has published details of bacterial and fungal PD-associated peritonitis in the Australian population including the predictors, treatment and outcomes over the 39-month period from 1st October 2003. A total of 4675 patients received peritoneal dialysis in Australia during this time, being followed for 6002 patient years. Forty-two per cent (1984) of patients had 3594 peritonitis episodes with an overall rate of 0.60 episodes per patient-year of treatment.

These reports have been updated with a summary document describing the nature of peritonitis, treatment and outcome of peritonitis from 1st October 2003 to 31st December 2008 [4].

Australia ranks quite poorly with regards to peritonitis rates in PD patients with an overall rate of 0.60 episodes per patient-year of treatment. Registries from the USA, Canada and Shanghai report rates of 0.37, 0.43 and 0.38, respectively.

Single organism peritonitis accounted for 77% of all episodes reported to the ANZDATA registry with 53.4% being Gram-positive and 23.6% Gram-negative. A further 11% were polymicrobial in nature. Thirteen per cent of episodes were culture negative and fungi accounted for 3% overall.

ANZDATA Registry reports: specific organisms

1. Gram-positive bacterial peritonitis

Coagulase-negative staphylococci (CONS) were reported to account for 26% (936/3594) of peritonitis episodes between 2003 and 2006 in ANZDATA studied patients [5]. A total of 620 of 4675 patients developed CONS peritonitis with an observed rate of 0.16 episodes/patient-year. A lower rate of CONS peritonitis was independently predicted by Asian racial origin (OR 0.52; 95% CI: 0.35-0.79), renovascular nephrosclerosis (OR 0.40, 95% CI: 0.18-0.86), early referral to renal unit prior to dialysis commencement (OR 0.38; 95% CI: 0.19-0.79), and treatment with automated PD at any time during PD career (OR 0.79; 95% CI: 0.66-0.96).

Antibiotic treatment was usually gentamicin with either intraperitoneal vancomycin or cephazolin. Fifty-seven per cent of patients had antibiotic therapy changed, often with conversion to vancomycin monotherapy. Methicillin sensitivity was available for 67% of CONS isolates and 68% of those were resistant to methicillin.

Peritonitis due to CONS was more likely to be cured by antibiotics alone when compared to non-CONS peritonitis (79% vs 64%, $P < 0.01$) and less likely to require hospitalisation (61% vs 73%, $P < 0.001$), catheter removal (10% vs 26%, $P < 0.001$), temporary haemodialysis (2% vs 5%, $P < 0.001$) or permanent haemodialysis (9% vs 21%, $P < 0.001$) or result in death (1.0% vs 2.7%, $P = 0.002$). Polymicrobial peritonitis and initial empiric vancomycin administration (compared to cephalosporins) independently predicted catheter removal and permanent haemodialysis transfer. Relapse was more frequent with CONS peritonitis (7% vs 13%, $P = 0.003$) and was more likely to result in catheter removal 22% vs 7%, $P < 0.001$). Repeat CONS peritonitis (> 4 weeks after last antibiotic dose or > 5 weeks if intermittent vancomycin used) occurred in 31% (194/620) of patients with highest risk in the second month after therapy (OR 1.87; 95% CI: 1.39-2.51 compared to > 2 months).

Staphylococcus aureus accounted for 14% of the peritonitis cases reported to the ANZDATA Registry with a rate of 0.08 episodes per patient-year of treatment [6]. Eight per cent of patients had peritonitis due to this organism. Of these, 23% had two or more episodes. Polymicrobial peritonitis involving *S. aureus* accounted for 8% of episodes. Univariate analysis identified late initial referral, current smoking, diabetic nephropathy, peripheral vascular disease and availability of baseline PET results as predictors of *S. aureus* peritonitis. Multivariate analysis identified younger age as a significant independent predictor [first quartile: reference; second quartile: adjusted odds ratio 0.69, 95% CI: 0.27-1.73; third quartile OR 0.27, 95% CI: 0.09-0.86; fourth quartile 0.13, 95% CI: 0.03-0.54).

Empiric therapy included IP vancomycin in 61% and cephazolin in 31%, usually with gentamicin. Antibiotic regimen was changed in 51% of episodes, most commonly with cephazolin being replaced by vancomycin and cessation of gentamicin. Overall median duration of treatment was 14 days which was the same as non-*S. aureus* peritonitis. Antifungal chemoprophylaxis was only used in 8% of *S. aureus* cases and in 7% of non-*S. aureus* peritonitis cases.

Twenty-three per cent of patients had repeat *S. aureus* peritonitis. Relapse occurred more frequently than with non-*S. aureus* peritonitis (20% vs 13%; $P < 0.01$). Regression modelling identified an increased risk of relapse associated with the presence of peripheral vascular disease (adjusted OR 2.75; 95%CI 1.43-5.29) and vancomycin use when compared with cephalosporin (adjusted OR 2.62; 95%CI 1.32-5.21). A reduced relapse risk was independently predicted by female gender and the middle tertile of age (OR 0.43; 95%CI 0.24-0.79 and OR 0.49; 95%CI 0.25-0.95). There were comparable rates of hospitalisation, catheter removal, haemodialysis transfer and death when compared with non-*S. aureus* peritonitis.

Methicillin-resistant *S. aureus* (MRSA) was independently predictive of permanent transfer to haemodialysis (OR 2.11; 95%CI 1.17-3.82). It also tended to be associated with increased hospitalisation (OR 2.00; 95%CI 0.96-4.19). While initial empiric therapy did not associate with MRSA clinical outcomes, subsequent treatment that did not include vancomycin was associated with more hospitalisation, catheter removal and death.

Streptococcal peritonitis was reported in 4.6% of peritonitis episodes observed in 256 individuals reported to ANZDATA between 2003 and 2006 [7]. Being of Aboriginal or Torres Strait Islander racial origin was the only identified independent predictor. Relapse risk was lower at 3% when compared with other organisms. Other outcomes identified were lower rates of catheter removal (10% vs 23%), permanent transfer to haemodialysis (9% vs 18%) and shorter duration of hospitalisation (5 vs 6 days). Eighty-seven per cent (249/256 patients) experienced successful treatment without relapse, being treated with either IP vancomycin or first generation cephalosporin. The median duration of treatment for successful patients was 13 days (IQR: 8-18 days). Choice of empiric therapy did not appear to influence the final outcome.

Enterococcal peritonitis data extracted from ANZDATA during the same period has been reported by Edey et al [7]. A total of 116 (3% of overall peritonitis) episodes occurred in 103 (2%) individuals. The enterococcal peritonitis rate was 0.02 episodes per patient-year of treatment compared with the overall peritonitis rate of 0.60. Polymicrobial peritonitis was more common with enterococcal than non-enterococcal peritonitis (45% vs 5%, $P < 0.001$, OR 13.4; 95% CI 9.45-19.0). It was associated with older age, Maori and Pacific Islander racial origin, renovascular and coronary heart disease, although none of these covariates achieved statistical significance.

Pure enterococcal peritonitis was treated with ampicillin in 8% of patients while 78% received vancomycin monotherapy.

Successful treatment was achieved in 51% of patients. An independent risk factor for adverse outcome was the identification of additional non-enterococcus bacteria. High rates of hospitalisation (83%), catheter removal (52%), permanent haemodialysis transfer (50%) or death (5.8%) were observed in patients with polymicrobial enterococcal peritonitis. Pure enterococcus peritonitis was associated with similar outcomes to those of non-enterococcal peritonitis but worse than Gram-positive peritonitis. Hospitalisation rates were 75%, 69% and 63%, respectively. Catheter removal occurred in 25%, 21% and 12% and permanent transfer to haemodialysis was 17%, 17% and 3%, respectively. Death rates were 1.6%, 2.2% and 0.6% for the three groups.

With *Corynebacterium* peritonitis, the overall cure rate with antibiotics alone was similar to other organisms at 67% [8]. Outcomes were similar across antibiotic regimens (vancomycin vs cephalosporins vs others) although vancomycin was the most common antibiotic used.

Sixty-seven per cent achieved a complete cure with antibiotics alone, 18% relapsed, and 15% had a repeat peritonitis. The secondary cure rate was 77%, hospitalisation occurred in 70%, 21% had catheter removal, 15% permanent haemodialysis transfer and 2% died. Independent predictors of hospitalisation were age (OR 1.07; 95% CI 1.00-1.15), presence of chronic lung disease (OR 92.0; 95% CI 1.95-4330), administration of cephalosporins (OR 6.83; 95% CI 1.00-47.0), or an agent other than vancomycin in the initial empiric antibiotic regimen (OR 30.8; 95% CI 1.17-809).

Increased body mass index (BMI) was associated with an increased risk of relapse with OR 1.61, 95% CI 0.97-2.67. Polymicrobial peritonitis was associated with a greater risk of permanent haemodialysis transfer (OR 19.8: 95% CI 0.84 -465, P=0.064).

2. Gram-negative bacterial peritonitis

Non-Pseudomonas Gram-negative (NPGN) peritonitis was observed in 256 ANZDATA studied patients on 837 occasions [9,10]. This accounts for 23.3% all peritonitis episodes or a rate of 0.14 episodes/ patient-year. Single organisms were isolated in 75% of episodes with 32.9% *E. coli*, 20.4% *Klebsiella*, 11.8% *Enterobacter*, 11.0% *Serratia*, 7.2% *Acinetobacter* and 3.7% *Proteus*.

The occurrence of NPGN peritonitis was independently predicted by older age (youngest tertile: reference; middle tertile adjusted OR 1.15: 95% CI 0.92-1.44; oldest tertile OR 1.68: 95% CI 1.34-2.11) and end-stage renal failure due to diabetic nephropathy (OR 0.66: 95% CI 0.52-0.83). A history of previous peritonitis was more common for NPGN than other peritonitis episodes (89% vs 31%, P <0.001) but time to next episode was not different between NPGN and other forms of peritonitis (median 77 days [IQR 37-185 days] vs median 80 days [IQR 29.25-172.25 days] P=0.3).

Treatment of NPGN peritonitis following standard empiric therapy with gentamicin and either intraperitoneal (IP) vancomycin or cephazolin was changed to second regimen in two-thirds of patients. Monotherapy with gentamicin, ciprofloxacin or ceftriaxone was used in 14%, 10% and 5% of episodes, respectively.

The characteristics of *Pseudomonas* peritonitis were described by Sivaet al in the Australian population [11]. This was defined as single or polymicrobial peritonitis for which *Pseudomonas* spp. was cultured. *Pseudomonas* infections included *P. aeruginosa*, *P. ceracia*, *P. stuzeri*, *Pseudomonas* other or *Pseudomonas* unknown. These represented 5.3% all peritonitis episodes with an incidence of 0.032 (95%CI 0.028-0.037) episodes per patient-year of treatment. Polymicrobial *Pseudomonas* infections represented 22% of these infections. Independent risk factors were Maori/Pacific Islander race (adjusted incidence risk ratio [IRR] 3.53; 95% CI 1.43-8.72), Aboriginal/Torres Strait Islander race (IRR 2.08; 95%CI 1.10-3.92), and the absence of a baseline peritoneal equilibration test (IRR 2.60; 95%CI 1.34-5.07). Previous peritonitis was not more common among patients with *Pseudomonas* infections (43% vs 45%; P=0.6). Time elapsed from previous peritonitis was also similar between patients who had *Pseudomonas* vs. non-*Pseudomonas* infections.

Empiric therapy was most commonly IP vancomycin or cephazolin with gentamicin. Specific therapy was most commonly with ciprofloxacin, often as monotherapy. Only 21% of patients had combination therapy with two effective anti-pseudomonal therapies. Ciprofloxacin with gentamicin was most commonly used followed by ticarcillin and gentamicin or ceftazidime and gentamicin. Total antibiotic therapy duration had a median of 16 days. Nystatin therapy was used in only 6% of patients.

Compared with non-*Pseudomonas* infection, *Pseudomonas* peritonitis had a lower risk for relapse and no increase in risk of death but this was in the context of greater duration of treatment, hospitalisation, catheter removal, temporary and permanent transfer to haemodialysis (HD). Choice of empiric antibiotics (vancomycin, cephalosporin or other) did not significantly influence outcomes, however, treatment with at least two agents with anti-*Pseudomonas* activity in combination was associated with less permanent transfer to HD (10% vs 38% single agent, P=0.03). Relapse rates, hospitalisation, catheter removal and death rates were similar for single and dual therapy.

Interestingly, treatment and outcomes were similar for single organism and polymicrobial *Pseudomonas* peritonitis episodes, with similar change and time to second and third antibiotics, relapse, hospitalisation (number and duration), catheter removal, temporary or permanent transfer to HD and death.

3. Polymicrobial bacterial peritonitis

Polymicrobial peritonitis occurred in 324 individuals over the 39-month study period. The 359 episodes represented 10% of all peritonitis episodes during 6002 patient-years [12]. Of the organisms cultured, 41% were mixed Gram-positive and -negative organisms, 25% were pure Gram-positive and 22% pure Gram-negative organisms. Mixed bacteria and fungi were observed in 13%. The presence of chronic lung disease was the only significant predictor of polymicrobial infection.

When compared with single organism peritonitis, polymicrobial disease was associated with increased hospitalisation, (83% vs 68%; $P < 0.001$), catheter removal (43% vs 19%; $P < 0.001$) permanent haemodialysis transfer (38% vs 15%; $P < 0.001$) and death (4% vs 2%; $P = 0.03$).

Pure Gram-positive polymicrobial peritonitis had a better outcome than other groups and the isolation of either fungi or Gram-negative bacteria was the primary predictor of adverse outcome. Patients with late catheter removal beyond one week were more likely to be permanently transferred to HD than patients who had earlier catheter removal (92% vs 81%; $P = 0.05$). The authors concluded that polymicrobial peritonitis could generally be treated successfully with antibiotics alone without catheter removal, particularly when only Gram-positive organisms are cultured. The presence of either Gram-negative bacteria or fungi carries a worse prognosis and catheter removal should be considered.

4. Culture-negative peritonitis

Culture-negative peritonitis should occur in less than 20% of cases or less than 10% in specialised academic centres. The ideal techniques for collection and culture are discussed in the ISPD 2010 guideline [1]. Briefly, both sediment culture of 50 mL of peritoneal dialysate effluent and bedside inoculation of 5-10 mL of effluent into two blood culture bottles should be used for the highest isolation rate. Specimens should be received within 6 hours of inoculation or incubation commenced at 37°C during transport.

Generally, culture-negative peritonitis has a relatively benign outcome. It occurred on 435 occasions in 361 ANZDATA studied patients, representing 12% of peritonitis episodes in 8% of patients [10]. Its occurrence was not associated with specific demographic or clinical variables. Previous antibiotic therapy for peritonitis was more common with culture-negative than culture-positive peritonitis (42% vs 35%; $P = 0.01$).

Culture negative peritonitis was more commonly associated with cure by antibiotics alone (77% vs 66%; $P < 0.001$). It was associated with better outcome in terms of hospitalisation (60% vs 71%; $P < 0.001$), catheter removal (12% vs 23%; $P < 0.001$), permanent HD transfer (10% vs 19%; $P < 0.001$), or death (1% vs 2.5%; $P = 0.04$). Relapse rates were 14% for both culture-negative and culture-positive populations. Catheter removal was more likely to occur following culture-negative relapse (29% vs 10%, $P < 0.001$; OR 3.83; 95% CI 2.00-7.32). Administration of vancomycin or cephalosporin as initial empiric therapy was not significantly associated with clinical outcomes.

5. Fungal peritonitis

The ANZDATA Registry report regarding fungal peritonitis is discussed in the fungal peritonitis guideline [13].

6. Peritoneal dialysis-associated peritonitis in children

Peritoneal dialysis was used to treat 167 children (<18 years of age) between October 2003 and December 2007 [14]. Peritonitis occurred at a rate of 0.71 episodes/patient-year. Sixty per cent of infections occurred in the first 6 months after commencing PD. Peritonitis-free survival was 72%, 56% and 36% at 6 months, 1 year and 2 years, respectively. Age at commencement of dialysis was weakly associated with PD infection on univariate analysis. However, previous peritonitis was the only independent predictor of developing peritonitis on multivariate Cox proportional hazard model (adjusted hazard ratio 2.02; 95%CI 1.20-3.40, P=0.008).

Peritoneal dialysis fluid cultures were positive in 86% of episodes; of these, 51% were monomicrobial Gram-positive, 30% monomicrobial Gram-negative and 7% were polymicrobial. Coagulase-negative Staphylococcus represented 24% and *S. aureus* accounted for 14% of all culture-positive episodes. Gram-negative organisms were represented by *Klebsiella* spp. 9%, *Pseudomonas aeruginosa* 7%, and *Enterobacter* spp. 5%. Anaerobic bacteria represented 1% and fungi 3% (fungi caused the first episode of peritonitis in 2/100 patients).

Most patients received first generation cephalosporin with either aminoglycoside or third generation cephalosporin as empiric therapy for their first episode. Empiric treatment in subsequent episodes was first generation cephalosporin alone or with aminoglycoside.

Patient outcomes that occurred were: relapse in 5% of episodes, recurrence in 7% and transfer to HD in 12% (5% temporary, 7% permanent). Catheter removal occurred in 16% of episodes. There were no deaths. There was no statistically significant difference in outcomes for polymicrobial peritonitis and either culture-negative or single organism peritonitis in children.

Observational studies

There were many observational studies reporting the local microbiological profile of peritonitis episodes and local treatment protocols. Treatment strategies largely adhered to the ISPD guidelines.

Questions that could not be answered by any of the studies reviewed included what is the most suitable choice and dosing regimens of antibiotic therapy.

Stability of antibiotics in peritoneal dialysis fluid

Peritoneal dialysis-associated peritonitis is frequently treated with IP antibiotics preloaded into the dialysate some days prior. The *in vitro* stability of antibiotics in PD fluids has been studied for commonly used medications. The stability of gentamicin, vancomycin and gentamicin with vancomycin, all with ceftazidime mixed in standard PD fluid was evaluated by Dooley et al [15]. They noted that antibiotic concentration (immunoassay) did not deteriorate significantly over a 14-day period when stored at either room temperature or refrigerated. Bioactivity of gentamicin and ceftazidime but not vancomycin did decline when refrigerated or stored at room temperature over 14 days, however they all retained enough activity to be clinically effective. Vancomycin activity was enhanced in combination bags, presumably reflecting synergy with gentamicin.

Voges et al reported that netilmycin, vancomycin, cefazolin and heparin were stable for at least 24 hours at 25°C in Physioneal, Nutrineal, Extraneal and Dianeal PD solutions [16]. Gentamicin had similar stability in Nutrineal, Extraneal and Dianeal but not in Physioneal (<24-hour stability at 25°C). Tobramycin was stable for at least 24 hours at 25°C in Nutrineal and Extraneal but not in Physioneal and Dianeal (<24-hour stability).

SUMMARY OF THE EVIDENCE

The only systematic review indicates that IP administration is superior to the intravenous route for the treatment of PD-associated peritonitis. There are no robust RCTs and recent publications report single centre experience or registry data. The ANZDATA Registry reports on current Australian practice but does not provide data on guideline implementation and variation in practice. They serve to highlight the poor rate of peritonitis in our population and our own treatment variance from guideline recommendations.

The ANZDATA peritonitis registry is ongoing and commenced collecting data on each peritonitis episode from 1st January 2011. This will allow feedback and publication of specific unit peritonitis rates, profiles and treatments.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendations.

UK Renal Association: Provides a limited set of recommendations regarding the treatment of PD associated peritonitis [17]:

Guideline 5.2.2 – PD infectious complications: Treatment: We recommend that methicillin resistant organisms (MRSA) will require systemic treatment (e.g. vancomycin) and will need to comply with local infection control policies. (1C)

Guideline 5.2.3 – PD infectious complications: Treatment: We recommend that initial treatment regimens for peritonitis should include cover for bacterial Gram positive and Gram negative organisms including *Pseudomonas* species until result of culture and antibiotic sensitivities are obtained. (1C)

Audit Measure 21: Routine annual audit of infection outcomes.
Rationale for guidelines 5.2.1 – 5.2.3

Canadian Society of Nephrology: No recommendations.

European Renal Best Practice Guidelines: Recommends use of ISPD: Peritoneal dialysis-related infections recommendations: 2005 update.

International Guidelines: The International Society of Peritoneal Dialysis (ISPD), 2010 [1]

- **Reporting peritonitis rate:** every program should regularly monitor infection rates at a minimum on a yearly basis (opinion). This may be reported as:
 - Rates either:
 - Months between episodes: months of peritoneal dialysis at risk, divided by number of episodes.
 - Episodes per year: number of infections by organism per time period divided by dialysis-years' time at risk.
 - Percentage of patients peritonitis-free per period of time.
 - Median peritonitis rate for program (calculate peritonitis rate for each patient then obtain median of these rates).
- **Exit site and tunnel infections:**
 - Definition: Purulent drainage from exit site indicates the presence of infection. Erythema may or may not represent infection (evidence).
- **Therapy:** most serious and common exit site pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. As these organisms frequently lead to peritonitis (evidence) such

infections must be treated aggressively. Oral antibiotic therapy is generally recommended, with the exception of MRSA (opinion).

- **Initial presentation and management of peritonitis**
 - Clinical presentation of peritonitis: PD patients presenting with cloudy effluent should be presumed to have peritonitis. Should be confirmed by obtaining effluent cell count, differential and culture (evidence).
 - It is important to initiate empiric antibiotic therapy for PD-associated peritonitis as soon as possible. There are potentially serious consequences of peritonitis that are more likely to occur if treatment is not initiated promptly (opinion).
- **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).
 - Treat for 14 days if clinical improvement evident. If no clinical improvement by 5 days of treatment then remove catheter.
- **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 on saving the peritoneal catheter (opinion).

SUGGESTIONS FOR FUTURE RESEARCH

1. Investigation of optimal time for catheter removal.
2. Optimal treatment of *Pseudomonas* spp. peritonitis.
3. Evaluation of aminoglycoside avoidance strategies in empiric and specific treatment of PD-associated peritonitis.

CONFLICT OF INTEREST

Amanda Walker has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1. Characteristics of included studies

| Study ID (author, year) | N | Study Design | Setting | Participants | Intervention (experimental group) | Intervention (control group) | Follow up (months) | Comments |
|-------------------------------|-----|--------------------------------------|-----------|------------------------------|--------------------------------------|---------------------------------|-----------------------|---|
| Leung et al 2004 | 102 | Randomized controlled clinical trial | Hong Kong | PD patients with peritonitis | imipenem / cilastatin monotherapy | cefazolin plus ceftazidime | 11 months | Further compared to a historic group treated with cefazolin plus netilmycin |

Table 2. Quality of randomised trials

| Study ID (author, year) | Method of allocation concealment * | Blinding | | | Intention-to-treat analysis † | Loss to follow up (%) | Comments |
|----------------------------|------------------------------------|----------------|-----------------|---------------------|-------------------------------|-----------------------|----------|
| | | (participants) | (investigators) | (outcome assessors) | | | |
| Leung et al 2004 | Unclear | No | No | Not stated | Unclear | 0 | (-) |

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

‡ Quality score: “How successfully do you think the study minimised bias?” Choose between: very well (+); okay (Ø); poorly (-).

Table 3. Results for dichotomous outcomes

| Study ID (author, year) | Outcomes | No. of studies | Intervention group (no. of patients with events/no. of patients exposed) | Control group (no. of patients with events/no. of patients exposed) | Relative risk (RR) [95% CI] | Risk difference (RD) [95% CI] |
|----------------------------|---------------------------|----------------|---|--|-----------------------------|-------------------------------|
| Leung et al 2004 | Tenckoff catheter removal | 1 | 6/51 | 6/51 | 1.00 (95%CI: 0.35, 2.89) | 0.00 (95%CI: -0.13, 0.13) |

Appendix 1. Explanation of definitions used

Peritonitis (1 or more)

- Presence of two clinical signs and symptoms: abdominal pain, nausea, vomiting, diarrhea, fever and cloudy dialysate
- Peritoneal dialysate WCC > 100/mL (dwell >2 hours) with 50% neutrophils, if dwell <2 hours then WCC may be less than 100/mL but usually PMN predominance persists
- Demonstration of bacteria on Gram stain or culture of peritoneal dialysate effluent

Clinical failure peritonitis (1 or more)

- Insufficient lessening of signs and symptoms of infection to qualify as improvement
- Continued symptoms or signs beyond day 4
- Dialysate WCC > 100/mm³ at day 14
- Removal of the catheter for failure to respond to treatment
- Recurrence of peritonitis with the same micro-organism (relapse) within 28-day follow up period after cessation of antibiotics
- Death due to uncontrolled infection

Clinical success

- Primary response – disappearance of the signs and symptoms of peritonitis and clear, sterile PD by day 10
- Relapsed – primary response but recurrence by day 28
- Complete cure – no relapse by day 28 after completion of antibiotics

Outcome indeterminate

- When evaluation is not possible for any reason

Bacteriologic response based on cultures before, during and after completion of therapy

Eradication

- Causative organisms absent and remaining absent for 28 days after completion of antibiotics

Persistence

- Causative organisms present at any culture dates after initiation of therapy

Super infection

- Presence of new infecting organisms and cultures dates during and just after (2 days) of therapy

Bacteriologic indeterminate

- When result not available for any reason including no growth in the first culture

Eradication with relapse

- Causative organisms absent at day 14 but present at or before 28+/- 2 days follow up

Eradication with reinfection

- Causative organisms absent at day 14 and presence of new organisms at or before 28+/- 2 days of follow up

Exit site infection

- Pustular discharge from the exit site with or without erythema of the skin at the catheter-skin interface. May be acute or chronic.

Tunnel infection

- Signs of inflammation (erythema, oedema and or tenderness) over the subcutaneous tunnel, with or without purulent discharge from exit site or after pressure along the tunnel.