13. Treatment of peritoneal dialysis-associated peritonitis in adults

Date written: February 2003
Final submission: July 2004

Guidelines
(Include recommendations based on level I or II evidence)

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 (Level II evidence).

Suggestions for clinical care
(Suggestions are based on level III and IV sources)

- There is no good evidence to support specific antibiotic choice, however, aminoglycosides should be avoided where possible, to avoid their adverse effects of nephrotoxicity and ototoxicity (Opinion).

Background

The data provided by the Twenty Sixth Report of the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA Registry) clearly establishes peritonitis as a clinically important problem confronting patients and the providers of dialysis services in Australia. At the end of the year to December 2002, there were 7205 patients (366 per million) receiving dialysis in Australia. Of those, 1770 were receiving peritoneal dialysis (PD) with 1163 patients on continuous ambulatory peritoneal dialysis (CAPD) and 607 on ambulatory peritoneal dialysis (APD).

Peritonitis complicating PD is associated with morbidity and mortality as well as failure of the PD modality, necessitating permanent transfer to haemodialysis. In Australia, the median peritonitis-free survival in 2002 was 18.4 months overall, with 30% of patients free of peritonitis at 3 years. In the period from April 1997 to March 2000, infective complications comprising recurrent or persistent peritonitis, acute peritonitis as well as tunnel and exit site infection (ESI) led to 715 (39%) primary technique failures and 15 (18%) secondary technique failures (26th ANZDATA Report, 2002).

The main objective of this review is to document the currently available data relating to evidence-based treatment of this clinically important problem. This then serves as an educational resource and identifies potential areas of research required to improve the health care and outcomes of paediatric and adult renal patients by

helping clinicians and nurses to adhere to evidence-based medical practice as often as possible. It also acts as a means of enhancing the quality, appropriateness, consistency and cost-effectiveness of renal health care. As definitions used in the studies undertaken to date have varied – relating to cure, relapse or treatment failure – definitions have been suggested for use in future research studies relating to this important area of clinical care (Appendix 1).

Search strategy

Databases searched: PubMed Medline from 1990-2002. Search terms were: peritoneal dialysis and (CAPD or CCPD or APD), peritonitis, antibiotic, cefazolin, cephalothin, ceftazidime, vancomycin.

Date of search/es: 22 November 2002; 6 December 2002.

What is the evidence?

Few well-designed, adequately described randomised controlled trials (RCTs) with appropriate patient numbers addressing the treatment of peritonitis in PD populations could be found. There were inconsistent definitions of response to treatment and days on which response was evaluated across the studies. There were a variety of protocols used for the drugs administration. Some studies considered the impact of residual renal function on antibiotic levels, however, many did not.

Most studies had poor description of study design and/or results, which limited the ability to manipulate the data to answer specific questions regarding the outcome of different initial antibiotic regimens.

No studies addressed the specific question of most appropriate initial antibiotic treatment. None reported outcome at 48 hrs or at time of bacterial sensitivities becoming available, so limited conclusions can be drawn regarding which initial treatment is best.

Most studies did not report time to clearing of bacteria so when the initial antibiotic treatment rendered the peritoneum sterile could not be ascertained. Some studies permitted modification of antibiotic choice based on the results of cultures while others continued medications even if in vitro resistance to the drug was detected.

Some studies included patients with exit site infections (ESIs) or tunnel infections. In others, these were exclusion criteria.

Local epidemiology varied from locations of low methicillin resistance (1%) to ones with as high as 30% of organisms isolated being resistant. The prevalence of colonisation with methicillin-resistant organisms was usually not reported.

No RCTs for the management of vancomycin-resistant enterococcus (VRE) peritonitis or VISA (intermediate sensitivity to vancomycin *Staphylococcus aureus*) in the PD population were identified (please refer to Table 1 in the Appendices for reported therapy combinations).

Randomised controlled prospective studies

Six RCTs relating to the treatment of bacterial peritonitis reported on outcomes in patients with culture negative peritonitis. Two studies (Schaefer et al 1999; Wong et al 2001) both reported outcomes of primary response to empiric antibiotics to be similar for different antibiotics trialled.

Schaefer and coworkers compared vancomycin and ceftazidime with teicoplanin and ceftazidime (continuous or intermittent dosing) and reported similar high primary success rates in patients with culture negative or mixed growth peritonitis with either antibiotic combination (Schaefer et al 1999).

Wong et al reported primary response rates of 87%-100% in culture negative patients receiving either cefepime or a combination of vancomycin and netilimicin, respectively (Wong et al 2001).

Gucek et al (1997) found similar primary cure rates (100%) in seven culture negative peritonitis patients who received either cefazolin with netilimicin or vancomycin and ceftazidime.

Cheng et al (1998) reported similar outcomes between patients receiving either oral levofloxacin with vancomycin or intraperitoneal netromycin with vancomycin when analysed in terms of primary cure rate, primary failure rate or relapse rate.

Lye et al (1993) compared different dosing regimens of gentamicin with vancomycin and found similar outcomes in six culture negative patients (4/6 primary cures). Merchant et al (1992) did not discuss the outcome of culture negative patients specifically.

No clear guideline regarding antibiotic choice in culture negative peritonitis can be drawn from the evidence. It appears that with continuation of broad cover empiric therapy, primary response and relapse rates are similar to those experienced with gram positive peritonitis. No clear evidence to support ISPD guideline opinion could be found.

Summary of the evidence

Please refer to the Evidence Tables shown in the Appendices.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: The management of peritonitis has not been addressed in the K/DOQI guidelines.

British Renal Association: Do not provide recommendations concerning the management of peritonitis.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: European Guidelines on Best Practice for the Management of Peritoneal Dialysis 2002:

Guideline 9.1
Each centre should analyse its incidence of peritonitis and exit-site infections. (Evidence C)

Guideline 9.5
The ISPD guidelines on peritonitis should be used for the antibiotic treatment and the indications for catheter removal. Adjustments of the initial treatment can be made depending on the patterns of the local flora (Peritoneal Dialysis 2000;19:396-411). (Evidence C)

International Guidelines: ISPD Guidelines/Recommendations - Adults 2000:
ISPD – (Adult) – also refer to Appendix 3 for recommended doses.
Empiric initial therapy for peritoneal related peritonitis should be stratified for residual renal function. If urine output < 100 mL/day: cefazolin or cephalothin (1 g/bag q.d. or 15 mg/kg BW/bag, q.d.) with ceftazidime (1 g/bag, q.d.) or gentamicin, tobramycin, netilmycin (0.6 mg/kg BW/bag, q.d. or amikacin 2 mg/kg BW/bag, q.d. If urine output > 100 mL/day cefazolin or cephalothin (20 mg/kg BW/bag, q.d.) and ceftazidime 20 mg/kg BW/bag, q.d. is recommended. Aminoglycosides and amikacin are not recommended in non-anuric patients.

If gram positive organisms are identified on culture then antibiotic therapy should be adjusted as outlined below:
Enterococcus: at 24-48 hours: stop cephalosporins, start ampicillin (125 mg/L/bag) and consider adding aminoglycoside. If ampicillin resistant, start vancomycin or clindamycin. If VRE, consider quinupristin/dalfopristin. Duration of therapy 14 days.

Staphylococcus aureus: at 24-48 hours: stop ceftazidime or aminoglycoside, continue cephalosporin, add rifampicin 600 mg/day p.o. If MRSA, start vancomycin or clindamycin. Duration of therapy 21 days.

Other gram positive organism (coagulase negative Staphylococcus): at 24-48 hours: Stop ceftazidime or aminoglycoside, continue cephalosporin. If MRSE and clinically not responding, start vancomycin or clindamycin. Duration of therapy 14 days.

At 96 hours in all gram positive cases: if no improvement, reculture and evaluate for exit site or tunnel infection, catheter colonization, etc. Choice of final therapy should always be guided by antibiotic sensitivities.

If gram negative organism is identified on culture at 24-48 hours:
Single gram negative organism: adjust antibiotics to sensitivity < 100 mL urine/day aminoglycoside, > 100 mL/day ceftazidime. Duration of therapy 14 days.

Pseudomonas/Stenotrophomonas: continue ceftazidime and add < 100 mL urine/day, aminoglycoside; > 100 mL/day ciprofloxacin 500 mg p.o. b.i.d. or piperacillin 4 g IV q 12 hours or sulphamethoxazole trimethoprim 1-2 DS/day or aztreonam load 1 g/L; maintenance dose 250 mg/L IP/bag. Duration of therapy 21 days.

Multiple gram negatives and/or anaerobes: continue cefazolin and ceftazidime and add metronidazole 500 mg q 8 hrs p.o., IV or rectally. If no change in clinical status, consider surgical intervention. Duration of therapy 21 days.

International Guidelines: ISPD Guidelines/Recommendations – Pediatric Patients 2000:
ISPD – (Pediatrics) – also refer to Appendix 4 for recommended doses.

Treatment for peritoneal dialysis associated peritonitis should be commenced if there is evidence of cloudy effluent and sample is evaluated by cell count and differential, gram stain and culture. If the patient presents afebrile, with mild or no abdominal pain and no risk factors for severe infection, then commence treatment with first generation cephalosporin and ceftazidime. If however, any of the following are present: history of MRSA infection or carriage, recent or current exit site/tunnel infection or fever, severe abdominal pain or age < 2 yrs then use empiric therapy of glycopeptide (vancomycin or teicoplanin) and ceftazidime.

If gram positive organisms are cultured:
Enterococcus, Streptococcus: discontinue empiric therapy and add ampicillin.
MRSA: modify empiric therapy discontinue ceftazidime, continue or substitute vancomycin, teicoplanin or clindamycin.
Other gram positive non-MRSA: discontinue ceftazidime, modify empiric therapy, continue or substitute first generation cephalosporins.

If gram negative organisms are cultured:
Pseudomonas: discontinue glycopeptide or first generation cephalosporin, continue ceftazidime, add second agent based on sensitivity.
E. coli, Proteus or other ceftazidime sensitive organism: discontinue glycopeptide or first generation cephalosporin, continue ceftazidime.
Anaerobes, multiple gram negative organisms: discontinue glycopeptide or first generation cephalosporin, consider intra-abdominal pathology, include metronidazole in regimen.

Implementation and audit

No recommendation.

Suggestions for future research

A multicentre RCT of patients presenting with peritoneal dialysis-associated peritonitis could be performed.

References

Anwar N, Merchant M, Were T et al. 1995. A prospective, randomized study of the comparative safety and efficacy of intraperitoneal imipenem versus vancomycin and netilmicin in the treatment of peritonitis on CAPD. Perit Dial Int 15(2): 167-71.

ANZDATA Registry Report 2003. Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia.

Bennett-Jones DN, Russell GI, Barrett A. 1990. A comparison between oral ciprofloxacin and intra-peritoneal vancomycin and gentamicin in the treatment of CAPD peritonitis. J Antimicrob Chemother 26(Suppl F): S73-S76.

Cheng IK, Chan CY, Wong WT. 1991. A randomised prospective comparison of oral ofloxacin and intraperitoneal vancomycin plus aztreonam in the treatment of bacterial peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 11(1): 27-30.

Cheng IK, Fang GX, Chau PY et al. 1998. A randomized prospective comparison of oral levofloxacin plus intraperitoneal (IP) vancomycin and IP netromycin plus IP vancomycin as primary treatment of peritonitis complicating CAPD. Perit Dial Int 18(4): 371-75.

de Fijter CW, ter Wee PM, Oe LP et al. 2001. Intraperitoneal ciprofloxacin and rifampicin versus cephradine as initial treatment of (C)APD-related peritonitis: a prospective randomized multicenter comparison (CIPPER trial). Perit Dial Int 21(5): 480-86.

Flanigan MJ and Lim VS. 1991. Initial treatment of dialysis associated peritonitis: a controlled trial of vancomycin versus cefazolin. Perit Dial Int 11(1): 31-37.

Friedland JS, Iveson TJ, Fraise AP et al. 1990. A comparison between intraperitoneal ciprofloxacin and intraperitoneal vancomycin and gentamicin in the treatment of peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD). J Antimicrob Chemother 26(Suppl F): S77-S81.

Gucek A, Bren AF, Hergouth V et al. 1997. Cefazolin and netilmycin versus vancomycin and ceftazidime in the treatment of CAPD peritonitis. Adv Perit Dial 13: 218-20.

Gucek A, Bren AF, Lindic J et al. 1993. Is monotherapy with cefazolin or ofloxacin an adequate treatment for peritonitis in CAPD patients? Adv Perit Dial 10: 144-46.

Keane WF, Bailie GR, Boeschoten E et al. 2000. Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. Perit Dial Int 20(4): 396-411.

Khairullah Q, Provenzano R, Tayeb J et al. 2002. Comparison of vancomycin versus cefazolin as initial therapy for peritonitis in peritoneal dialysis patients. Perit Dial Int 22(3): 339-44.

Lupo A, Rugiu C, Bernich P et al. 1997. A prospective, randomized trial of two antibiotic regimens in the treatment of peritonitis in CAPD patients: teicoplanin plus tobramycin versus cephalothin plus tobramycin. J Antimicrob Chemother 40(5): 729-32.

Lye WC, Lee EJ, van der Straaten J. 1993. Intraperitoneal vancomycin/oral pefloxacin versus intraperitoneal vancomycin/gentamicin in the treatment of continuous ambulatory peritoneal dialysis peritonitis. Perit Dial Int 13(Suppl 2): S348-50.

Merchant MR, Anwar N, Were A et al. 1992. Imipenem versus netilmicin and vancomycin in the treatment of CAPD peritonitis. Adv Perit Dial 8: 234-37.

Schaefer F, Klaus G, Muller-Wiefel DE et al. 1999. Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). J Am Soc Nephrol 10(1): 136-45.

Tapson JS, Orr KE, George JC et al. 1990. A comparison between oral ciprofloxacin and intraperitoneal vancomycin and netilmicin in CAPD peritonitis. J Antimicrob Chemother 26(Suppl F): S63-S71.

Warady BA, Schaefer F, Holloway M et al. 2000. Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. Perit Dial Int 20(6): 610-24.

Wong KM, Chan YH, Cheung CY et al. 2001. Cefepime versus vancomycin plus netilmicin therapy for continuous ambulatory peritoneal dialysis-associated peritonitis. Am J Kidney Dis 38(1): 127-31.

Appendices

Appendix 1 - Explanation of definitions used

Peritonitis
Presence of two clinical signs and symptoms:- abdominal pain, nausea, vomiting, diarrhoea, fever and cloudy dialysate
Peritoneal dialysate WCC > 100/mm^3 with 50% neutrophils
Demonstration of bacteria on gram stain or culture

Clinical failure
Insufficient lessening of signs and symptoms of infection to qualify as improvement
Continued symptoms or signs beyond day 4
Dialysate WCC > 100/mm^3 at day 14
Removal of the catheter for failure to respond to treatment
Recurrence of peritonitis with 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 on day 10
Relapsed – primary response but recurrence by day 28
Complete cure – no relapse by day 28 after completion of antibiotics

Outcome indeterminate
When no evaluation is 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

Superinfection
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. Maybe divided into acute or chronic. Use the definition of Twardowski and Prowant 1996. Classification of normal and diseased exit sites. Perit Dial Int 1996;16(Suppl 3):S32-S50.

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.

Appendix 2

Table 1 Therapy combinations that have been reported

Study ID (author, year)	N	Treatment combinations	Outcome
		Cephalosporin, aminoglycoside, glycopeptide Rx	
(Wong et al 2001) Hong Kong	81	**Group A** Cefepime 2g IP loading dose with dwell > 6/24 then 1 g/day IP x 9 days **Group B** Vancomycin 1g IV day 0 and day 7 with netilmicin 80 mg IP loading dose (dwell > 6 hrs) then netilmicin 40 mg/day IP x 9 days	Similar primary response (82%, 32/39 vs 85%, 29/34 vancomycin and complete cure between cefepime (72%, 28/39) and vancomycin/ netilmicin (76%, 26/34) groups. Note only 1/73 MRSA infections. Not statistically significant.
(Khairullah et al 2002) Detroit, USA	30	**Group A** Gentamicin 40 mg IP daily with vancomycin 1g IP day 1, day 5 or day 8 **Group B** Gentamicin 40 mg IP daily with cefazolin 1g as loading dose (in the first PD bag) then 125 mg/L each exchange for 2 or 3 weeks	Similar response rate vancomycin vs cefazolin, with 16/31 with gram-positive peritonitis treated with vancomycin and 15/31 treated with cefazolin. Mean abdominal pain scores fell to < 1 in both groups, at 96 hrs. No statistically significant difference between the 2 groups. WBC counts decreased rapidly and were < 100/mL at 96 hrs in both treatment groups. No statistically significant difference between the 2 groups.
(Lupo et al 1997) Ljubljana, Slovenia	68	**Group A** Teicoplanin & tobramycin vs **Group B** Cephalothin & tobramycin **Group A** Teicoplanin 400 mg IV plus tobramycin 120 mg IM then teicoplanin 40 mg + tobramycin 10 mg into each dialysis bag. **Group B** Cephalothin 2 g IV plus tobramycin 120 mg IM then cephalothin 500 mg + tobramycin 10 mg into each dialysis bag.	**Clinical cure** 35/37 (94.6%) for teicoplanin and tobramycin 21/28 (75%) for cephalothin plus tobramycin **Bacteriological cure** 23/26 (88.5%) teicoplanin and tobramycin 14/19 (73.7%) cephalothin and tobramycin Not statistically significant
		Cephalosporin, aminoglycoside Rx	

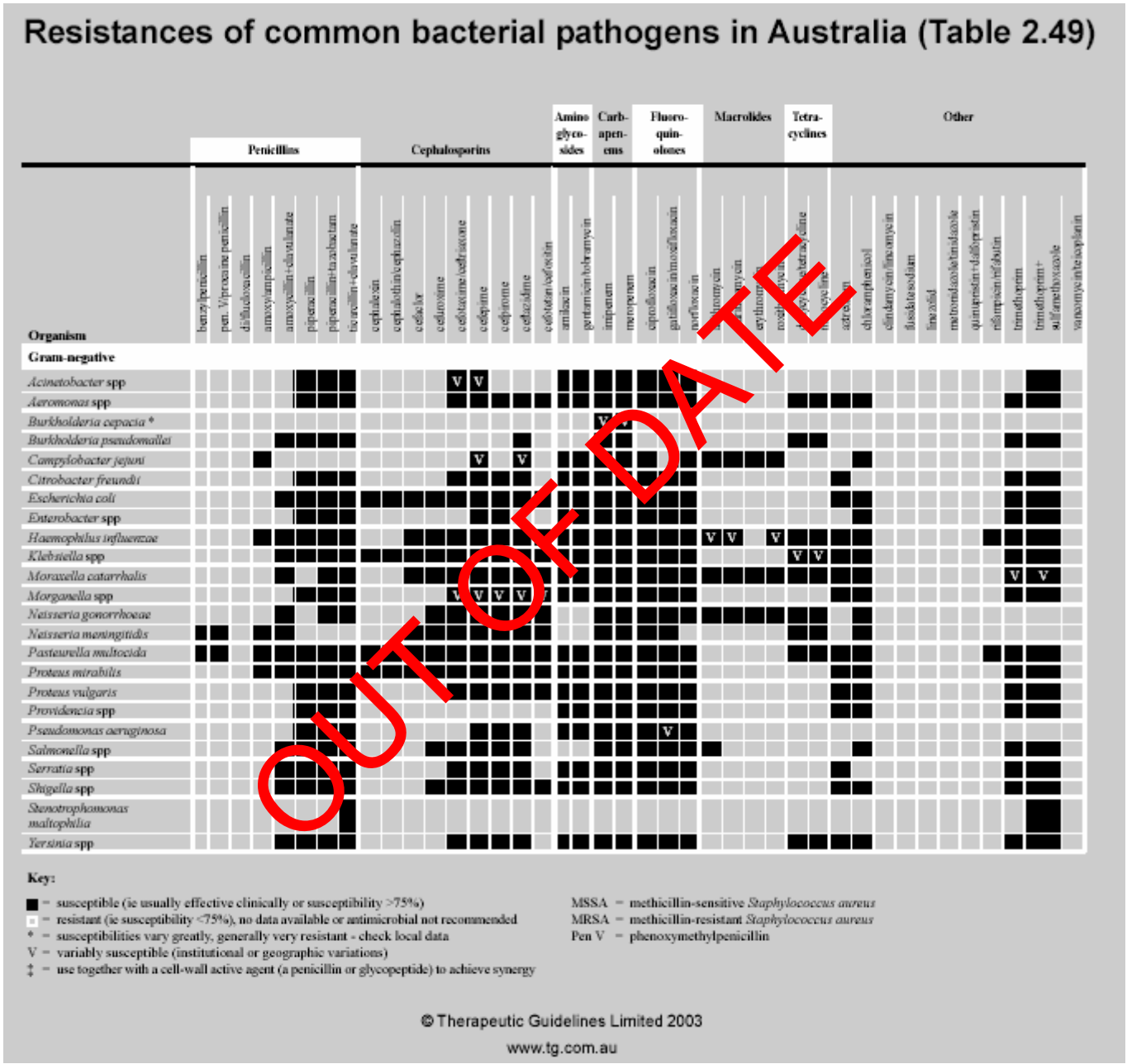
Study ID (author, year)	N	Treatment combinations	Outcome
(Gucek et al 1997) Ljubljana, Slovenia	34	**Group A** Cefazolin (500 mg loading dose then 250 mg/2L maintenance dose) with netilmicin 80-120 mg loading dose, 40 mg/2L x 1 exchange/day maintenance dose) **Group B** Vancomycin (2000mg/5-7 days) & ceftazidime (1000mg loading dose, 250mg/2L maintenance dose) duration 14-28 days	Overall failure of initial therapy: cefazolin/ netilmicin 4/26 (15.6%) vs vancomycin/ ceftazidime 5/26 (19.2%) Not statistically significant
(Flanigan and Lim 1991) Iowa, USA	131	Vancomycin 25 mg/L to all exchanges vs cefazolin 50 mg/L to each exchange	Vancomycin 67/122 (81%) vs 126/141 (67%) cefazolin p = 0.009
		Cephalosporin, quinolone Rx	
(Gucek et al 1993) Ljubljana, Slovenia	23	**Group A** Cefazolin 100 mg IP loading dose then 250 mg every exchange (volume of exchange not given) x 10 days vs **Group B** Ofloxacin p.o. 300 mg then 200 mg daily for average of 10 days	Cefazolin group 13/20 (65%) treatment success (not defined); ofloxacin therapy 12/18 (67%) treatment response Not statistically significant
(de Fijter et al 2001) Multicentre, Netherlands	367	**Group A** Cephradine IP 250 mg/L **Group B** Ciprofloxacin 50 mg/L and rifampicin 50 mg/L	Clinical response (response to treatment and no relapse up to day 42) 37% cephradine vs 63.6% ciprofloxacin & rifampicin p = 0.02
		Cephalosporin, glycopeptide Rx	
(Schaefer et al 1999) Mid European Paediatric PD Study Group, Germany, Czech Republic, Austria, France	152	Group I a and b Ceftazidime with vancomycin Group II a and b Ceftazidime with teicoplanin a = continuously 10 days vancomycin 15 mg/kg body weight teicoplanin 7.5 mg/kg body weight ceftazidime 250 mg/L dialysate with each bag b = intermittent glycopeptide day 0& 7 vancomycin 30 mg/kg body weight teicoplanin 15 mg/kg body weight ceftazidime 500 mg /L dialysate once daily	Note: a paediatric trial. Included CAPD and APD patients Second dose glycopeptide given day 5 instead of 7 if level low at 60 hour assessment In gram positive peritonitis (79%) of cases overall primary success rate was 95% and relapse rates 21%. Residual renal function deteriorated regardless of treatment modality No statistically significant difference between continuous or intermittent vancomycin and teicoplanin

Study ID (author, year)	N	Treatment combinations	Outcome
		Aminoglycoside, glycopeptide, quinolone Rx	
(Cheng et al 1998) Hong Kong	101	Group I p.o. levofloxacin 300 mg daily & IP vancomycin (1gram body weight < 50 kg or 2 grams (body weight > 50 kg) Group II IP netromycin 20 mg/L & IP vancomycin (1gram body weight < 50 kg or 2 grams (body weight > 50 kg) first exchange then maintenance IP netromycin 20 mg/L first bag exchange of the day IP vancomycin 1 or 2 grams on day 7	Primary cure outcome 74.5% p.o. levofloxacin & vancomycin 73.6% for IP netromycin & vancomycin No statistically significant difference Signifcant correlation between in vitro bacterial sensitivity to levofloxacin and history of previous exposure to fluoroquinolones
(Lye et al 1993) Singapore	60	p.o. pefloxacin 400 mg b.d. or IP gentamicin 80 mg then 15 mg/2L. Both had single dose 1g vancomycin Culture & sensitivity at 72 hrs & antibiotics changed	73.3% perfloxacin primary cure vs 80% IP gentamicin Gastrointestinal side effects 20% patients on perfloxacin No statistically significant difference
(Friedland et al 1990) Oxford, UK	40	Ciprofloxacin IP 20 mg/L each bag vs vancomycin 1.5 mg/L each bag and gentamicin 4 mg/L to alternate bags	18/20 ciprofloxacin cured 16/20 vancomycin/gentamicin cured. No statistically significant difference
(Bennett-Jones et al 1990) Stoke on Trent, UK	51	Group I: vancomycin 25 mg/L and gentamicin 8 mg/L reducing to 4 mg/L at 48 hours Group II: ciprofloxacin oral 750 mg t.d.s. for 24 hours then 750 mg b.d.	Primary outcome 45% for ciprofloxacin 65% for vancomycin and gentamicin No statistically significant difference
(Tapson et al 1990) Newcastle upon Tyne, UK	55	Group I Oral ciprofloxacin with each exchange 500 mg if > 70 kg body weight, 250 mg if < 70 kg. Group II Vancomycin 30 mg/2L exchange Netilmycin 30 mg in alternate bags	Primary response 19/25 ciprofloxacin vs 18/25 vancomycin and netilmycin Bacteriological cure 13/25 ciprofloxacin vs 15/25 vancomycin and netilmycin Significance data not provided
		Glycopeptide, quinolone & monobactam	
(Cheng et al 1991) Hong Kong	46	Oral ofloxacin Loading 400 mg then 300 mg daily for 10 days vs IP vancomycin and aztreonam loading vancomycin 500 mg/L then 30 mg/L Loading aztreonam 500 mg/L then 250 mg/L	Outcome 77.3 % ofloxacin vs 87.5% vancomycin and aztreonam No statistically significant difference

Study ID (author, year)	N	Treatment combinations	Outcome
		Glycopeptide, quinolone & carbapenem	
(Anwar et al 1995) Manchester, UK	60	Vancomycin and netilmycin vs imipenem (initially 1 gram in alternate exchange then 1 gram per day)	Imipenem 2 gram dose: outcome similar to vancomycin/netimycin 85% vs 82% but 2/30 patients had seizures Imipenem 1 gram dose: 42% No statistically significant difference
		Glycopeptide, aminoglycoside & carbapenem	
(Merchant et al 1992) Manchester, UK	41	**Group A** IP imipenem/cilastatin (loading & maintence dose 2 gm/day) vs **Group B** IP netilmycin (60 mg(< 60 kg) or 100 mg (> 60 kg) load 40-50 mg/day) & vancomycin (500 mg load then 1[illegible] mg/day). All patients 4 exchanges/day with alternate antibiotic added. Once sensitivity known then cease either vancomycin or netilmycin. Antibiotics for [illegible] days	Complete resolution: Group A (imipenem/cilastatin) 16/17 (94%) Group B netilmicin/vancomycin 15/18 (83.3%) No statistically significant difference

Appendix 3

Figure 1 Resistances of common bacterial pathogens in Australia



Appendix 4: ISPD Recommended antibiotic doses – Adult (Keane et al 2000)

Table 2 Antibiotic Dosing Recommendations for CAPD (Only) Patients With and Without Residual Renal Function[a]

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
Aminoglycosides				
Amikacin	2 mg/kg	Increase all doses by 25%	MD 24 mg	Increase all MD by 25%
Gentamicin	0.6 mg/kg		MD 8 mg	
Netilmicin	0.6 mg/kg		MD 8 mg	
Tobramycin	0.6 mg/kg		MD 8 mg	
Cephalosporins				All LD same as anuric
Cefazolin	15 mg/kg	20 mg/kg	LD 500 mg, MD 125 mg	MD increase by 25%
Cephalothin	15 mg/kg	ND	LD 500 mg, MD 125 mg	MD, ND
Cephradine	15 mg/kg	ND	LD 500 mg, MD 125 mg	MD, ND
Cephalexin	500 mg p.o., q.i.d.	ND	As intermittent	MD, ND
Cefuroxime	400 mg p.o./IV, q.d.	ND	LD 200 mg, MD 100 - 200 mg	MD, ND
Ceftazidime	1000 - 1500 mg	ND	LD 250 mg, MD 125 mg	MD, ND
Ceftizoxime	1000 mg	ND	LD 250 mg, MD 125 mg	MD, ND
Penicillins				All LD same as anuric
Piperacillin	4000 mg IV, b.i.d.	ND	LD 4 g IV, MD 250 mg	MD, ND
Ampicillin	250 - 500 mg p.o., b.i.d.	ND	MD 125 or 250 - 500 mg p.o., b.i.d.	MD, ND
Dicloxacillin	250 - 500 mg p.o., q.i.d.	ND	250 - 500 mg p.o., q.i.d.	MD, ND
Oxacillin	ND	ND	MD 125 mg	MD, ND
Nafcillin	ND	No change	MD 125 mg	MD, no change
Amoxicillin	ND	ND	LD 250 - 500 mg, MD 50 mg	MD, ND
Penicillin G	ND	ND	LD 50 000 U, MD 25 000 U	MD, ND
Quinolones				
Ciprofloxacin	500 mg p.o., b.i.d.	ND	LD 50 mg, MD 25 mg	ND
Ofloxacin	400 mg p.o., then 200 mg p.o., q.d.	ND	As intermittent	ND
Others				
Vancomycin	15 - 30 mg/kg q.5 - 7 d	Increase doses by 25%	MD 30 - 50 mg/L	Increase MD by 25%
Teicoplanin	400 mg IP, b.i.d.	ND	LD 400 mg, MD 40 mg[b]	ND
Aztreonam	ND	ND	LD 1000 mg, MD 250 mg	ND
Clindamycin	ND	ND	LD 300 mg, MD 150 mg	ND
Metronidazole	250 mg p.o., b.i.d.	ND	As intermittent	ND
Rifampin	300 mg p.o., b.i.d.	ND	As intermittent	ND
Antifungals				All LD same as anuric
Amphotericin	NA	NA	MD 1.5 mg	NA
Flucytosine	2 g LD, then 1 g q.d., p.o.	ND	As intermittent	ND
Fluconazole	200 mg q.d.	ND	As intermittent	ND
Itraconazole	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr	100 mg q.12 hr
Antituberculars	Isoniazid 300 mg p.o., q.d. + rifampin 600 mg p.o., q.d. + pyrazinamide 1.5 g p.o., q.d. + pyridoxine 100 mg/d	ND	As intermittent	ND
Combinations				All LD same as anuric
Ampicillin/sulbactam	2 g q.12 hr	ND	LD 1000 mg, MD 100 mg	ND
Trimeth/sulfamethox	320/1600 mg p.o., q.1 - 2 days	ND	LD 320/1600 mg p.o., MD 80/400 mg p.o.	ND

MD = maintenance dose; LD = loading dose; ND = no data; p.o. = oral; q.i.d. = four times per day; IV = intravenous; q.d. = once per day; b.i.d. = twice per day; IP = intraperitoneally; NA = not applicable.

CAPD patients with residual renal function may require increased doses or more frequent dosing, especially when using intermittent regimens. For penicillins: "No change" is for those predominantly hepatically metabolized, or hepatically metabolized and renally excreted; "ND" means no data, but these are predominantly renally excreted, therefore probably an increase in dose by 25% is warranted; "NA" = not applicable, that is, drug is extensively metabolized and therefore there should be no difference in dosing between anuric and nonanuric patients. Anuric = < 100 mL urine/24 hours; nonanuric = > 100 mL/24 hours. These data for CAPD only.

[a] The route of administration is IP unless otherwise specified. The pharmacokinetic data and proposed dosage regimens presented here are based on published literature reviewed through January 2000, or established clinical practice. There is no evidence that mixing different antibiotics in dialysis fluid (except for aminoglycosides and penicillins) is deleterious to the drugs or patients. Do not use the same syringe to mix antibiotics.

[b] This is in each bag × 7 days, then in 2 bags/day × 7 days, and then in 1 bag/day × 7 days.

Table 3 Dosing of antibiotics, by IP Intermittent Route, in Automated PD (These data for APD only)

(Keane et al 2000)

Drug	
Piperacillin[a]	4000 mg IV, b.i.d.
Vancomycin[a]	Loading dose 35 mg/kg
	Maintenance dose 15 mg/kg IP q.d.
Cefazolin[b]	20 mg/kg q.d., in first or second ambulatory dwell
Tobramycin[b]	Loading dose 1.5 mg/kg day 1
	Maintenance dose 0.5 mg/kg q.d., in first or second ambulatory dwell.
Fluconazole	200 mg IP, q.24-48 hr

IP = intraperitoneal; PD = peritoneal dialysis; IV = intravenous; b.i.d. = two times daily; q.d. = every day.
Unless otherwise specified, IP doses to be added to the 1st ambulatory dwell after the automated exchanges.

Appendix 5 ISPD guidelines/recommendations

Consensus Guidelines for the Treatment of Peritonitis in Pediatric Patients Receiving Peritoneal Dialysis

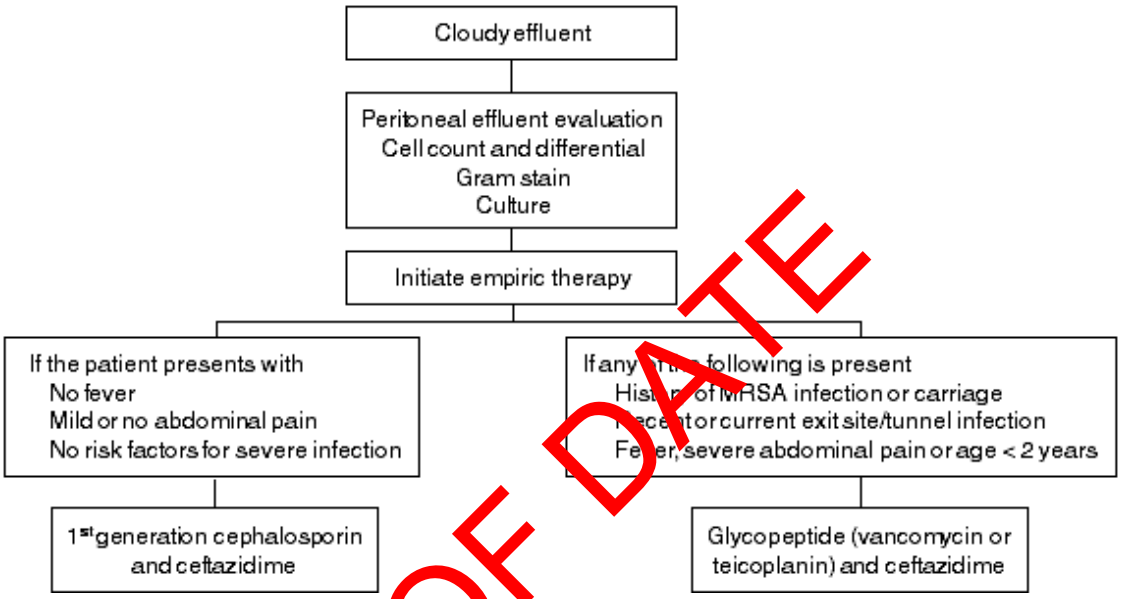


Figure 2 Empiric therapy. MRSA = methicillin-resistant *Staphyloccous aureus*

Table 4 Antibiotic dosing recommendations. Administration should be via intraperitoneal route unless specified otherwise

	Continuous therapy		
	Loading dose[a]	Maintenance dose	Intermittent therapy[b]
Glycopeptides[b]			
Vancomycin	500 mg/L	30 mg/L	30 mg/kg q 5–7 days
Teicoplanin[c]	200 mg/L	20 mg/L	15 mg/kg q 5–7 days
Cephalosporins			
Cefazolin/Cephalothin	250 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefuroxime	200 mg/L	125 mg/L	15 mg/kg q 24 hrs
Cefotaxime	500 mg/L	250 mg/L	30 mg/kg q 24 hrs
Ceftazidime	250 mg/L	125 mg/L	15 mg/kg q 24 hrs
Ceftizoxime	250 mg/L	125 mg/L	〃
Antifungals			
Amphotericin B	1 mg/kg IV	1 mg/kg/day IV	〃
Fluconazole	〃	〃	3–6 mg/kg IP, IV, or PO q 24–48 hrs (max dose 200 mg)
Flucytosine	50 mg/kg IV or PO (max dose 2.0 g)	25–37.5 mg/kg PO q 24 hrs (max dose 1.0 g)	〃
Aminoglycosides[d]			
Amikacin	25 mg/L	12 mg/L	〃
Gentamicin	8 mg/L	4 mg/L	〃
Netilmycin	8 mg/L	4 mg/L	〃
Tobramycin	8 mg/L	4 mg/L	〃
Penicillins[d]			
Azlocillin	500 mg/L	250 mg/L	〃
Piperacillin	〃	250 mg/L	150 mg/kg IV q 12 hrs
Ampicillin	〃	125 mg/L	〃
Oxacillin	〃	125 mg/L	〃
Nafcillin	〃	125 mg/L	〃
Amoxicillin	250–500 mg/L	250 mg/L	〃
Quinolones			
Ciprofloxacin	50 mg/L	25 mg/L	〃
Combinations			
Ampicillin/Sulbactam	1000 mg/L	100 mg/L	〃
Imipenem/Cilastatin	500 mg/L	200 mg/L	〃
Trimethoprim/ Sulfamethoxazole	320/1600 mg/L	80/400 mg/L	〃
Others			
Clindamycin	300 mg/L	150 mg/L	〃
Metronidazole	〃	〃	35–50 mg/kg/day PO in 3 doses
Rifampin	〃	〃	20 mg/kg/day PO (max dose 600 mg/day)
Aztreonam	1000 mg/L	250 mg/L	〃

q = every; IV = intravenously; IP = intraperitoneally; PO = orally.

[a] Loading dose should be administered during a standardized 3– to 6–hour dwell period. Concentration–related loading doses assume usual patient–specific fill volume (*i.e.*, approximately 1100 mL/m^2 body surface area). If a smaller volume is instilled, the concentration must be increased to ensure infusion of an equal mass of antibiotic. Intermittent antibiotic dosing should be administered over ≥ 6 hours in one bag per day for CAPD patients, or during a full fill volume daytime dwell for APD patients, unless otherwise specified.

[b] Accelerated glycopeptide elimination may occur in patients with residual renal function. If intermittent therapy is used in this setting, the second dose of antibiotic should be time–based on a blood level obtained 3–5 days after the initial dose. Redosing should occur when the blood level is < 12 mg/L for vancomycin, or 8 mg/L for teicoplanin. Intermittent therapy is not recommended for patients with residual renal function unless serum drug levels can be monitored in a timely manner.

[c] Teicoplanin is not currently available in the United States.

[d] Aminoglycosides and penicillins should not be mixed in dialysis fluid because of the potential for inactivation.

The therapeutic recommendations provided above are those of the ISPD Advisory Committee on Peritonitis Management in Pediatric Patients and are, in large part, based upon adult experiences.

Table 5 Situations in which catheter removal and subsequent replacement should be strongly considered in pediatric peritoneal dialysis patients.

TABLE 4
Situations in Which Catheter Removal and Subsequent Replacement Should Be Strongly Considered in Pediatric Peritoneal Dialysis Patients

Clinical setting	Antibiotics	Interval between catheter removal and replacement (weeks)
Relapse of treated *Staphylococcus aureus* peritonitis with a *S. aureus* catheter-related infection	2 weeks (intravenous); simultaneous catheter removal and replacement with 3 weeks of antibiotics is possible in patient with low (<100/μL) effluent white blood cell count	2-3
Relapse of treated *Pseudomonas*/*Stenotrophomonas* peritonitis	2 weeks (intravenous)	2-3
Fungal peritonitis	≥ 2 weeks (intravenous/oral)	≥ 2-3
Refractory (at 72-96 hours) peritonitis (any pathogen or culture negative)	2 weeks (intravenous)	2-3
Refractory (at 72-96 hours) anaerobic peritonitis	2 weeks (intravenous)	2-3
Refractory (1 month) catheter exit-site/tunnel infection	2 weeks (intravenous); simultaneous catheter removal and replacement is possible unless infection is severe with purulent discharge	2-3

There are no data in the pediatric or adult literature that permit an evidence-based recommendation with respect to the length of antibiotic treatment following catheter removal. The recommendation of 2-3 weeks takes into consideration the absence of data and the treatment goal of long-term peritoneal membrane function in children. In all cases, recommendations concerning the duration of antibiotic therapy and the timing of catheter replacement may require modification based upon the patient's clinical response.

(Warady et al 2000)

Appendix 6

Table 6 Characteristics of randomised controlled trial evidence

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Anwar et al 1995	60	Randomised controlled clinical trial	Teaching hospital	CAPD patients with peritonitis	Vancomycin and netilmicin i.p. in alternate exchanges (dose depending on body weight)	Imipenem 0.5-1 g in alternate exchanges	0.5	
Bennett-Jones et al 1990	51	Randomised controlled clinical trial	Teaching hospital	CAPD patients with peritonitis	Vancomycin 25 mg/l i.p. and gentamicin 8 mg/l i.p. reducing to 4 mg/L at 48 h; total treatment 10 days	Oral ciprofloxacin 750 mg tds x 24 h reduced to 750 mg bd thereafter; total treatment 10 days	Unclear	
Cheng et al 1991	46	Randomised controlled clinical trial	University	CAPD patients with peritonitis	Oral ofloxacin 400 mg loading dose followed by 200 mg/day x 10 days	Vancomycin plus aztreonam i.p. 500 mg/L loading dose and 30 mg/L and 250 mg/L respectively for maintenance	Unclear	
Cheng et al 1998	101	Randomised controlled clinical trial	Teaching hospital, Multicentre	CAPD patients with peritonitis	Oral levofloxacin 300 mg/d	Netromycin 20 mg/L i.p. and vancomycin i.p. 1 g (body weight <50 kg) or 2 g (body weight >50 kg) in first PD exchange; maintenance 20 mg/L for first bag exchange for netromycin and 1 or 2 g on day 7 for vancomycin; total treatment 10 days	1	
De Fijter et al 2001	367	Randomised controlled clinical trial	Multicentre	CAPD patients; treatment administered if peritonitis occurred	Cephradine 250 mg/L i.p. for 14 days	Ciprofloxacin 50 mg/L i.p. and rifampicin 50 mg/L i.p. for up to 14 days on both antibiotics	1	

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Flanigan and Lim 1991	131	Randomised controlled clinical trial	University	CAPD and CCPD patients; treatment administered when signs or symptoms of peritonitis occurred	Cefazolin 50 mg/L i.p. x 14 days if laboratory results consistent with bacterial peritonitis	Vancomycin 25 mg/L i.p. x 14 days if laboratory results consistent with bacterial peritonitis	1	
Friedland et al 1990	40	Randomised controlled clinical trial	Teaching hospital	CAPD patients with peritonitis	Ciprofloxacin 20 mg/l i.p. x 10 days	Vancomycin 12.5 mg/l to each bag i.p. and gentamicin 4 mg/l to alternate bags i.p. x 10 days	1	
Gucek et al1997	34	Randomised controlled clinical trial	University	CAPD patients with peritonitis	Cefazolin 500 mg load then 250 mg/2L maintenance dose with netilmicin 80-120 mg load then 40 mg/2 L in one exchange/day maintenance dose (14-28 days)	Vancomycin 2000 mg/5-7 days and ceftazidime 1000 mg load, 250 mg/2L maintenance (14-28 days)	Unclear	
Gucek et al 1993	23	Randomised controlled clinical trial	University	CAPD patients with peritonitis	Cefazolin 1000 mg i.p. load, 250 mg i.p. at each exchange x 10 days	Oral ofloxacin 300 mg load, then 200 mg/day x 10 days	Unclear	
Khairullah et al 2002	30	Randomised controlled clinical trial	Teaching hospital	CAPD patients; treatment administered if peritonitis occurred	Vancomycin 1 g/L i.p.	Cefazolin 125 mg/L i.p.	0.5	
Lupo et al 1997	73	Randomised controlled clinical trial	Multicentre	CAPD patients with peritonitis	Teicoplanin 400 mg i.v. load plus tobramycin 120 mg i.m. followed by teicoplanin 0 mg i.p. plus tobramycin 10 mg i.p. in each bag; minimum duration of treatment 15 days	Cephalothin 2 g i.v. load plus tobramycin 120 mg i.m. followed by cephalotin 500 mg i.p. pus tobramycin 10 mg i.p. in each bag; minimum duration of treatment 15 days	1	
Lye et al 1993	60	Randomised controlled clinical trial	University	CAPD patients with peritonitis	Oral pefloxacin 400 mg b.i.d. plus 1 g vancomycin i.p.; duration of treatment 14 days	Gentamicin (load dose 80 mg followed by 15 mg/2L bag) i.p. plus 1 g vancomycin i.p.; duration of treatment 14 days	Unclear	

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Merchant et al 1992	41	Randomised controlled clinical trial	Teaching hospital	CAPD patients with peritonitis	Imipenem/cilastatin i.p. (loading and maintenance dose 2 g/day) Treatment duration 5 days	Netilmicin i.p. (60 mg if <60 kg or 100 mg if > 60 kg load, then 40-50 mg/day and vancomycin 500 mg load, then 100 mg/day; treatment duration 5 days	Unclear	
Schaefer et al 1999	152	Randomised controlled clinical trial	Multicentre	CAPD and APD patients with peritonitis	Continuous treatment with vancomycin/ceftazidime or teicoplanin/ceftazidime (i.p. load 15 mg/kg body weight for vancomycin, 7.5 mg/kg for teicoplanin, 250 mg/L for ceftazidime)	Intermittent treatment with vancomycin 30 mg/kg or teicoplanin 15 mg/kg and ceftazidime 500 mg/L	19	
Tapson et al 1990	35	Randomised controlled clinical trial	Teaching hospital	CAPD patients; treatment administered in 50 episodes of peritonitis	Oral ciprofloxacin 500 mg bd if body weight >70 kg or 250 mg qds if body weight <70 kg for 2 days, then modification of treatment according to sensitivities of isolates; treatment duration 10 days	Vancomycin 30 mg i.p. plus netilmicin 30 mg i.p. in alternate bags for 2 days, then modification of treatment according to sensitivities of isolates; treatment duration 10 days	1	
Wong et al 2001	81	Randomised controlled clinical trial	Teaching hospital	CAPD patients with symptoms suggestive of peritonitis	Cefepime 2 g i.p. load, then 1 g/d i.p. for 9 or more consecutive days	Vancomycin 1 g i.v. and netilmicin 80 mg i.p. load then 1 g i.v. day 7 and netilmicin 40 mg/d i.p. for 9 or more consecutive days	1	

Table 7 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Anwar et al 1995	Unclear	No	No	No	No	1.6
Bennett-Jones et al 1990	Unclear	No	No	No	No	5.9
Cheng et al 1991	Unclear	No	No	No	No	2.2
Cheng et al 1998	Unclear	No	No	No	Yes	0.0
De Fijter et al 2001	Unclear	No	No	No	No	1.0
Flanigan and Lim 1991	Inadequate	No	No	No	Yes	Unclear
Friedland et al 1990	Unclear	No	No	No	Yes	0.0
Gucek et al 1997	Unclear	No	No	No	No	0.0
Gucek et al 1993	Unclear	No	No	No	Yes	0.0
Khairullah et al 2002	Unclear	No	No	No	Yes	0.0
Lupo et al 1997	Unclear	No	No	No	No	6.3
Lye et al 1993	Unclear	No	No	No	Yes	0.0
Merchant et al 1992	Unclear	No	No	No	No	19.0
Schaefer et al 1999	Unclear	No	No	No	No	Unclear
Tapson et al 1990	Unclear	No	No	No	No	Unclear
Wong et al 2001	Unclear	No	No	No	No	9.8

Table 8 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Anwar et al 1995	Withdrawal of study drug due to adverse events	1/30	2/30	0.50 (0.05 to 5.22)	-0.03 (-0.14 to 0.08)
	Fungal peritonitis	1/30	0/30	3.0 (0.13 to 70.83)	0.03 (-0.05 to 0.12)
	Seizures	0/30	2/30	0.20 (0.01 to 4.00)	-0.07 (-0.17 to 0.04)
Bennett-Jones et al 1990	Successful treatment of peritonitis	17/26	10/22	1.44 (0.84 to 2.46)	0.20 (-0.08 to 0.48)
Cheng et al 1991	Successful treatment of peritonitis	18/23*	22/25*	0.89 (0.69 to 1.15)	-0.10 (-0.31 to 0.11)
Cheng et al 1998	Cure rate	35/47	39/54	1.03 (0.81 to 1.30)	0.02 (-0.15 to 0.20)
	Failure rate	7/47	10/54	0.80 (0.33 to 1.95)	-0.04 (-0.18 to 0.11)
	Relapse rate	5/47	4/54	1.44 (0.41 to 5.04)	0.03 (-0.08 to 0.14)
De Fijter et al 2001	Bacteriological eradication	16/54	26/44	0.50 (0.31 to 0.81)	-0.29 (-0.48 to -0.11)
Flanigan and Lim 1991	Bacteriological eradication*	57/82	127/181	0.99 (0.83 to 1.18)	-0.01 (-0.13 to 0.11)
Friedland et al 1990	Cure rate	18/20	16/20	1.13 (0.86 to 1.46)	0.10 (-0.12 to 0.32)
Gucek et al 1997	Treatment failure†	4/26	5/26	0.80 (0.24 to 2.65	-0.04 (-0.24 to 0.17)
Gucek et al 1993	Treatment failure†	7/20	6/18	1.05 (0.43 to 2.54)	0.02 (-0.29 to 0.32)
Khairullah et al 2002	Peritonitis relapse in patients with gram positive peritonitis	3/18	2/12	1.00 (0.20 to 5.12)	0.00 (-0.27 to 0.27)
Lupo et al 1997	Cure rate	35/37	21/28	1.26 (1.00 to 1.58)	0.20 (0.02 to 0.37)
Lye et al 1993	Cure rate	22/30	24/30	0.92 (0.69 to 1.21)	-0.07 (-0.28 to 0.15)
Merchant et al 1992	Cure rate	16/17	15/20	1.25 (0.95 to 1.66)	0.19 (-0.03 to 0.41)
Schaefer et al 1999	Treatment failure	NA†	NA†	NA†	NA†
Tapson et al 1990	Cure rate for peritonitis episodes†	19/25	18/25	1.06 (0.76 to 1.47)	0.04 (-0.20 to 0.28)
Wong et al 2001	Cure rate	28/39	26/34	0.94 (0.72 to 1.23)	-0.05 (-0.25 to 0.15)

* Relates to number of episodes of eradication of peritonitis over the total number of episodes of peritonitis, as this study randomised peritonitis episodes (rather than patients with peritonitis) to the treatment.
† NA = raw data not available for calculation of these estimates. Authors report that the risk of treatment failure according to the treatment did not differ between the continuously treated patients (RR 1.17, 95% CI 0.51 to 2.67) and the intermittently treated patients (RR 0.83, 95% CI 0.30 to 2.27).