

Peritoneal dialysis associated infections: An update on diagnosis and management

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Abstract

Peritoneal dialysis (PD) is associated with a high risk of infection of the peritoneum, subcutaneous tunnel and catheter exit site. Although quality standards demand an infection rate < 0.67 episodes/patient/year on dialysis, the reported overall rate of PD associated infection is 0.24-1.66 episodes/patient/year. It is estimated that for every 0.5-per-year increase in peritonitis rate, the risk of death increases by 4% and 18% of the episodes resulted in removal of the PD catheter and 3.5% resulted in death. Improved diagnosis, increased awareness of causative agents in addition to other measures will facilitate prompt management of PD associated infection and salvage of PD modality. The aims of this review are to determine the magnitude of the infection problem, identify possible risk factors and provide an update on the diagnosis and management of PD associated infection. Gram-positive cocci such as *Staphylococcus epidermidis*, other coagulase negative staphylococci, and *Staphylococcus aureus* (*S. aureus*) are the most frequent aetiological agents of PD-associated peritonitis worldwide. Empiric antibiotic therapy must cover both gram-positive and gram-negative organisms. However, use of systemic vancomycin and ciprofloxacin administration for example, is a simple and

efficient first-line protocol antibiotic therapy for PD peritonitis - success rate of 77%. However, for fungal PD peritonitis, it is now standard practice to remove PD catheters in addition to antifungal treatment for a minimum of 3 wk and subsequent transfer to hemodialysis. To prevent PD associated infections, prophylactic antibiotic administration before catheter placement, adequate patient training, exit-site care, and treatment for *S. aureus* nasal carriage should be employed. Mupirocin treatment can reduce the risk of exit site infection by 46% but it cannot decrease the risk of peritonitis due to all organisms.

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Key words: Exit site infection; Peritonitis; Tunnel infection; Polymicrobial infection; Catheter removal; Dialysis modality change; Fungal peritonitis; Sclerosing encapsulating peritonitis; Peritoneal dialysis

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INTRODUCTION

All dialysis treatments include a certain risk of infection because of the decreased immune defenses of patients in established renal failure (ERF) and because dialysis techniques increase the potential of microbial contamination. Peritoneal dialysis (PD), and in particular continuous ambulatory PD (CAPD), is associated with a high risk of infection of the peritoneum, subcutaneous tunnel and catheter exit site^[1]. Exit site infection (ESI) and tunnel

infection (TI) *per se* pose little risks but the possibility of developing PD peritonitis demands careful attendance to these problems. It is estimated that 12% of cases of ESI and TI result in PD peritonitis^[2]. As many as 15%-50% of ERF patients are on PD, but recurrent or prolonged peritonitis may cause technique failure in PD.

The majority of catheter related problems are of an infection nature - mainly represented by peritonitis (61%); ESI and TI (23%); catheter obstruction, dislocation and leakage making up the rest. Peritonitis can be associated with severe pain leading to hospitalisation, catheter loss, and a risk of death; and it therefore continues to be a serious complication for PD patients^[3-6]. PD peritonitis usually has an excellent prognosis with resolution within days but it can lead occasionally to the much dreaded sclerosing encapsulated peritonitis (SEP).

The incidence of peritonitis has markedly decreased since the late 1980s, but the infection remains a significant complication of chronic PD. Very low rates of peritonitis in a program are possible if close attention is paid to the causes of peritonitis and protocols implemented to reduce the risk of infection^[3]. Although several organisms are involved in causing PD associated infections (PDAI), coagulase negative staphylococci (CoNS) appear to be the most common^[7]. However, rare forms of PD infection, for example, rapidly growing non tuberculous mycobacterium are associated with catheter loss (80%) and significant mortality (40%)^[8].

Action to decrease the risk of PDAI should start in the pre-catheter insertion phase. In order to obtain a reduction of the complications, achieve prolonged catheter duration and a better quality of life for PD patients, the surgical technique requires strict adherence to a standardised procedure and a dedicated team^[4]. Improved diagnosis, increased awareness of causative agents in addition to other measures will facilitate prompt management of PDAI and salvage of PD modality. The aims of this review are to determine the magnitude of the infection problem, identify possible risk factors and provide an update on the diagnosis and management of PDAI.

EPIDEMIOLOGY

Peritonitis continues to be the most frequent cause of PD failure, with an important impact on patient mortality. Peritonitis risk is not evenly spread across the PD population or programs. During a median follow-up of 1.9 years, about 50% a large cohort of 7401 PD patients aged 65-100 years had at least one infection-related hospitalisation^[6]. In another series, catheter-related peritonitis occurred in about 20% of patients and ESI was responsible for catheter removal in more than one-fifth of cases^[9]. The infection may be caused by the surgical procedure to insert a PD catheter or the conduct of PD. Over a 4-year period in one institution, the complications seen with 384 catheters inserted into 319 patients (95% were in ERF) by 22 different operators were 24 cases (6.3%) of ESI, 14 (3.6%) of culture-proven wound infection and 11 (2.9%)

post-insertion peritonitis^[10]. The UK Renal Association standard for peritonitis is one episode per 18 mo in adults (0.67 episodes per patient-year)^[11]. The overall rate of PDAI is between 0.24 to 1.66 episodes per patient years on dialysis (Table 1)^[8,11-25]. Even though technological advancements such as use of double-bag, disconnect and other connector systems have continuously reduced peritonitis rates worldwide, the extremely low rates of infection reported in Asia (Table 1) is difficult to explain, prompting the belief that Asian patients are probably different from their Western counterparts. Possible reasons include a relatively younger patient group compared to the West, increased PD education as the modality is more prevalent in Asia than in the West. Though the reasons for the outstanding results reported by Han *et al*^[25] were not fully explained, reducing PDAI would improve PD technique survival.

Peritonitis remains a leading complication of PD. Around 18% of the infection-related mortality in PD patients is the result of peritonitis. Although less than 4% of peritonitis episodes result in death, peritonitis is a "contributing factor" to death in 16% of deaths on PD. In addition, severe and prolonged peritonitis can lead to peritoneal membrane failure and peritonitis is probably the most common cause of technique failure in PD^[26]. It is estimated that for every 0.5-per-year increase in peritonitis rate, the risk of death increases by 4%^[27] and 18% of the episodes resulted in removal of the PD catheter and 3.5% resulted in death^[28,29].

Organisms

Gram-positive cocci such as *Staphylococcus epidermidis* (*S. epidermidis*), other CoNS, and *Staphylococcus aureus* (*S. aureus*) are the most frequent aetiological agents of PD-associated peritonitis worldwide^[1,2,8,30]. The spectrum of organisms associated with PD peritonitis varies geographically as does the rate of culture negative episodes^[30,31]. For example, Gram-negative (G-ve) PD peritonitis is more frequent than G+ve peritonitis in the CAPD population in India and is associated with worse outcome^[19]. There was no significant difference in causative agents between home and hospital acquired peritonitis^[32]. Though a wide spectrum of organisms are responsible for PDAI (Table 2)^[8,12,16,31,33-45], it must be borne in mind that a significant proportion of the infections are culture negative - about 20% to 32.5%^[12,31]. As there is a culture-negative rate of 20%, it is recommended by the Renal Association that appropriate laboratory samples are obtained before commencement of antibiotics^[11].

Enterococcal peritonitis though uncommon, is a serious complication of PD. A review of 116 episodes of enterococcal peritonitis in 103 individuals showed its tendency to be associated with older age, renovascular disease and coronary artery disease. Polymicrobial peritonitis was significantly more common when an enterococcus species was isolated than when it was not (45% *vs* 5%, respectively)^[18]. It is also associated with increased risk of catheter loss, change in dialysis modality and death. In

Table 1 Incidence and spectrum of peritonitis in peritoneal dialysis patients

Ref.	No.	Infection rate (episodes/ patient-year)	Organisms	Comments
Lobo <i>et al</i> ^[12] 2003-2007	330	0.42	<i>S. aureus</i> 27.5% <i>E. coli</i> 13.4% Culture negative 32.5%	Brazil Hypoalbuminaemia a risk factor
Shyr <i>et al</i> ^[13] 1990-1993	55	0.56 0.36 (ESI)		Experience surgeon may be a factor preventing infection
Cleper <i>et al</i> ^[14] 1997-2007	29	1.66	<i>S. aureus</i> 32.5% Pseudomonas 16%	Children; modality change in 18%
Shigidi <i>et al</i> ^[15] 2003-2007	241	0.24 ± 0.1	<i>S. aureus</i> 21% <i>E. coli</i> 9% Culture negative 28%	Qatar; Catheter loss 19%; Mortality 3% due to candida and pseudomonas peritonitis
Kofteridis <i>et al</i> ^[16] 1990-2007	82	0.89	G+ve 42% G-ve 19% Polymicrobial 5% Fungal 4%	Greece
Freitas <i>et al</i> ^[17] 2005-2008	137	0.31 (ESI)	G+ve 56% G-ve 27% Pseudomonas Fungi	Cure rate 96% Catheter loss in 3 patients; peritonitis in two
Edey <i>et al</i> ^[18] 2003-2006	103	116 episodes in 103 pts	Polymicrobial	Enterococci peritonitis is associated with catheter loss
Prasad <i>et al</i> ^[19] 1993-2001	168	0.63	G-ve 60% G+ 40% Polymicrobial Fungal	G-ve peritonitis has worse outcome than G+ve
Boehm <i>et al</i> ^[20] 1994-2003	30	0.82		USA and European data
Goffin <i>et al</i> ^[21] 1991-2000	101	0.41	G+ve 51.5% G-ve 27.7% Polymicrobial 13% Culture negative 7.9%	
Nessim <i>et al</i> ^[22] 1996-2005	4247	0.36		Double cuff catheters had better results
Tan <i>et al</i> ^[23]	64	0.23		Singapore
Li <i>et al</i> ^[24]	110	0.29		Hong Kong
Han <i>et al</i> ^[25] 1981-2005	2301	0.38	G+ve 42.6% G-ve 17.0% Fungal 2.1% Culture negative 37.3%	Korea Peritonitis rates fell from 0.57 in earlier to 0.29 in latter period

S. aureus: *Staphylococcus aureus*; *E. coli*: *Escherichia coli*.

a 5-year retrospective series from a single-centre multi-ethnic Asian population, rapidly growing non tuberculous mycobacterium constituted 3% of all culture-positive ESI and PD peritonitis^[8]. Mycobacterial peritonitis can be caused by *Mycobacterium tuberculosis* or non tuberculous mycobacteria, such as *Mycobacterium fortuitum*, *Mycobacterium avium*, *Mycobacterium abscessus*, and *Mycobacterium chelonae*. The incidence of tuberculous peritonitis is higher in Asia than elsewhere probably because the infection is endemic in their population. It is important to differentiate patients with miliary tuberculosis, whose peritonitis is part of the disseminated disease, from those with isolated tuberculous peritonitis without extraperitoneal infection.

Fungal peritonitis is usually preceded by multiple episodes of bacterial peritonitis and poses a significant risk of dropout of the patient from the PD program^[37]. Fungal peritonitis is relatively uncommon and is caused mainly by *Candida albicans*, entering the peritoneal cavity via the catheter lumen or vagina in females. Kazancioglu *et al*^[38] reported 15 cases in a 10-year period with a mean

duration of dialysis from the initiation of treatment until the development of fungal peritonitis of 41 mo^[38]. *Candida* species were the most common pathogens and *Candida albicans* was the most frequent, but high prevalence of *Candida parapsilosis* has been observed in the last decade^[36,46].

Risk factors for PDAI

The incidence of chronic PD-associated peritonitis has decreased largely due to technical advances and the identification and control of risk factors such as ESI, poor technique of catheter insertion and use, colonisation with *S. aureus* and lack of patient motivation. Treatment of bacterial colonisation by current antimicrobial protocols may not permit adequate dosing to penetrate bacterial biofilm and be a reason for recurrent or repeat episodes of peritonitis^[11]. The risk factors for infection include extremes of age, female sex, diabetes, heart failure, pulmonary disease, anaemia and low serum albumin level^[6,47,48]. A retrospective analysis of 330 patients over

Table 2 Organisms causing peritoneal dialysis associated infections

Organism	Comments	Ref.
Gram-positive cocci	Commonest cause of PDAI	Gupta <i>et al</i> ^[30] ; Fedorowsky <i>et al</i> ^[33] , Renaud <i>et al</i> ^[8]
<i>Staphylococcus epidermidis</i>		
<i>Staphylococcus aureus</i>		
<i>A and β-haemolytic Streptococcus</i>		
Micrococci		
Gram-negative	Recent change from HD to PD	Gupta <i>et al</i> ^[30] ; Chang <i>et al</i> ^[34] , Lobo <i>et al</i> ^[12] ; Koffleridis <i>et al</i> ^[16] , Krishnan <i>et al</i> ^[35]
Enterobacteriaceae		
<i>Pseudomonas aeruginosa</i>		
VRE		
<i>Escherichia coli</i>		
<i>Klebsiella oxytoca</i>	Polymicrobial/catheter loss/transfer to HD	García-Agudo <i>et al</i> ^[36] , Predari <i>et al</i> ^[37] ; Kazancioglu <i>et al</i> ^[38] , Troidle <i>et al</i> ^[31]
<i>Acinetobacter sp</i>		
<i>Serratia marcescens</i>		
Enterococci		
Fungi		
<i>Candida albicans</i>	India and mainly developing economies	Troidle <i>et al</i> ^[31]
<i>Candida parapsilosis</i>		
<i>Candida glabrata</i>		
<i>Neosartorya hirsutiae</i>		
<i>Aspergillus fumigatus</i>		
Anaerobes	More common in immunosuppressed patients	Lunde <i>et al</i> ^[39] ; Chan <i>et al</i> ^[40] , Vera <i>et al</i> ^[41] ; Renaud <i>et al</i> ^[8] , Mendoza-Guevara <i>et al</i> ^[42] , Byrd <i>et al</i> ^[43] ; Kimura <i>et al</i> ^[44]
Unusual		
<i>Mycobacteria sp</i>		
Rapidly growing nontuberculous <i>Mycobacteria</i>		
<i>Listeria monocytogenes</i>		
<i>Serratia marcescens</i>	May be confused with peritoneal macrophages or lymphocytes	Tilak <i>et al</i> ^[45]
<i>Bordetella bronchiseptica</i>		
<i>Corynebacterium ulcerans</i>		
<i>Acanthamoeba</i>		

PD: Peritoneal dialysis PDAI: PD associated infections.

a 5-year period identified hypoalbuminaemia, inadequate education and ESI as significant risk factors for PD associated peritonitis but failed to confirm gender, age, family income, diabetes mellitus, type of PD treatment, type of catheter and its surgical implant as risk factors for PDAI^[12]. In another series of 141 PD patients in which 8 patients died and 40 patients had major cardiovascular or infection events, the malnutrition-inflammation score (closely associated with the Charlson comorbidity index) was shown to be an independent predictor of cardiovascular and infection events^[49].

Age

The pattern of PDAI in children is different from adults. Yinnon *et al*^[50] isolated 481 organisms from 378 peritoneal fluid specimens collected from 135 patients (45 children, 90 adults). The number of different organisms as well as the total number of isolates per patient were significantly greater in children than in adults. After *S. epidermidis*, *S. aureus* was the most frequently isolated organism, occurring in 18% of episodes in adults and 12% in children ($P < 0.01$). CAPD-associated peritonitis occurs significantly more often in children than adults^[50]. Recent US registry data and a European multicenter study described the increased risk of peritonitis in young children on PD. Boehm *et al*^[20] identified six risk factors in a univariate analysis (age, APD treatment, ESI, low urinary volume, low residual GFR and low normalised protein

catabolic rate), which were significantly correlated with two or more of the outcome indices, but only ESI and residual urine volume were strong independent predictors of PDAI on multivariate analysis. Other risk factors for peritonitis in children include: first infection within less than 6 mo from starting treatment, *Pseudomonas* exit-site colonisation, and contaminating conditions (gastrostomies, diaper use, enuresis) and age < 5 years^[14].

Type of PD catheter

A review of 298 patients from 49 European centres showed that the type of catheter and the frequency of dressing changes were associated with a high infection risk^[51]. Though it has been hypothesized that double-cuff catheters might be superior to single-cuff catheters in preventing peritonitis caused by periluminal entry of organisms, no catheter type has consistently been shown to reduce the peritonitis risk. The association between the number of catheter cuffs and peritonitis was tested using data collected in the multicentre Canadian Baxter Peritonitis Organism Exit-Sites Tunnel Infections project. There were 2555 peritonitis episodes in 4247 incident patients (0.364 per dialysis year at risk) with double-cuff catheter use being associated with a lower peritonitis rate ratio (RR) = 0.90, 95% CI: 0.80-1.01, $P = 0.08$. This trend was largely due to a decreased *S. aureus* peritonitis rate in those with a double-cuff catheter (RR = 0.46, 95% CI: 0.33-0.64, $P < 0.001$)^[22].

Lo *et al*^[52] compared outcomes for catheters with different configurations: conventional straight, swan-neck straight tip, and swan-neck curled tip. They randomized 93 new CAPD patients without prior PD catheter insertion to receive a conventional straight, double-cuffed catheter, a swan-neck straight catheter, or a swan-neck curled tip catheter in 2:1:1 ratio. Swan-neck catheters were associated with a slightly better ESI rate, but had a high migration rate. The Cochrane review of 17 trials (1089 patients) did not find any significant difference in the risk of peritonitis, peritonitis rate, ESI or TI, or catheter removal/replacement between straight *vs* coiled intraperitoneal portion catheters^[53].

Method of PD catheter insertion

Effective immobilisation of the peritoneal catheter has repeatedly been associated with positive catheter-related outcomes. A single-center retrospective community study compared infectious complication rates for peritoneal catheters that exit from a highly mobile structure (the abdomen) with rates for catheters exiting from a structure with minimal associated motion (the chest). Patients undergoing catheter implantation were divided into two groups: 22 patients with 23 abdominal catheters; 21 patients with 22 presternal catheters. For abdominal and presternal catheters respectively, the rates of exit-site infection were 0.22 episodes/patient-year and 0.11 episodes/patient-year, and the incidences of peritonitis were 0.41 episodes/patient-year and 0.27 episodes/patient-year with removal of two abdominal catheters. Though the rates were not significantly different, the more effective catheter immobilisation on the chest may lower the frequency of infectious complications^[54].

An alternative peritoneal catheter exit-site location is sometimes needed in patients with obesity, floppy skin folds, intestinal stomas, urinary and fecal incontinence, and chronic yeast intertrigo. Two-piece extended catheters permit remote exit-site locations away from problematic abdominal conditions. The effect on clinical outcomes by remotely locating catheter exit sites to the upper abdomen or chest was compared to conventional lower abdominal sites. In a non randomised design, peritoneal access was established with 158 extended catheters and 270 conventional catheters based upon body habitus and special clinical needs. Time until first ESI was longer for extended catheters ($P = 0.03$) but there was no difference in ESI, TI and peritonitis rates^[55]. Guidelines for optimal PD access support both downward and lateral exit-site directions. Crabtree and co-workers^[56] conducted a prospective study comparing infectious and mechanical complications between 85 catheters with a preformed arcuate bend to produce a downward exit site and 93 catheters with a straight intercuff segment configured to create a lateral exit site. There were no differences in rates (episodes/patient-year) of ESI, TI, peritonitis, or catheter loss for downward and lateral exit sites. Several PD catheter-related interventions (catheter designs, surgical insertion approaches, and connection methods)

have been purported to reduce the risk of peritonitis in PD. Strippoli *et al*^[57] conducted a systematic review of randomised trials (37 eligible trials and 2822 patients) of catheter types and related interventions in PD using The Cochrane CENTRAL Registry, MEDLINE, EMBASE, and reference lists. Their review demonstrates that of all catheter-related interventions designed to prevent peritonitis in PD, only disconnect (twin-bag and Y-set) systems have been proved to be effective.

Type of PD Solution

The acidity and high glucose degradation product concentration of standard dialysates is thought to inhibit the function of polymorphonuclear leucocytes and macrophages within the peritoneal cavity^[58]. The newer, more biocompatible solutions such as bicarbonate/lactate (have a neutral pH and a low concentration of glucose degradation products) are thought to be less cytotoxic to mesothelial cells and to improve the function and viability of peritoneal membrane and cells associated with host defence^[59]. Ahmad *et al*^[58] reported a significantly lower peritonitis rate of 1 per 52.5 patient-months (0.29 episodes per patient-year) in patients using biocompatible solutions compared to those using standard lactate (1 per 26.9 patient-months or 0.47 episodes per patient-year) - $P = 0.0179$. However, the results from clinical trials are conflicting. Kim *et al*^[60] reported a higher peritonitis rate in the group using biocompatible solutions compared to those using conventional solutions (0.24 episodes per patient-year *vs* 0.09 episodes per patient-year) but others demonstrated no significant difference in rates^[61,62]. Srivastava and co-workers^[63] conducted a prospective randomised controlled open label trial of incident patients starting PD comparing the use of biocompatible and conventional solutions. Of a total of 267 patients entered into their study, 139 used biocompatible whereas 128 used conventional solutions. Neither the peritonitis-free survival (23.1 mo *vs* 26.7 mo) nor the peritonitis rates (1 per 34.7 patient-months *vs* 1 per 31.5 patient-months) between those using biocompatible and conventional solutions respectively were significantly different ($P = 0.61$). This study though representing the largest randomised study to date comparing different PD solutions is probably limited by statistical power in producing conclusive evidence of the beneficial effect of biocompatible dialysates on PD peritonitis.

Nasal carriage of bacteria

Surveillance for nasal methicillin resistant *S. aureus* (MRSA) carriage and infection among dialysis patients, healthcare workers and their family members in a dialysis centre was prospectively undertaken using molecular typing to determine epidemiological relationship. Among 1687 samples collected, MRSA colonisation rates were 2.41% (2/83) for PD patients and 2.36% (12/509) for haemodialysis patients. Five (5/14) subjects subsequently had MRSA infection. The clinical MRSA isolates had the same molecular type as the colonized strains of the same person,

indicating MRSA colonisation preceded clinical infection. Monitoring and eradication of MRSA from patients, health care workers and their family members should be considered to prevent continuous spread between health-care facilities and the community^[64]. Luzar *et al*^[65] studied 140 consecutive patients beginning CAPD at one of seven hospitals to assess the relation of the nasal carriage of *S. aureus* to subsequent catheter-exit-site infection or peritonitis. The carriers of *S. aureus* had a significantly higher rate of exit-site infection than the noncarriers (0.40 vs 0.10 episode per year, $P = 0.012$).

Amato *et al*^[66] found 17 of 27 patients (63%) carried an identical strain of staphylococcus species causing peritonitis being present in the exit site, nose, or nails. The most frequently colonised site with strains identical to that causing the peritonitis episode was the catheter exit site, followed by nose and nails. Aktaş *et al*^[67] demonstrated a clear association between *S. aureus* carriage and *S. aureus* infection in PD patients. Determining the *S. aureus* carriage state of patients undergoing dialysis can help guide infection prevention measures and treatment strategies^[65,67]. A Cochrane review of randomised controlled trials (19 trials and 1949 patients) to evaluate what evidence supports the use of different antimicrobial approaches to prevent peritonitis in PD patients demonstrates that nasal mupirocin reduces ESI/TI but not peritonitis^[68].

Developing economy

PD is eminently suited to developing countries due to its relative cheapness, lack of HD facilities and unsatisfactory road network making access to HD centres problematic. However, the wide application of PD is hampered by infection. Hot tropical climate and poor hygiene among patients is thought to be responsible for the high rate of peritonitis^[48]. The spectrum of bacterial peritonitis in patients on CAPD in India may be different from that seen in developed countries because of differences in culture and in social, environmental, financial, and educational status^[19].

DIAGNOSIS OF INFECTION

ESI and TI

An exit-site infection is defined by the presence of purulent drainage, with or without erythema of the skin at the catheter-skin interface. Pericatheter erythema without purulent discharge 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^[26].

TI may present as erythema, edema, or tenderness over the subcutaneous pathway but is often clinically occult, as shown by ultrasound studies^[69]. TI usually occurs in the presence of an ESI but rarely occurs alone. *S. aureus* and *Pseudomonas aeruginosa* ESI are often associated with concomitant TI and are the organisms that most often result in catheter infection-related peritonitis.

Any purulent discharge from the exit site should be swabbed for culture and Gram-stain in addition to culture of the peritoneal dialysate. The extent of involvement of the subcutaneous PD catheter tract is of major importance in the management of PD peritonitis. The diagnosis of these infections as well as the more sinister TI is based mainly on clinical signs. Korzets *et al*^[70] examined the usefulness of ultrasound examination (US) of the catheter tract in delineating catheter-related (exit-site and tunnel) infections, and their relationship to each other and to peritonitis. They regarded the findings as positive if an area of hypoechogenicity (indicative of fluid collection) > 2 mm in width along any portion of the catheter tract. They performed a total of 56 US (26 episodes of peritonitis, four TI, 13 ESI and 13 controls) and reported that majority of the collections (13/16 in episodes of peritonitis and 5/8 ESI) were localised to the internal cuff region^[70]. Other imaging techniques like positron emission tomography scanning and scintigraphy, may be useful for diagnosing and managing PD catheter infections^[71].

PD peritonitis

PD patients presenting with cloudy effluent should be presumed to have peritonitis and confirmed by obtaining effluent cell count > 100 WBC/mL, differential count, culture and Gram staining^[72-74]. Peritonitis should always be included in the differential diagnosis of any PD patient with abdominal pain, even if the effluent is clear, as a small percentage of patients present in this fashion. Other causes, such as constipation, renal or biliary colic, peptic ulcer disease, pancreatitis, and acute intestinal perforation, should also be investigated in the PD patient with abdominal pain and clear fluid. The degree of pain is somewhat organism specific (e.g., generally less with CoNS and greater with streptococcus, G-ve rods, *S. aureus*) and can help guide the clinician in the decision to admit or treat as an outpatient^[26].

The diagnosis of peritonitis in patients on automated PD with night dwell (dry daytime) is slightly more cumbersome than in those on CAPD. The International Society for Peritoneal Dialysis recommends using the proportion of polymorphonuclear cells rather than the absolute numbers (> 50% is diagnostic even if the cell count is < 100/ μ L). Alternatively, the clinician is advised to instil one litre of dialysate, draining it after 1-2 h to check for turbidity, cell count/differential count and culture. Sometimes a second exchange with a dwell time of at least 2 h is required to clinch the diagnosis^[26].

Given the immunocompromised state of most patients on PD, a high index of suspicion is required for making a timely diagnosis. Any patient on PD presenting with evidence of infection (fever, peripheral leucocytosis) without an obvious cause should have aspirate cultures done even if the aspirate is clear and abdominal pain is absent^[75]. Other causes of abdominal pain should be investigated in PD patients with clear fluid. A cloudy effluent does not always equate to PD peritonitis as this may

be caused by chemical inflammation, haemoperitoneum, eosinophilia of the effluent, malignancy, chylous effluent or specimen taken from “dry” abdomen^[26,74].

Correct microbiological culturing of peritoneal effluent is of great importance in establishing the micro-organism(s) 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^[30,37]. Concentration methods not only facilitate correct microbial identification but also reduce the time necessary for bacteriological cultures. However, 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. Two recent prospective studies also support the routine use of the broth culture technique^[76,77], while the lysis-centrifugation technique needs further evaluation. Yoon *et al*^[78] evaluated 112 dialysates from 43 patients suspected of CAPD peritonitis between 2000 and 2008 by inoculating 5 to 10 mL of dialysate into a pair of BacT/Alert blood culture bottles, and comparing it with 50 mL of centrifuged dialysate simultaneously inoculated into a solid culture media for conventional culture. The blood culture method was positive in 78.6% (88/112) of dialysate specimens and the conventional culture method in 50% (56/112, $P < 0.001$). They showed that the blood culture method using the BacT/Alert system is useful for culturing dialysates and improves the positive culture rate in patients with suspected peritonitis compared to the conventional culture method.

A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis including leucocyte esterase reagent strip, broad-spectrum PCR with RNA sequencing, quantitative bacterial DNA PCR assays (especially in patients with previous or current antibiotic use), matrix metalloproteinase-9 test kit and *in situ* hybridization have been summarised by Li and co-workers^[26]. The lysozyme (muramidase) content of peritoneal fluid samples has been found to be an early indicator of the onset of infection in the course of PD. A level of 10.0 mug/mL indicates peritoneal infection and one of 7.5 mug/mL is highly suspicious^[79].

Mycobacteria are an infrequent cause of peritonitis and can be difficult to diagnose. 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. There should be a high index of suspicion of tuberculosis as cause of PD peritonitis in endemic areas. Mycobacterial infections should be suspected in the presence of persistently elevated mononuclear cell counts in the presence of negative cultures. Acid-fast bacilli may be negative in 90% of cases but formal cultures are likely to be positive^[80]. When under clinical consideration, special attention must be paid to culture techniques^[26].

PATHOLOGICAL CONSIDERATIONS

Pathophysiology

Infection of the peritoneal cavity occurs *via* the catheter lumen, bacterial migration *via* the tract or in females, through the vagina. The localisation of infection to the internal cuff region in cases of ESI probably occurs as a result of downward migration of bacteria along the catheter tract. This supports the notion that the exit site should be pointing caudally or that the peritoneal catheter have a swan-neck configuration. Though staphylococci cannot grow in commercial peritoneal dialysate solutions, these fluids are modified during dialysis and become enriched by a plasma ultrafiltrate which can support bacterial growth^[7]. With regard to peritonitis, infection within the peritoneal cavity appears to extend and involve the internal cuff region challenging the traditional thinking that both the internal and external cuffs offer an effective barrier against the spread of infection^[70].

Peritonitis is associated with peritoneal inflammation leading to hyperaemia and changes in peritoneal transport. The changes of impaired ultrafiltration^[81], increased peritoneal transport of low-molecular-weight solutes and increased rates of glucose absorption, are usually transient and typically resolve within a month after resolution of the peritonitis^[82,83].

Fungal infection

Fungal infection is rare but it is associated with high morbidity, PD modality change and mortality. Its incidence varies from 4% to 10% of all peritonitis episodes in children and from 1% to 23% in adults^[36,38]. Risk factors include a history of multiple episodes of bacterial peritonitis and treatment with broad-spectrum antibiotics^[84]. Fungal peritonitis is very closely associated with polymicrobial infections. Barraclough *et al*^[46] examined the frequency, predictors, treatment, and clinical outcomes of PD-associated polymicrobial peritonitis in a large observational cohort study using The Australia and New Zealand Dialysis and Transplant Registry data. They reported 359 episodes of polymicrobial peritonitis in 324 individuals, representing 10% of all peritonitis episodes during 6002 patient-years. The organisms isolated included mixed G+ve and G-ve organisms, and mixed bacteria and fungi. There were no significant independent predictors of polymicrobial peritonitis except for the presence of chronic lung disease^[46]. But fungal peritonitis can be the primary episode of infection.

Sclerosing encapsulating peritonitis

SEP is a serious complication of PD characterized by thickened peritoneal membrane, which lead to decreased ultrafiltration and intestinal obstruction. Its early clinical features are nonspecific, and it is often diagnosed late following laparotomy and peritoneal biopsy, when the patient develops small bowel obstruction. However, this is changing with increasing awareness of computed tomography (CT) findings in SEP. CT can yield an early, non-invasive diagnosis that may improve patient outcome^[85].

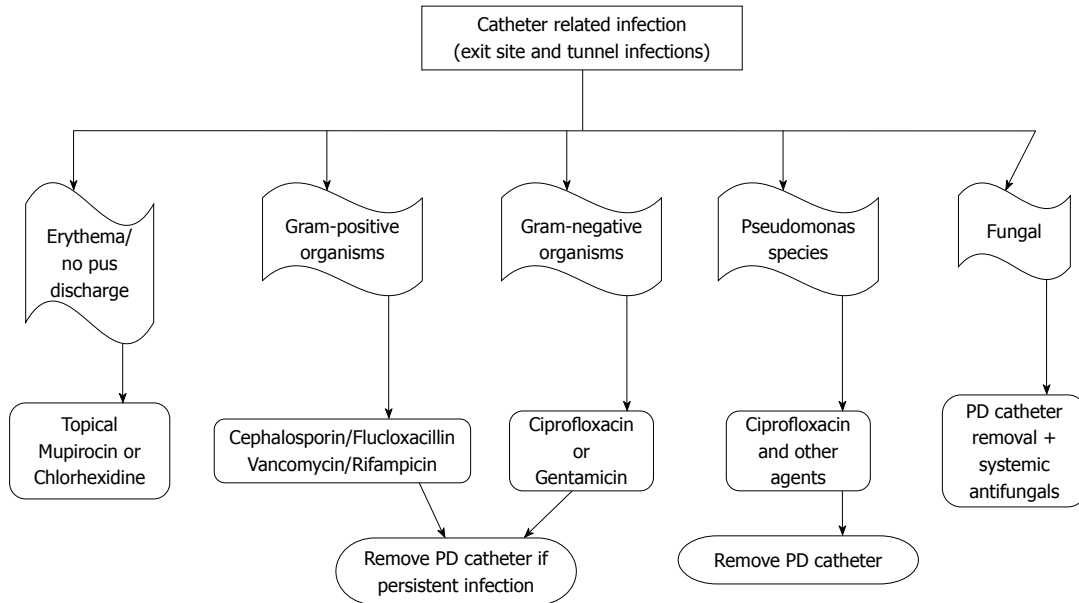


Figure 1 Treatment of Peritoneal dialysis catheter related infections. PD: Peritoneal dialysis.

Ultrasonography can also be useful in diagnosis, the main features being: increased small bowel peristalsis, tethering of the bowel to the posterior abdominal wall, intraperitoneal echogenic strands and, in the late stages of the disease, membrane formation^[86].

SEP is thought to be due to a persisting expression of *TGF β 1* gene on peritoneal mesothelial cells^[87]. Predisposing factors include recurrent peritonitis, presence of acetate in the dialysate, antiseptics used during bag exchanges, chlorhexidine gluconate in alcohol, glucose-based dialysis solutions, plasticizers and particles^[88,89]. Sclerosing encapsulating peritonitis frequently leads to intestinal obstruction, small-bowel necrosis, enterocutaneous fistulas, and malnutrition^[90,91]. Patients are typically seriously ill, with evidence of infection and requirement for parenteral nutrition. A mortality rate of 60%-73% has been reported^[91,92]. A high index of clinical suspicion for sclerosing peritonitis is desirable, perhaps facilitated by routine screening of at-risk patients^[92].

TREATMENT OF ESI AND TI

Antiseptic and non antiseptic agents have both been used for exit-site cleansing. An ideal cleansing agent should reduce the number of microorganisms, be harmless to the body's defenses and not interfere with wound healing. Antimicrobial soap is recommended for cleansing a healed exit site, but biocompatible solution is preferred for the postoperative, infected, or traumatised exit site. *In vivo* studies on the effectiveness of some cleansing agents are still lacking, and clinical study of exit-site cleansing is needed to determine the most effective agents for the task^[93].

Appropriate care of the exit site will avoid loss of catheter and unnecessary dialysis modality change. Reports from Italy show the efficacy of treating ESI caused by *Pseudomonas* with sodium hypochlorite packs as well

as systemic and local antibiotic therapy. Considering the encouraging results obtained on *Pseudomonas* infection, the same schedule for the treatment of ESI caused by other organisms which are generally difficult to eradicate was used. Sodium hypochlorite (50% packs) has a wide antimicrobial spectrum and a rapid onset of action by creating a protective barrier on the exit-site^[9].

Antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time; treatment for 3 wk is probably necessary for ESI caused by *P. aeruginosa*. If prolonged therapy (longer than 3 wk) with appropriate antibiotics fails to resolve the infection, the catheter can be replaced as a single procedure under antibiotic coverage^[94]. If the cuffs are not involved, revision of the tunnel may be performed in conjunction with continued antibiotic therapy. This procedure, however, may result in peritonitis, in which case the catheter should be removed. Ultrasound examination 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^[95]. In general, catheter removal should be considered earlier for ESI caused by *P. aeruginosa* or if there is TI^[26].

The strategy for managing ESI and TI is shown in Figure 1. Every effort must be made to make a diagnosis including determining the presence of peritonitis before antibiotic treatment is commenced. If there is no improvement within 1 wk, and for G+ve infections, catheter or catheter salvage measures - cuff shaving^[96]; simultaneous removal and reinsertion of PD catheter with a new exit site (especially in cases with *Pseudomonas*) may be applied. A patient with an ESI that progresses to peritonitis, or who presents with an ESI in conjunction with peritonitis with the same organism, will usually re-

quire catheter removal. Catheter removal should be done promptly rather than submitting the patient to prolonged peritonitis or relapsing peritonitis. Antibiotics are usually continued for about 2 wk^[2,26].

TREATMENT OF PD PERITONITIS

Empirical therapy

Peritonitis due to PD is best treated empirically while waiting for the results of dialysate culture. Empirical treatment is based on the organisms that are most frequently isolated and their susceptibilities. Antibiotics are preferentially delivered *via* the peritoneal route to ensure maximal concentrations are delivered at the site of infection. It must be borne in mind however, that drugs administered intraperitoneally can be absorbed into the systemic circulation. Drugs excreted by the kidneys accumulate in PD patients, increasing the risk of toxicity^[97]. The optimal treatment strategy for peritonitis caused by CoNS species remains controversial. A 3-wk course of antibiotic can probably achieve a higher cure rate in relapse or repeat episodes^[98]. Gentamicin should be considered over other agents for empiric G-ve coverage as it also provides synergy in the setting of *S. aureus*. Also, the newer anti-staphylococcal drugs should be tested for their performance in a biofilm using the MBEC method^[99].

Rapid exchanges in automated PD may lead to inadequate time to achieve intraperitoneal levels of antibiotics. It is therefore necessary to administer vancomycin or teicoplanin intermittently and monitor the serum levels when treating such patients^[26]. It is still not clear whether to lengthen the dwell times on the cyclor or convert automated PD to CAPD.

The duration of antibiotics treatment depends on clinical improvement of the patient and the organisms responsible for the infection. Therapy must be adequate but not too long as to precipitate fungal infections or resistance to antibiotics. It has been suggested that, if sensitivity testing shows resistance to cephalosporin but the patient is improving on intraperitoneal cephalosporin, then there may be no need to change the antibiotic as the intraperitoneal concentration of cephalosporin is higher than concentrations used in the microbiology laboratory to determine sensitivity or resistance. However, Heywood *et al*^[100] advice caution due to the increased risk of relapsing peritonitis with such an approach. They conducted a retrospective review looking at the incidence and treatment of CoNS peritonitis reported as resistant to cephalosporins. Of the 200 new cases of peritonitis, 65 (32.5%) were identified as CoNS. All were treated empirically with cefazolin (or vancomycin if allergic) for G+ve coverage and either tobramycin or ceftazidime for G-ve coverage. Of the 38 episodes of CoNS reported as resistant, 10 were treated throughout with cephalosporin (with four relapsing) whereas 28 either started with or were changed to vancomycin (with two relapsing). Their study suggests that, although cephalosporin-resistant cases of CoNS initially resolve with cephalosporin treatment, they are

indeed associated with a greater risk of relapse. Patients with CoNS peritonitis reported resistant to cefazolin may benefit from a change to vancomycin to reduce the risk of relapse^[100]. A high degree of resistance to third generation cephalosporins (66.7%) was noted amongst the G-ve bacilli. Also, all the G-ve bacilli isolated from patients who had prior empirical antibiotic therapy with ceftazidime, were resistant to third generation cephalosporins^[30].

Goffin *et al*^[21] evaluated the efficiency of a vancomycin and ciprofloxacin combination given as the first-line treatment for PD peritonitis as these covered all CoNS and 96% of G-ve bacilli. They explored a systemic route of administration of the antibiotics as an alternative to the usually cumbersome intraperitoneal drug administration. Intravenous vancomycin 15 mg/kg body weight, intravenous, and oral ciprofloxacin 250 mg two times per day (500 mg twice per day if residual creatinine clearance was above 3 mL/min) were prescribed at diagnosis of peritonitis. Vancomycin injections were repeated (when blood trough level was expected to be below 12 µg/mL) in cases of G+ve organisms for a total duration of 3 wk. Ciprofloxacin was given for a total of 3 wk in cases of G-ve and a total of 10 d for susceptible G+ve infections. The overall treatment success rate was 77.2% (78 of the 101 peritonitis episodes): 61.4% at first intention and 15.8% after optimization of the antibiotic therapy (second intention). Systemic vancomycin and ciprofloxacin administration is a simple and efficient first-line protocol antibiotic therapy for PD peritonitis. Oral ciprofloxacin provides satisfactory results in G-ve infections, comparable to those obtained with intraperitoneal ceftazidime or aminoglycosides^[21]. Shigidi *et al*^[15] reported a 79% response rate to antibacterial therapy (cefazoline and ceftazidime or vancomycin and gentamicin if allergic to β-lactams).

Fungal peritonitis

An earlier report^[101] indicated the possibility of retaining catheter use by low dose intravenous amphotericin B but in more recent series the PD catheter was removed in seven out of eight cases of fungal peritonitis^[37]. It is now standard practice to remove PD catheters in all cases in addition to antifungal treatment for a minimum of 3 wk^[36] and subsequent transfer to hemodialysis. Fluconazole and amphotericin B are the recommended antifungal agents but newer drugs such as voriconazole and caspofungin are effective^[36,84]. The 2010 International Society of Peritoneal Dialysis update on the treatment of fungal peritonitis advocates catheter removal immediately after fungi are identified by microscopy or culture^[26]. Use of intraperitoneal taurolidine (a non-antibiotic antimicrobial, with broad bactericidal and fungicidal properties) solution did not prevent PD catheter removal^[102].

SEP

Bearing in mind that several factors/mechanisms are involved in producing SEP, it is not surprising that several

therapies have been applied. The initial step in therapy should be the cessation of PD^[103] and removal of the PD catheter. Removal of the PD catheter is controversial as some leave it in to allow peritoneal lavage as a way of discouraging adhesion formation between loops of bowel^[104]. Additional treatment options include: steroid therapy^[105]; anti-inflammatory and immunosuppressive drugs^[87,103,106-108]; and use of tamoxifen^[87,103]. The management of SEP can be summarised as follows: (1) painstaking resection of the membrane when feasible; (2) in case of inadvertent intestinal wound(s), the most proximal one should be brought out as a stoma, and partial resections should not be anastomosed primarily; and (3) no surgical treatment is required in ascites, asymptomatic SEP or subacute intestinal obstruction^[90,109].

TISSUE PLASMINOGEN ACTIVATOR

There have been anecdotal reports of the use of tissue plasminogen activator for obstructed PD catheters in both adults and children. Tissue plasminogen activator was also administered to 5 patients with relapsing peritonitis; 3 patients, all with *S. epidermidis*, recovered and did not experience further recurrence^[110].

REMOVAL OF PD CATHETER

This is to prevent further damage to the peritoneal membrane in order to salvage PD modality where possible. The indications for PD catheter removal in PDAI include: ESI/TI with peritonitis; ESI/TI due to gram-negative organisms not responding to antibiotics; fungal peritonitis; lack of improvement by 5 d on appropriate antibiotics (irrespective of causative organisms); relapsing peritonitis; and refractory catheter related infection (ESI/TI)^[2]. The duration of antibiotics varies depending on clinical course and the organisms involved but this is generally for 2 to 3 wk.

OUTCOME OF PDAI

Infection related hospitalisation

Infection remains a major problem for the ERF patient whether he/she is managed by HD or PD. Williams *et al*^[111] studied the effect of infection related hospitalisation between 97 HD and 71 PD patients and showed no difference between PD and HD in the risk of access loss (28% *vs* 35%), modality change (22% *vs* 0%), or death (17% *vs* 6%) following hospitalisation for infection.

PD catheter removal and modality change

PD catheter survival ranges from 80%-93% at 1 year to 58%-91% at 3 years^[4,112]. Severe and prolonged PD peritonitis can lead to peritoneal membrane failure and is the most common cause of technique failure in PD^[15,26]. In a large retrospective study of 315 patients, PD catheter survival was not significantly linked to factors such as age, body mass index, diabetic status, previous abdominal

surgery or infections^[102]. PD catheters were removed in 19% of episodes of PD peritonitis^[113]. Change in dialysis modality is reported in up to 42% due to peritonitis and access-related infections^[19,114]. The outcome of PD peritonitis depends on the type of sepsis and the offending organism. Catheter loss (17/45 *vs* 5/20, $P = 0.04$), hospitalization (31/45 *vs* 13/30, $P = 0.03$), death [9/45 *vs* 3/30, $P = \text{non significant (NS)}$], switch to hemodialysis (8.9% *vs* 3.3%, $P = \text{NS}$), and reimplantation of the catheter (6.6% *vs* 3.3%, $P = \text{NS}$) were all more frequent in G-ve episodes than in G+ve episodes^[19].

PD function

A single, isolated episode of peritonitis ($n = 86$) had no significant effect on longitudinal peritoneal function, whereas recurrences or clusters of infection ($n = 70$) caused increases in dialysate/plasma ratio of creatinine and reductions in ultrafiltration, the significance of which increased with the number of episodes. Davies *et al*^[115] demonstrated that solute transfer increases and ultrafiltration declines with time on PD. This process is exacerbated and accelerated by peritonitis, and appears to be proportional to the degree of associated inflammation and number of infections in close proximity.

Mortality

Less than 4% of PD peritonitis results in death, but peritonitis is a contributing factor to death in 16% in^[26]. Mortality is more likely in patients with PD peritonitis due to *Candida* species and *Pseudomonas aeruginosa*. Sepsis (42%) and cardiac related causes (31%) were the two major causes of death^[113]. Fungal peritonitis is associated with high morbidity and mortality.

Factors influencing outcome

Several factors act together or alone to influence the outcome of PDAI. Krishnan and co-workers^[35] after analysing 399 episodes of bacterial peritonitis in 191 patients on dialysis, did not find the number of peritonitis episodes (before the episode in question), vancomycin-based initial empiric treatment, serum albumin level, total lymphocyte and initial dialysate white blood cell count, age, sex, diabetes, previous renal transplantation, and use of steroids to have a significant effect on the outcome of peritonitis. Not all agree on the role of various factors. In a multivariate analysis of 247 episodes of PD peritonitis in 82 patients, Kofteridis *et al*^[116] found the presence of a purulent ESI, more than 5 d PD effluent cell count $> 100 \times 10^6/\text{L}$, use of antimicrobials during the preceding 3 mo, and low serum total protein level on admission were independent predictors of a complicated course of PDAI^[116].

Patient related factors

Patients receiving enhanced training (mean training time of 29 h) had significantly fewer ESI (0.38 episodes per patient year) compared with patients receiving standard training (mean training time of 22.6 h; ESI rate of 0.67

episodes per patient year, $P = 0.003$). They also had a reduced rate of peritonitis (0.33 per patient year *vs* 0.43 episodes per patient year, $P = 0.098$)^[116].

Species/virulence

Bacterial species and virulence factors rather than antibiotic resistance have more important influence on the outcome of staphylococcal peritonitis^[117]. G+ve peritonitis has a significantly higher resolution rate than either polymicrobial peritonitis or G-ve peritonitis. *S. aureus* episodes have poorer resolution than other G+ve infections. Non pseudomonal peritonitis has a better outcome than *Pseudomonas aeruginosa* episodes^[32]. Barretti *et al*^[117] studied 86 new episodes of staphylococcal peritonitis in a single university hospital (35 due to *S. aureus*, 24 to *S. epidermidis* and 27 to other CoNS). The oxacillin susceptibility rate was 85.7% for *S. aureus*, 41.6% for *S. epidermidis*, and 51.8% for other CoNS. Production of toxins and enzymes, except for enterotoxin A and α -hemolysin, was associated with *S. aureus* episodes, whereas slime production was positive in 23.5% of CoNS and 8.6% of *S. aureus* strains. The resolution odds were 68 times higher for non-slime producers and were not influenced by oxacillin resistance among vancomycin-treated cases. Also slime and α -haemolysin production were independent predictors of non-resolution.

Compared with single-organism infections, polymicrobial peritonitis are associated with higher rates of hospitalisation, catheter removal, permanent haemodialysis transfer, and death^[18,46]. In a study by Barraclough and co-workers^[46], isolation of fungus or G-ve bacteria was the primary predictor of adverse clinical outcomes. Patients who had their catheters removed > 1 wk after polymicrobial peritonitis onset were significantly more likely to be permanently transferred to hemodialysis therapy than those who had earlier catheter removal (92% *vs* 81%, $P = 0.05$). Isolation of G-ve bacteria (with or without G+ve bacteria) or fungi carries a worse prognosis and generally should be treated with early catheter removal and appropriate antimicrobial therapy^[46].

Dialysate cell count and duration of PD

For those peritonitis episodes in which the PD fluid cell count was > 100/ μ L for more than 5 d, the non resolution rate was 45.6%, compared to a 4.2% non resolution rate when the cell count returned to 100/ μ L or less in less than 5 d. Those patients that had a successful outcome had been on CAPD for a significantly shorter period of time than those patients that had nonresolution. The non resolution rate for those patients that had been on PD for more than 2.4 years was 24.4%, compared to 16.5% for those that had been on PD for less than 2.4 years ($P = 0.05$)^[35].

Relapse

The largest multicenter, prospective study on relapsing peritonitis (specifically the relationship of postempiric antibiotic treatment regimens to the subsequent risk of

relapse in children) was produced recently by the International Pediatric Peritonitis Registry^[118]. An online, prospective data entry on peritonitis cases by participating centers including 490 episodes of non fungal peritonitis, 52 (11%) of which were followed by a relapse was analysed. There was no significant difference between relapsing and non-relapsing peritonitis in the distribution of causative organisms and antibiotic sensitivities. Switching to monotherapy with a first-generation cephalosporin on the basis of culture results was associated with a higher relapse rate (23%) than other final antibiotic therapies. Other risk factors included young age, single-cuff catheter, downward-pointing exit site, and chronic systemic antibiotic prophylaxis were additional independent risk factors for relapsing peritonitis in the multivariate analysis. Compared with non-relapsing, relapsing peritonitis was associated with a lower rate of full functional recovery, higher ultrafiltration problems, and higher rate of permanent PD discontinuation^[118].

PREVENTION OF PD PERITONITIS

Despite advances in technology, prevention of peritonitis remains one of the major challenges in PD patients. Several innovative developments like antimicrobial coating of PD catheters, flushing before fill, avoiding spiking of solution bags, connectology and double-bag systems have shown an impact on peritonitis rates. New PD solutions with neutral pH and low concentrations of glucose degradation products have also shown beneficial effects on cell viability and have improved peritoneal host defenses but without any difference in peritonitis rates^[119]. Nasso^[120] initiated a continuous quality improvement project to address the problem of PD peritonitis involving: analysis of data to ensure accuracy about causative organisms; education for the home dialysis nurses; creation of a home visit form, revisions to routine doctors' orders, revision of PD education tools; use of specialty materials for high-risk patients; one-time use for all drain equipment; change to peritonitis treatments; and group education for patients. These measures did not reduce their peritonitis rates after a 12-mo period. Further actions including making changes to patient training and developing a home visit protocol; partnership with local Community Care Access Centre and teaching of community nurses on how to help patients with their PD were required to significantly improve peritonitis rates^[120]. This indicates that intensive patient training with careful attention to their home environment is critical in achieving good PD outcomes.

The Kidney Disease Outcomes Quality Initiative guidelines for PD emphasize the need for quality improvement interventions to improve outcomes in PD. Qamar *et al*^[121] reported their 17 years experience of initiatives focused on lowering peritonitis rates in a single PD program. The peritonitis rate declined from 0.5 episodes per year at risk in 1990-1991 to 0.25 episodes per year at risk in 2005-2007 ($P < 0.004$). The ESI rate de-

Table 3 Exit site management

Ref.	No.	Trial/protocol	Results	Comments
Mahaldar <i>et al</i> ^[132]	100	Mupirocin <i>vs</i> Gentamicin	No difference in ESI rates	Trend to higher peritonitis in gentamicin group. Retrospective study
Wong <i>et al</i> ^[133]	154	Mupirocin <i>vs</i> Control	Mupirocin effective in preventing G+ve peritonitis	Randomised controlled trial. No adverse effects with mupirocin
Fong ^[122]	69	Providone-iodine <i>vs</i> Control	PVI 2.9% Control 8.8%	Nasal carriers high in PVI group! Randomised controlled trial
Bernardini <i>et al</i> ^[134]	133	Gentamicin (67) <i>vs</i> Mupirocin (66)	0.23 peritonitis episodes per patient-year (gentamicin) <i>vs</i> 0.54 for mupirocin	Time to first infection longer with Gentamicin
McQuillan <i>et al</i> ^[135]	201	Polysporin Triple Ointment (P3) <i>vs</i> Mupirocin	No difference in time to ESI or peritonitis but higher rate of fungal infections and more redness of exit site in P3 group	Multicentre randomised controlled trial

ESI: Exit site infection.

clined from 0.72 episodes per year at risk to 0.1 episodes per year at risk over the same period ($P < 0.0001$) clearly showing that quality improvement initiatives can reduce infection rates in PD patients^[121-123].

Protocols to decrease infection risk in PD patients include proper catheter placement^[13], exit-site care that includes *S. aureus* prophylaxis, careful training of patients and periodic retraining, treatment of contamination, and prevention of procedure-related peritonitis. Quality improvement programs with continuous monitoring of infections, both of the catheter exit site and peritonitis, are important to decrease PDAI. Continuous review of every episode of infection to determine the root cause of the event should be routine in PD programs^[3]. The efficacy of silver-ion treated catheters in reducing PDAI was tested in prospective, randomised controlled trial. Patients were implanted with either a silver-treated study catheter (67) or a control catheter (72). ESI rates for the study group and control group (0.52 and 0.45 episodes/patient-year of dialysis respectively) were not different by Poisson regression analysis ($P = 0.4$) and peritonitis rates were identical for the two groups (0.37 episodes/patient-year)^[124].

Nasal carriers

Eradication of *S. aureus* colonising the catheter exit site may be more important and have a greater likelihood of success than maneuvers directed to more distant locations^[66]. However, nasal carriage status should be routinely identified in all patients entering PD programme and the carriers properly treated^[125]. The nasal carriage of *S. aureus* is associated with an increased risk of catheter-ESI and that the performance of nasal cultures before the implantation of the catheter can identify patients at high risk of subsequent morbidity^[65].

Antimicrobial prophylaxis

Perioperative intravenous antibiotics compared with no treatment significantly reduced the risk of early peritonitis (four trials, 335 patients, RR = 0.35, 95% CI: 0.15-0.80) but not ESI and TI (three trials, 114 patients, RR = 0.32, 95% CI: 0.02-4.81)^[68]. A single dose of an intravenous

antibiotic (first-generation cephalosporin or vancomycin) should be given at the time of catheter insertion^[126,127].

Majority of fungal peritonitis episodes are preceded by courses of antibiotics^[84]. The International Society for Peritoneal Dialysis recommends fungal prophylaxis in patients undergoing prolonged antibiotic therapy as a way to decreasing the incidence of fungal peritonitis in programs characterised by high fungal infection rates^[26].

ESI

Meticulous exit-site care is vital in preventing ESI. Avoiding trauma to the exit-site and daily cleaning of the exit-site with a dedicated antimicrobial soap is essential for the longevity of the PD catheter. Antibiotics cream and disinfectant agents including povidone-iodine, chlorhexidine, electrolytic chloroxidizing solutions (Amuchina 10% - ExSept Plus, Amuchina 5% - ExSept) are useful to keep the resident micro-organisms inhibited. ESI rates in PD patients treated with Amuchina 10% (ExSept Plus) and Amuchina 5% (ExSept) for the exit-site care are similar or lower compared to povidone-iodine or chlorhexidine^[128] or pH neutral soap^[42]. Amuchina 10% solution is effective in preventing infection on the exit-site, without any secondary topical reaction.

Topical application of antimicrobial agents such as mupirocin, gentamicin and polysporin triple ointment to prevent exit-site infections has been successfully used. Mupirocin application at the exit site significantly lowers the incidence of ESI and peritonitis caused by *S. aureus* without any significant side effects^[17,129]. Strong support for the use of mupirocin in preventing ESI and peritonitis comes from a systemic analysis of 13 articles (1233 patients *vs* 1217 controls). Based on the six non randomised trials, the reduced risk rate for mupirocin therapy was found to be 80% (95% CI: 0.39-0.93, $P = 0.004$) in ESI and 91% (95% CI: 0.72-0.97, $P < 0.0001$) in peritonitis due to *S. aureus*; 70% (95% CI: 0.47-0.82, $P < 0.0001$) in ESI and 42% (95% CI: 0.25-0.55, $P < 0.0001$) in peritonitis due to all organisms among mupirocin-treated and non treated subjects. Based on three randomised controlled trials, ESI and peritonitis due to *S. aureus* were reduced by 73% (95% CI: 0.63-0.80, $P < 0.0001$) and

40% (95% CI: 0.17-0.56, $P = 0.002$), respectively. The randomised controlled trial evidence is that mupirocin treatment can reduce the risk rate of ESI by 46% (95% CI: 0.35-0.55, $P < 0.00001$) but it cannot decrease the risk rate of peritonitis due to all organisms ($P = 0.56$)^[130]. Lobbedez *et al*^[131] found no significant increase in the mupirocin resistant *S. aureus* prevalence in PD patients who routinely apply mupirocin ointment at the catheter exit site. Studies involving comparison of topical cleaning solutions or agents are shown in Table 3^[122,132-135].

Bacteria hiding within biofilms are known to be responsible for chronic PDAI. Branger *et al*^[136] developed a new approach in the prevention of chronic PD-related infection by regular injection of specific formulations containing detachment-promoting agents. Compared to daily treatment with taurolidine which left 48% of the biomass, weekly treatment with these agents led to a 97% reduction of surface coverage. Weekly treatment with such agents is recommended to reduce the frequency of chronic PDAI.

LIMITATIONS

There was a dearth of randomised controlled trials on the big questions regarding PDAI. Most reports were retrospective, describing small series from single units. There were a number of large studies, for example Cochrane reviews but the studies reviewed were not always optimal. There was a general lack of details of social care and the dependency status of PD patients.

CONCLUSION

PDAI is a significant reason for removal of PD catheter, loss of PD function, modality change and death.

Nasal and nail carriage status should be routinely identified in all patients entering PD programme and the carriers properly treated.

The surgical technique requires a strict adherence to a standardized procedure and a dedicated team, in order to obtain a reduction of the complications, prolonged catheter duration and a better quality of life.

Every effort must be made to identify the causative organism(s) responsible for PDAI.

Isolation of fungus or G-ve bacteria is a strong predictor of adverse clinical outcomes. Pure G+ve peritonitis are associated with the best clinical outcomes while delay in PD catheter removal of > 1 wk after polymicrobial peritonitis onset is significantly associated with dialysis modality change and increased morbidity. Isolation of G-ve bacteria (with or without G+ve bacteria) or fungi carries a worse prognosis and generally should be treated with early catheter removal and appropriate antimicrobial therapy.

Recurrent episodes of PD peritonitis must be followed by careful monitoring of PD function and surveillance for complications of PD like SEP.

Intensive patient training is a key to successful infec-

tion-free PD. All patients must be trained in aseptic techniques in order to avoid contamination of the PD fluid.

Given the large number of patients on PD and the importance of peritonitis, the lack of adequately powered RCTs to inform decision making about strategies to prevent peritonitis needs to be addressed.

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