10. Treatment of peritoneal dialysis–associated fungal peritonitis

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

The use of oral nystatin should be considered at the time of antibiotic administration to peritoneal dialysis patients to reduce the occurrence of fungal peritonitis. (Level II evidence)

Suggestions for clinical care
(Suggestions are based on Level III and IV evidence)

- There is insufficient evidence to determine choice of antifungal agent, duration of treatment or to recommend removal of catheter.
- Treatment with an appropriate antifungal agent should be commenced as soon as fungal peritonitis is identified and catheter removal should take place if the patient is unwell or fails to improve after 2 to 3 days of treatment.
- Initial therapy could include both early catheter removal and antifungal treatment.

Background

Fungal peritonitis is a rare but serious complication of peritoneal dialysis (PD) and is associated with significant mortality. Observational studies suggest that fungal peritonitis accounts for approximately 3% of all peritonitis episodes. Fungal peritonitis can be difficult to clear, can result in catheter loss, and frequently leads to conversion to haemodialysis (Michel et al 1994; Goldie et al 1996; Bren 1998).

The objective of this guideline is to provide a summary of the evidence available to date to assist with antibiotic therapy choice and also to highlight deficiencies in current knowledge.

Search strategy

Databases searched: MeSH terms and text words for PD were combined with MeSH terms and text words for antibiotics used for fungal infections, and then combined with MeSH terms and text words for peritonitis. The search was carried out in Medline (1966 – October Week 5, 2002). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search: 9 December 2002.

What is the evidence?

Only one randomised controlled trial (RCT) was found relating to this topic. This was the trial by Lo et al (1996).

Lo and coworkers performed an RCT in PD patients who received antibiotics for any reason. The intervention comprised the addition of oral nystatin tablets four times a day (500,000 units) for the duration of antibiotic therapy, with an additional 3 or 7 days being given with aminoglycoside or vancomycin, respectively. The 2-year study involved 199 patients in the intervention arm and 198 patients in the control arm. A reduction in *Candida* peritonitis rates from a rather high 6.4/100 peritonitis episodes to 1.9/100 peritonitis episodes in the nystatin group ($p < 0.05$) was noted. The cumulative probability of *Candida* peritonitis-free survival at 2 years was 0.974 for the intervention group compared with 0.915 ($p < 0.05$) for the control group (Lo et al 1996).

Summary of the evidence

Please refer to the Evidence Tables shown in the Appendices.

Evidence from non-randomised studies

There are no clear patient demographic characteristics or causes of end-stage renal failure (ESRF) that predispose to fungal peritonitis. Kan et al (2003), in a retrospective cohort study, however, report an increased rate of fungal peritonitis in Aboriginal patients in Western Australia. Observational studies suggest that previous exposure to antibiotics within the past month or the use of immunosuppression is more common in patients who develop fungal peritonitis. In these studies, between 61% and 95% of patients with fungal peritonitis had received antibiotics or had a bacterial infection in the previous month (Michel et al 1994; Goldie et al 1996; Bren 1998). The use of nystatin at the time of antibiotic use has been proposed as one strategy to reduce the frequency of fungal peritonitis in these patients.

The treatment of fungal peritonitis usually involves combination antifungal therapy with removal of the dialysis catheter. There are no RCTs that have investigated treatment but three observational studies exist which describe a total of 88 episodes of fungal peritonitis (20, 55, 13 episodes; Michel et al 1994, Goldie et al 1996, Bren 1998). Treatment regimens were highly variable and often changed over the course of the study. They included amphotericin (intravenous [IV] or intraperitoneal [IP] route), fluconazole (oral or IP), 5-flucytosine miconazole and ketoconazole as sole agents or in combination. Removal of the catheter occurred either at the time of diagnosis or later during treatment.

Michel et al (1994) compared the outcomes of patients who received antifungal therapy and either catheter removal at the time of diagnosis or delayed removal. In

the early group, 2/8 patients remained on PD, 5/8 changed to haemodialysis (HD) and 1/8 had died by 3 months. Delayed catheter removal was associated with 5/5 patients requiring a change to HD. Seven patients received antifungal therapy without catheter removal and of these, 3/7 remained on or returned to PD by 3 months and 4 died (Michel et al 1994).

Goldie et al (1996) reported the outcomes of 55 patients, 47 of whom received anti-fungal therapy and had catheters removed within 1 week of diagnosis. At 6 months, 40% (19/47) had returned to PD, 31% (15/47) remained on HD and 13 (28%) had died. A further 8 patients were managed with antifungal therapy without catheter removal; at 6 months, half (4/8) had remained on PD and 4 had died (Goldie et al 1996).

Although there was no evidence to support the choice of antifungal therapy, Bren (1998) reported abdominal pain with the use of IP amphotericin and concern has been raised regarding the peritoneal penetration of systemic amphotericin B (Warady et al 2000a). There was no discussion regarding long-term peritoneal function in these patients.

The paediatric population

Data relating to the paediatric population is derived from one registry report from the North American Paediatric Renal Transplant Cooperative Study, which is a voluntary registry involving approximately 130 paediatric centres across the US, Canada, Mexico and Costa Rica. A total of 51 patients with 51 episodes of fungal peritonitis were described between January 1992 and May 1996 (Warady et al 2000a). This accounted for 2.9% of all peritonitis episodes (1729 episodes in 1732 years of PD follow-up). The overall rate of peritonitis (bacterial, fungal or culture-negative) was 2.21 episodes per patient-year in patients with fungal peritonitis compared with an overall rate of 0.96 episodes per patient-year for registry patients.

Fungal peritonitis was more common in young patients and patients who had received antibiotics within 1 month of the peritoneal infection. Annualised rates of fungal peritonitis were 0.05 for infants (0-1 yr), 0.04 for 2-5-year-olds, and 0.02 for 6-12-year-olds. There was no difference in rates according to race, gender, aetiology of ESRF, catheter type or orientation of exit site. The presence of gastrostomy was similar in both patient groups.

Treatment included catheter removal in 90% of fungal peritonitis episodes and the prescribing of a combination of antifungal agents, most often amphotericin (IP or IV), flucytosine or fluconazole.

Six-month follow-up data suggest that 53% (27/51) of patients remained on PD and fewer – 24% (12/51) – were on HD. A further 4 patients (8%) received transplants and 3 died from causes unrelated to fungal peritonitis. No significant relationship between conversion to HD, specific type of fungal peritonitis, use of combination therapy, or time of catheter removal was found.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

British Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: ISPD Guidelines/Recommendations, 2000:

– Adults (Keane et al 2000)

TABLE: Treatment Recommendations if Yeast or Other Fungus Identified on Gram Stain or Culture

At 24 to 48 hours
Flucytosine Loading dose 2 g p.o.; maintenance dose 1 g p.o.
and
Fluconazole 200 mg p.o., or intraperitoneally, daily
If organism is resistant, consider itraconazole
At 4 to 7 days
If clinical improvement, duration of therapy 4 - 6 weeks
If no clinical improvement, remove catheter and continue therapy for 7 days after catheter removal

– Paediatrics (Warady et al 2000b)

Guideline 7: Modification of therapy for fungal peritonitis

If fungi are identified by Gram stain or culture, treatment should be initiated with either intravenous amphotericin B or a combination of an imidazole/triazole (e.g. intraperitoneal or oral fluconazole) and flucytosine. In each case, it is recommended that treatment should be associated with early catheter removal. In patients in whom the catheter is not removed initially, immediate catheter removal should take place if improvement does not occur within 3 days of treatment initiation. Treatment duration following catheter removal for all patients should be 2 weeks or longer following complete resolution of the clinical symptoms of infection. Treatment duration without catheter removal should be 4 - 6 weeks.

Implementation and audit

No recommendation.

Suggestions for future research

1. Trial the use of antifungal agents such as nystatin in addition to antibiotic treatment.

2. Establish a registry of patients with fungal peritonitis and document the treatments given and the outcomes.

3. Run an RCT for nystatin prevention of fungal peritonitis.

References

Bren A. 1998. Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Eur J Clin Microbiol Infect Dis 17: 839-43.

Goldie SJ, Kiernan-Troidle L, Torres C et al. 1996. Fungal peritonitis in a large chronic peritoneal dialysis population: a report of 55 episodes. Am J Kidney Dis 28(1): 86-91.

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

Lo WK, Chan CY, Cheng SW et al. 1996. A prospective randomized control study of oral nystatin prophylaxis for *Candida* peritonitis complicating continuous ambulatory peritoneal dialysis. Am J Kidney Dis 28(4): 549-52.

Michel C, Courdavault L, al Khayat R et al. 1994. Fungal peritonitis in patients on peritoneal dialysis. Am J Nephrol 14: 113-20.

Warady BA, Bashir M, Donaldson LA. 2000a. Fungal peritonitis in children receiving peritoneal dialysis: a report of the NAPRTCS. Kidney Int 58(1): 384-89.

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

Appendix

Table 1 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**
Lo et al 1996	397	Randomised controlled clinical trial	Multicentre	CAPD patients receiving antibiotic treatment for peritonitis; 17% diabetic	Nystatin 500,000 units x 4/day when other antibiotics were administered	No nystatin	24	None

Table 2 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)**		
Lo et al 1996	Inadequate	No	No	No	Yes	0

Table 3 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]**
Lo et al 1996	Peritonitis rate*	4/894	12/274	0.10 (0.03 - 0.31)	-0.04 (-0.06 to -0.01)

* Given as episodes/total patient months on PD