Treatment of peritoneal dialysis–associated fungal peritonitis

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GUIDELINES

a. Oral antifungal prophylaxis should be considered when antibiotics are administered to patients undergoing peritoneal dialysis to reduce the risk of developing fungal peritonitis. (Evidence level II)

SUGGESTIONS FOR CLINICAL CARE
(Suggestions are based on level III and IV evidence)

- Urgent removal of the peritoneal dialysis catheter within 24 hours is indicated when fungi are identified by microscopy or culture.
- Although no specific agent can be recommended for prophylaxis, oral nystatin may be preferred to fluconazole because of the risk of developing resistance to fluconazole with increased exposure.
- Prophylactic antifungals should be administered before gynaecological procedures.
- No recommendation can be provided about specific treatment, duration of treatment, or timing for reinserting peritoneal dialysis catheters. Fungi species and their sensitivities should be identified to guide treatment choice.

IMPLEMENTATION AND AUDIT

- Establish the incidence of fungal peritonitis in Australian and New Zealand Units. Undertake a cohort analysis as well as profile of organisms isolated and sensitivity, using the ANZDATA registry.
- Audit the use of antifungal prophylaxis.
- Investigate the timing of catheter removal and mortality rates.

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% to 15% of all peritonitis episodes in people undergoing PD.

Clinical signs and symptoms of fungal peritonitis are non-specific and can resemble bacterial peritonitis. On presentation, it is common for there to be few signs of peritonitis; although catheter obstruction [1] caused by fungal casts is an exception. The Gram stain may be positive but a high degree of suspicion must be maintained for cultures and Gram stains that are negative. Antibiotics may fail to resolve peritonitis, especially when predisposing conditions are present.

Risk factors associated with the development of fungal peritonitis include:
- an episode of bacterial peritonitis with the previous month or recurrent peritonitis
- broad spectrum antibiotic use within the previous one to three months
malnutrition or serum albumin <30g/L
- admission to hospital within the previous 10 days
- extra-peritoneal site of infection
- bowel perforation or diverticulosis
- peritoneal-vaginal communication or following gynaecological procedures
- use of immunosuppressive agents [2]
- administration of desferoximine (Mucor)
- direct environmental contamination, such as waste biocontainers [3], inadequate hygiene in exchange settings [4], or bathing at a public swimming pool [5]
- hot climates [6,7], and
- type of connect system [8].

The type of fungus determines the success rate of return to PD. Rates of successful return to PD appear to be reduced after filamentous fungal peritonitis. Although about 40 fungi species and other organisms have been reported as potentially infective (Table 1, Appendix A), Candida spp. are the most common fungi associated with fungal peritonitis. In culture-negative peritonitis, the presence of eosinophilia should raise suspicion of the presence of fungal peritonitis. Fungal colonisation of the PD catheter may be visible.

Reported mortality rates vary. An overall mortality rate of 60.5% has been reported but this rate escalated to 94.4% for patients whose catheters were in situ at one month [9]. It was further reported that two-thirds (66.6%) of patients whose catheter removal was delayed (median duration 7 days) died and the mortality rate at one month among patients whose catheters were removed at less than 24 hours was 18.8%. [9] Other studies have also documented that mortality rates rise when PD catheter removal is delayed.

Aside from death, other complications of fungal peritonitis include peritoneal adhesions, abscess formation, recurrent peritonitis and progressive sclerosing peritonitis. Systemic spread, as a complication of fungal peritonitis, appears to be rare. Fungal peritonitis can be systemically spread from other organs or developed following Coccidioidal spp. [10] or Cryptococcus spp. [11] infections. Direct invasion of blood vessels has been reported [12] and infiltration of the colic artery resulted in a pseudo-aneurysm.

Catheter removal and the transfer of patients to permanent haemodialysis, without a retrial of PD has been the standard clinical management. Although there are no randomized controlled trials (RCTs) investigating a retrial of PD, in centres where immediate catheter removal was applied, successful recommencement of PD has been reported.

Return to PD after fungal peritonitis is decreased when catheter removal is delayed. Although several reports have suggested that the optimal timing for catheter reinsertion is after four to six weeks, this has not been investigated in RCTs.

The objective of this guideline is to provide a summary of the evidence available to date to assist with the prevention and management of fungal peritonitis, including the timing of catheter removal impacting on mortality rates and return to peritoneal dialysis, antifungal therapy choice and also to highlight deficiencies in current knowledge.

SEARCH STRATEGY

Databases searched: Databases searched: MeSH terms and text words for peritoneal dialysis were combined with MeSH terms and text words for antifungals used for fungal infections, and then combined with MeSH terms and text words for peritonitis. The search was carried out in Medline (1950 – October Week 1, 2010). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. EMBASE was searched – August 2012.
WHAT IS THE EVIDENCE?

Use of oral nystatin or fluconazole for prevention of fungal peritonitis

Randomized controlled trials

A RCT conducted in Hong Kong over two years investigated prevention of fungal peritonitis using oral nystatin during antibiotic administration for any reason (n=397). [13] Oral nystatin tablets were given to 199 participants four times daily (500,000 units) for the duration of antibiotic therapy, and extended by 3 or 7 days respectively, when an aminoglycoside or vancomycin was used. There was a significant reduction in Candida spp. peritonitis rates (from 6.4/100 episodes to 1.9/100 episodes in the nystatin group (P < 0.05). The cumulative probability of Candida spp. peritonitis-free survival at 2 years was 0.974 for the intervention group and 0.915 (P < 0.05) for the control group. The incidence of antibiotic-related Candida spp. peritonitis was not significantly different – 1.39 and 3.19 per 100 peritonitis episodes and 0.66 and 1.43 per 100 antibiotic prescriptions for patients with or without nystatin, respectively. The authors concluded that oral nystatin prophylaxis with each antibiotic prescription reduced the rate of Candida spp. peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD) irrespective of its apparent temporal relationship with antibiotic prescription.

A prospective RCT conducted in Colombia (June 2004 to October 2007) on CAPD and automated PD patients investigated the efficacy of oral fluconazole during the treatment of bacterial peritonitis, exit site infections or tunnel infections in preventing secondary fungal peritonitis [14]. Secondary fungal peritonitis was defined as occurring within 30 to 150 days following the end of antibiotic administration. Patients were randomised to receive either oral fluconazole 200 mg every 48 hours or no fluconazole for the duration of antibiotic administration by any route. Patients with exit site or tunnel infections were given prophylactic fluconazole only if they were prescribed antibiotics. Data on the administration of antibiotics for other than PD-related purposes were not reported. Historical data from the study centre between 1 March 2000 and 30 June 2003 indicated a peritonitis rate of 1 episode per 19 patient-months; of these, 8.8% were cases of fungal peritonitis. A total of 88.9% of the patients with fungal peritonitis had had bacterial peritonitis in the previous two months.

A total of 434 episodes of peritonitis occurred in 226 patients and 172 exit site or tunnel infections occurred in 114 patients, of which only 52 were treated with oral antibiotics. There were 32 (7.3%) cases of fungal peritonitis reported (7.3%) (Candida spp. 30, Trichosporon beigeli sp. 1 and Geotrichum sp. 1); of these, 14 (43.8%) were classified as primary and 18 (56.3%) as secondary cases of fungal peritonitis. In the group receiving prophylaxis, there were 3 cases of fungal peritonitis (2 after bacterial peritonitis and 1 post exit-site or tunnel infection) within 30 to 60 days. In the group that did not receive prophylaxis, there were 15 cases of fungal peritonitis. This followed bacterial peritonitis for 10 patients 30-60 days before, 2 patients 90-120 days, 1 patient for 90-120 days and 1 patient for 120-150 days. Only one patient had an exit site infection 30-60 days before developing fungal peritonitis. Two patients died. In all cases the PD catheter was removed. Time from diagnosis to removal of the catheter is not provided.

All patients received oral fluconazole at 200 mg every 48 hours for 3 weeks. After three weeks, reinsertion of the PD catheter was attempted. Eleven patients had adhesion or peritoneal fibrosis leading to obliteration of the peritoneal cavity. Reintroduction was successful in 19 patients. Sensitivity was available for 10 patients with Candida spp. infections. For 4 patients the organism was sensitive to fluconazole (3 C. parapsilosis and 1 C. guilliermondii) and resistant in 6 (2 with secondary peritonitis and 4 primary; 5 C. albicans and 1 C. tropicalis). Caspofungin 50 mg daily for 14 days was administered. Overall, the prophylactic administration of fluconazole showed a statistically significant (P=0.0051) reduction in secondary fungal peritonitis (0.92% fluconazole versus 6.45% incidence in the control group). There was no statistically significant difference
between the fluconazole and no fluconazole groups in the prevention of peritonitis in patients with fungal exit-site or tunnel infections. The authors noted that the number of strains of Candida spp. resistant to fluconazole is growing, which may impact on its future effectiveness. [14]

Non-randomized studies

Other reports relating to the prophylactic use of antifungals during antibiotic administration have yielded a variety of outcomes.

Prabhu et al 2010 reported on a single-centre retrospective cohort study of peritonitis (June 2003 to December 2008) incidence and outcomes for 115 patients. At this centre, it was routine for the patients to take of oral fluconazole 50 mg daily during courses of antibiotics for any indication. A total of 82 patients received antibiotics for peritonitis and 137 oral or IV antibiotics were given for non-peritonitis related indications. All patients received fluconazole prophylaxis. There were 6 episodes of fungal peritonitis. All were due to Candida spp. None of the episodes occurred within 3 months of a patient having had antibiotics. The PD catheters were removed for all patients with fungal peritonitis. No data is provided about the timing of catheter removal after the diagnosis of fungal peritonitis. No patient died from fungal peritonitis. Three transferred permanently to haemodialysis and three had a PD catheter reinserted. The overall peritonitis rate for the centre was 0.38 episodes per patient-year on PD. [15]

Moreiras-Plaza et al 2007 reported the experience of a single centre in Spain. [16] This was a retrospective review and compared a 10-year experience of using oral antifungals whenever antibiotics were used (1996-2005, 2269 patient-months) to the prior 10 years without fungal prophylaxis (1986-1995, 1450 patient-months). There were no cases of fungal peritonitis in the 131 episodes of peritonitis (in 44/96 patients on CAPD) when antifungals were being used during 1996-2005 compared with the prior 10 years when antifungals were not used (P value not reported). From 1986 to 1995, there were a total of 121 episodes (in 58/70 patients on CAPD). Fungal peritonitis occurred in 7 patients in 8 of the 121 episodes. There was no significant difference in the numbers of patients experiencing frequent peritonitis (3 or more episodes per year) or in the type of bacterial peritonitis. The change in management during the two time periods was use of oral nystatin 500,000 IU orally three times daily or oral fluconazole 100 mg daily in diabetic patients for the first 5 years. This was changed to fluconazole for all patients and during the last 3 years of the reporting period, to fluconazole 100 mg second daily whenever antibiotics were used and not just during treatment for bacterial peritonitis. The use of the antifungal was for the same time as the antibiotic unless vancomycin was also used in which case antifungal treatment was extended for 5 additional days after cessation of the vancomycin.

Wong et al 2007 conducted a non-randomised historically-controlled trial in Hong Kong and reported fungal peritonitis rates of 0.014 episodes per patient-year without prophylaxis compared with 0.003 episodes per patient year with prophylaxis (P < 0.001). [17] The total number of fungal peritonitis cases was not altered. However, there was a major difference between the groups as only 34.4% of the control group were using the disconnect system while 91.7% of the nystatin group were using the disconnect system. The disconnect system reduces the risk of both bacterial and fungal peritonitis rates and antibiotic exposure for bacterial peritonitis.

A study conducted in Taiwan reported that the incidence of fungal peritonitis was for the spike, Y-set and UV antiseptic system 5.69, 6.20 and 2.93 times, respectively, higher than the incidence in those who used the disconnect twin-bag system (P < 0.001). [8]

Williams et al 2000 did not find any significant impact on total or antibiotic-related fungal peritonitis rates in a 30-month study run from July 1997 to December 1999. [18] The study involved two centres in the United Kingdom and was prospective. It was, however, not randomised. In the treatment unit, nystatin was administered during antibiotic therapy for peritonitis and exit-site infection (2124 patient-months). This differs from other studies in which antifungals were administered during antibiotic exposure for any indication. In the treatment unit, there were 103
episodes of peritonitis. Three were fungal (2.9%); one of these was polymicrobial due to bowel perforation and two were antibiotic-related. The other unit constituted the control group and oral nystatin was not given (3911 patient-months). There were 187 episodes of peritonitis; 2 were fungal (1.1%) and antibiotic-related. The incidence of fungal peritonitis in the two units was 3.4% in the six years preceding the study. The authors suggested that antifungal prophylaxis is not required in units that have a low incidence of fungal peritonitis.

Thodis et al 1998 reported on a short historically-controlled single-centre trial from Ontario, Canada looking at the impact of nystatin (500,000 IU four times per day) administered at the beginning of antibiotic therapy for any indication and continued for 5 days after completion of the antibiotic course. [19] The time periods examined were January 1996 to November 1996 with no nystatin prophylaxis (2400 patient months) and January 1997 to November 1997 when nystatin was administered (2400 patient months). During the no nystatin period there were 6 episodes of fungal peritonitis (4.5%) out of a total 133 episodes; 3/6 had received antibiotics for bacterial peritonitis in the 2 months before the fungal peritonitis. During the nystatin administration period, there were 12 fungal episodes (12.5%) out of a total of 99 peritonitis episodes; 4/12 had received antibiotics. Two of 6 cases died in the first period and 4/12 died in the second period of fungal peritonitis i.e. 33% of patients during each period. Note that 50% and 66% of the cases of fungal peritonitis during the two periods had occurred without any reported prior antibiotic exposure.

Wadhwa et al 1996, from New York, USA, used fluconazole prophylaxis during antibiotic therapy for any reason for patients on CAPD from August 1993 to December 1995 (n = 112, 1705 patient-months) and compared this with January 1991 to July 1993 (n = 122, 1832 patient-months) [20]. Oral fluconazole was given at the onset of antibiotic therapy and continued for one week after the completion of antibiotics. The rate of fungal peritonitis was reduced from 15 episodes (in 11 patients) per 1832 patient-months to 4 episodes per 1705 patient-months (P < 0.05). Fungal peritonitis related to antibiotic exposure fell from 12 episodes to 2 episodes (P < 0.02). In each time period, there was one case of fungal peritonitis as a complication of bowel perforation. There were two cases and one case, respectively, of fungal peritonitis not associated with antibiotic exposure. There was no statistically significant difference in the total episodes of peritonitis (105 episodes and 95, respectively).

Robitaille et al 1995 reported a prospective study conducted in Canada, in which antifungals were given whenever antibiotics were used for the treatment of bacterial infections in all paediatric patients on PD. [21] It commenced in March 1991 and also included children with feeding gastrojejunostomies, who have been reported to be at higher risk of developing fungal peritonitis. Patients were followed to March 1993. These were compared with historical controls for the period from April 1989 to March 1991. The use of antifungals significantly reduced the risk of developing peritonitis (P < 0.05). The prophylaxis consisted of nystatin 10,000 units/kg/day in three doses (3 patients) and then ketoconazole 10 mg/kg/day daily for 22 patients. Twenty of the 25 patients had at least one episode of bacterial peritonitis (range: 1-5 episodes). The bacterial peritonitis was treated for 10-14 days with antibiotics given IV, IP or orally. Seven of the 25 patients had feeding gastrojejunostomies. There were no episodes of fungal peritonitis. For the historical controls (n = 33) there were 87 episodes of bacterial peritonitis and an additional 13 bacterial infections other than peritonitis, that were treated with antibiotics. Twenty-five patients had at least one episode of bacterial peritonitis (range: 1-5 episodes). Ten had feeding gastrojejunostomies and one had a gastrostomy. There were five fungal peritonitis episodes due to Candida spp. in five patients. Two of the children survived but three died directly or indirectly from complications due to the Candida peritonitis. Three of the 5 patients with fungal peritonitis had a feeding gastrojejunostomy. In total, 11/33 had a gastrojejunostomy; 3/11 (27%) developed Candida peritonitis compared with 2/22 (9%) without a gastrojejunostomy (P > 0.05). There was a significant reduction in fungal peritonitis for patients with feeding gastrojejunostomies when antifungal prophylaxis was used compared with no prophylaxis (P < 0.01).

Zaruba et al 1991 reported on a 6-year experience of administering nystatin at 500,000 IU three times a day during antibiotics for any indication. [22] They compared two periods – from April 1979
to December 1982 when no prophylaxis was given and from January 1979 to March 1989 when nystatin was administered. Fungal peritonitis rates fell from 10/415 patient-months to 4/2102 patient-months.

Summary relating to the use of oral nystatin or fluconazole for prophylaxis against fungal peritonitis during exposure to antibiotics

Oral nystatin is a safe, low cost treatment. The one RCT supports the use of nystatin prophylaxis for patients on PD when given antibiotics regardless of the indication. The subsequent studies have methodological flaws and while raising some doubt about the effectiveness of nystatin in units with a low background incidence of fungal peritonitis do not demonstrate any adverse effects. Fungal peritonitis occurs even in the absence of exposure to antibiotics and routine nystatin prophylaxis within units will not prevent such episodes.

Uncertainty remains about the use of fluconazole for prophylaxis against fungal peritonitis. Data relating to the development of resistance to antifungals such as fluconazole used for prophylaxis in patients on CAPD is lacking. However, Restrepo et al noted an increased incidence of fluconazole-resistant Candida in their randomized study of the use of prophylactic fluconazole. [14] In other settings such as haematology/oncology, resistance to fluconazole has developed. [23] Consistent use of nystatin in burns units has also seen the selection of nystatin-resistant Candida spp. such as Candida rugosa. Data on this is lacking for patients on CAPD.

Two studies reported on cases of fungal peritonitis following gynaecological procedures. [24,25] This is also an area of uncertainty but prophylactic antifungals administered before gynaecological procedures would appear reasonable.

Randomized controlled multi-centre trials of the use of prophylactic antifungals during antibiotic therapy should be considered and could include the prophylactic use of antifungals prior to gynaecological procedures. To gather sufficient data at individual centres is not possible due to small patient numbers.

Use of prophylactic mupirocin or Polysporin triple ointment on exit sites as a risk factor for fungal peritonitis

McQuillan et al 2012 conducted a double-blind RCT at two centres in which 201 patients (both prevalent and incident) were randomised using stratified block randomisation to apply either mupirocin (n=100) or polysporin triple ointment (n=101) to their PD exit site. [26] Patients were followed for 2742 patient-months (median: 18 months, range: 0.1-18 months). The primary end point was time to first PD infection, which could consist of exit-site infection (ESI), tunnel infection or PD peritonitis. There was no statistically significant difference in the time to first PD-related infection. The overall incidence was 0.39 per patient-year for peritonitis (1 in 26 patient-months) and 0.59 per patient-year (1 in 17 patient-months) for ESIs. There were four fungal peritonitis episodes in the polysporin group (rate 0.04 per patient-year) but none in the mupirocin group (P = 0.05). One fungal peritonitis episode was the first PD infection experienced by the patient. There were eight fungal ESIs in the polysporin group (rate 0.07 per patient-year) and one in the mupirocin group (rate 0.01 per patient-year) (P = 0.02). None of the patients with a fungal infection had exposure to oral or systemic antibiotics in the previous three months. None of the patients who had a fungal ESI had fungal peritonitis during the follow up. It is unclear how colonisation of the exit site was distinguished from infection in the study. Polysporin triple was not superior to mupirocin in preventing PD-related infections although there was a higher rate of Gram negative peritonitis in the mupirocin group (rate 0.11 versus 0.04 per patient-year, P = 0.03). The higher rate of fungal infections in the group applying Polysporin, which has a broader range of cover, is of concern and it must be noted that the longest follow up was for 18 months.

Although Polysporin has broader coverage and may protect against Gram negative infections, there was a higher incidence of fungal infection or colonisation of the exit site.

Peritonitis Treatment and Prophylaxis (February 2014)
Registry data on incidence, types of fungi causing peritonitis, outcomes and treatments

Using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) data, Miles et al 2009 [27] examined the predictors and outcomes of fungal peritonitis in PD patients in Australia. The data was from 66 centres over a 39-month period (1 October 2003 to 31 December 2006) and included 4675 PD patients. There were 162 episodes in 158 individuals. Fungal peritonitis caused 4.5% of all peritonitis episodes.

Candida spp. were the most common isolate with C. albicans causing 25% of infections; other Candida spp. caused 44% of cases. Other fungi were cultured in 33% of episodes and 22% had bacterial and fungal peritonitis. Independent predictors included prior treatment of bacterial peritonitis and also being an Aboriginal and Torres Strait Islander and living in Western Australia or the Northern Territory. This may relate to climate or living standards, which could not be examined. Only 7% of people were prescribed antifungal prophylaxis during any peritonitis episode.

The majority of people received empirical antibiotics consisting of either vancomycin or cephazolin IP in combination with gentamicin. Antifungal was administered in the initial empirical treatment in 33 episodes (20%). A total of 105 episodes (65%) were treated with antifungals either alone (7%) or in combination with catheter removal (58%) and 48 (30%) were treated with catheter removal alone. Nine (6%) patients died before receiving antifungal therapy or catheter removal.

The most common antifungal treatment in the initial, second or third course was fluconazole alone (90%) followed by amphotericin monotherapy (20%), fluconazole and flucytosine (3%), amphotericin and fluconazole (2%) and ketoconazole (1%). Thirteen episodes initially treated with amphotericin monotherapy changed to fluconazole monotherapy in four episodes. Ninety-one episodes that were initially treated with fluconazole monotherapy changed to amphotericin monotherapy in 7, combination amphotericin and fluconazole in 2 and combination fluconazole and flucytosine in 3 cases. The median duration of antifungal treatment was 15 days. Heparin was administered in 22% of cases and streptokinase in 1%. There was no difference in management across the states.

Outcomes included hospitalisation for 98% and catheter removal for 88%. Permanent transfer to haemodialysis occurred in 74% of cases and death in 9%. There was longer hospitalisation and the risk of death was greater with antifungal alone (18%) than with catheter removal alone (6%) or catheter removal plus antifungal therapy. The risk of a subsequent fungal peritonitis episode was significantly lower with combined catheter removal and antifungal therapy than antifungal alone or catheter removal alone.

The ANZDATA registry data is consistent with reports from single-centre studies, which have reported significant numbers of cases of fungal peritonitis. Wang et al 2000 reported a higher mortality of 44% but that was in the context of a lower rate of removal of the PD catheter and lower rates of transfer to haemodialysis. [28] Outcomes were also modified by the presence of greater proportion of non-C. albicans species. These are generally more resistant to antifungal therapy than C. albicans. [29]

Raaijmakers et al 2007 reported on a retrospective multi-centre study involving 159 Dutch paediatric patients between 1980 and 2005. [30] A total of 321 peritonitis episodes occurred in the 159 patients. Fungal peritonitis occurred in 2.9% (n = 9). Candida spp. were the most common cause of fungal peritonitis (78%). Seven of the 9 patients (78%) had had antibiotics in the preceding month. The other two patients developed fungal peritonitis within one month of starting PD. None had a gastrostomy catheter nor were any on immunosuppressive therapy. None of the patients died. The PD catheter was removed in all patients at varying intervals from immediately fungal peritonitis was diagnosed (33%) to more than 2 months after diagnosis (n = 1). Four patients restarted PD 6 to 10 weeks after the development of fungal peritonitis. Patients who
developed fungal peritonitis had a higher previous bacterial peritonitis rate than the total population (0.13 vs 0.09 episodes per patient-month, P = 0.009) and twice as many Gram negative infections.

Levallois et al in 2012 reported a retrospective single-centre study of 288 patients run between August 1996 and July 2006. [31] Nine cases of fungal peritonitis were identified (7 men and 2 women). The incidence was 1 episode per 806 patient-months (1 episode per 67 patient-years). Fungal peritonitis represented 3.1% of all cases of peritonitis during that period. Of the patients with fungal peritonitis, 67% had been treated with antibiotics in the previous 3 months for bacterial peritonitis. One episode was related to appendicitis. None had been given antifungal prophylaxis. All episodes were due to Candida spp with only one being due to C. Albicans. Three were due to C. parapsilosis, three C. tropicalis, one C. krusei and one C. glabrata. The in vitro sensitivities varied. Four were sensitive to amphotericin, triazoles and echinocandins and three were resistant to amphotericin. Of those three, C. tropicalis was resistant to both itraconazole and voriconazole and intermediate to fluconazole. C. krusei was intrinsically resistant to fluconazole. C. parapsilosis had higher MICs for caspofungin and micafungin than the other Candida spp. Initial empirical antifungal therapy was fluconazole in six patients, amphotericin in two and caspofungin in one case. Resistance to the initial antifungal resulted in a switch to the appropriate antifungal in three cases. One isolate was highly resistant to micafungin (MIC =16). All patients had the PD catheter surgically removed after the diagnosis of fungal peritonitis with a mean lag time of 7.6 days (range: 2-13 days). The mean duration of therapy was 23.4 days. All patients survived but only one resumed PD 12 months later. One patient developed sclerosing peritonitis during the initial hospitalisation with fungal peritonitis.

The variable pattern of susceptibility requires consideration of the initial empirical antifungal. Identification of fungi species and susceptibility testing of each species is required for definitive treatment.

Khan et al in 2011 reported a retrospective single-centre study from Qatar conducted from 1 January 2005 to 31 December 2008. [32] Of 294 patients on CAPD, 141 episodes of peritonitis occurred, of which 14 (9.9%) were fungal; 13/14 (93%) had experienced one or more previous episodes of bacterial peritonitis treated with multiple broad spectrum antibiotics. Eighty-five per cent had received broad spectrum antibiotics within the preceding month, 92% within three months prior and 62% within six months prior. None of the patients had received antifungal prophylaxis. All patients had their PD catheter removed within 24 hours of diagnosis of fungal peritonitis. All patients received empirical intravenous amphotericin B (20 mg once daily) and oral fluconazole (200 mg once daily) pending sensitivities. All were Candida spp. – C albicans (14.3%). Non-C. albicans spp. (85.7%) included C. parapsilosis (57%), C. tropicalis (21.4%) and C. krusei (7.2%). Two species (C. albicans and C. parapsilosis) were identified in two cases (14.3%). Five patients (35.7%) died during the fungal peritonitis episode. All who survived remained on haemodialysis. The time from onset of peritonitis to the diagnosis of fungal peritonitis is not provided although catheters were removed promptly once the diagnosis was established. There may, however, have been delay in giving effective treatment, which impacts on mortality. All isolates were reported to be sensitive to amphotericin B, fluconazole, 5-fluorocytosine, itraconazole and ketoconazole.

In summary, yeasts of the Candida species cause 70% to 90% of cases of fungal peritonitis in adults and 80% to 100% in children. Filamentous fungi (moulds) result in 10% of cases. There are case reports of many different fungi causing peritonitis in CAPD and at least one case report of an alga (Prototheca wickerhamii) causing peritonitis in patients on PD (see Table 1 in Appendix). For some there are only one or two cases whereas others have been reported more frequently. The outcome for the filamentous fungi is generally worse than that for Candida species. C. albicans represents the most common Candida spp. but other more resistant Candida species are increasing in frequency (e.g. C. glabrata and C. parapsilosis) and there are concerns that the use of fluconazole as a prophylactic agent may increase the incidence of the resistant species.

Fungal peritonitis is associated with an increased mortality, which is increased by delayed peritoneal dialysis catheter removal.
Registry data

Miles et al 2009 reported on the predictors and outcomes of fungal peritonitis for PD patients in Australia. [27] This ANZDATA report included 66 centres over a 39-month period (from 1 October 2003 to 31 December 2006) and included 4675 patients on PD. The incidence of fungal peritonitis was 4.5% (162 episodes in 158 patients) of all peritonitis episodes. The overall death rate was 9% for patients with fungal peritonitis, compared with a non-fungal death rate of only 2% (P < 0.001). The death rate for antifungal therapy alone was 18% compared with either catheter removal alone (6%) or catheter removal and antifungal treatment (7%). These did not reach statistical significance due to the small numbers in each group. The risk of a subsequent repeat fungal episode was significantly lower with combined catheter removal and antifungal therapy (0%) than with antifungal therapy alone (9%) or catheter removal alone (6%, P = 0.03). There was no difference in transfer to haemodialysis numbers but in this study, early removal was defined as within 5 days and delayed as more than 5 days.

Ghali et al 2011 reported on the microbiology and outcomes of peritonitis for PD patients in Australia from 1 October 2003 to 31 December 2008. [33] The overall rate of peritonitis was 0.54 episodes per patient-year. The incidence of fungal peritonitis as a single organism was 3.1% with a rate of 0.02 per patient-year (170 fungal episodes of a total of 5536 episodes). Fungus was present in 6.7% of polymicrobial peritonitis episodes (99 of 1477 organisms cultured). The median time to catheter removal was 4 days. The median duration of the hospital admission for fungal infection was 10 days. Overall, hospital admission occurred in 70% of cases of peritonitis with a median duration of 4 days. Fungal peritonitis was identified as the cause of death within 30 days after the onset of peritonitis in 18 (6.0%) of the 301 patients who died.

Mujas 2006 reported on data from centres in the USA and Canada, using the Peritonitis Organism Exit site Tunnel infection (POET) monitoring system (Baxter Healthcare), representing data on 10% of prevalent patients on PD in the USA and the majority of the Canadian PD population. [34] The incidence of fungal peritonitis was 3.9% in the USA and 3.7% in Canada. There was however, a much higher mortality rate for fungal peritonitis in Canada (18.8%) compared with the USA (4.2%). The author suggests that this relates to practices relating to catheter removal. In the USA, catheter removal occurred in 95.8% of cases while in Canada catheters were removed in 75.2% of cases. The overall mortality rates for PD peritonitis were 3.5% in the USA and 3.4% in Canada.

Single centre reports

Wang et al 2000 from Hong Kong reviewed 70 cases of fungal peritonitis, which had occurred between January 1989 and June 1998. [28] The incidence rate per year for fungal peritonitis varied from 1.4% to 7.8% of all cases of peritonitis. Antibiotic use within 3 months of the fungal peritonitis occurred in 94% of patients with fungal peritonitis complicating bacterial peritonitis compared with 61% of patients with de novo fungal peritonitis (P = 0.001). The outcome is not known for one patient. The overall death rate was 44% for those with fungal peritonitis. The overall mortality rate for catheter removal was 31% versus non-removal of the catheter of 91% (P = 0.0006). For Candida spp. the mortality rate was 100% if the catheter was not removed, regardless of the antifungal therapy. The rate was significantly reduced to 28% with catheter removal. The mortality rate was zero when the catheter was removed within 24 hours compared with 31% if the removal was delayed until after 24 hours but this difference was not statistically significant.

Prasad et al 2004 reported an Indian single-centre study that had a mortality rate of 100% when the catheter was left in situ with no influence by the antifungal therapy used. [35] However, when the catheter was removed the mortality rate was 40.9%. Candida spp. alone were isolated in 89.3% of cases. Of the Candida spp. C. albicans was present in 35.7% of cases and seven different kinds of non-C.albicans in 53.6%. The most common non-C. albicans species were C. parasilopsis and C. tropicalis (26.7% each). Of the three cases with dematiaceous fungi Curvularia species was isolated from one patient as the only pathogen. Another had Phaeoacremonium
parasiticum along with C. tropicalis and in a third patient Exophiala jeanselmei and C. kefyr were both isolated.

Ram et al 2008 reported on a retrospective single-centre study from India. [9] A total of 303 patients received CAPD between January 1998 and 2008. There were a total of 137 bacterial peritonitis and 43 episodes of fungal peritonitis (23.8% of all peritonitis episodes). Three factors predicted mortality: non-Candida species (P = 0.02, OR 0.13, 95% CI: 0.01–0.79), catheter left in situ (P = 0.0001, OR 30.22, 95% CI: 3.33-339.45), and serum albumin <30 g/L (P = 0.02). Multivariate analysis yielded only the catheter in situ (P = 0.0033) and serum albumin <3 g/dL (P = 0.0146) as predictors of mortality. Sex, presence of fever, diabetes mellitus, intraperitoneal antibiotics, gastrointestinal symptoms, abdominal pain and residual renal function did not show an effect on mortality. The overall death rate was 60.5% however, this was strongly altered by the management approach. For 18 patients, the Tenckhoff catheter was not removed and antifungals were given. Seventeen of the 18 were dead at one month (94.4%). Nine patients had their Tenckhoff catheter removed after a median duration of 7 days; 6/9 were dead at one month (66.6%). For sixteen who had their Tenckhoff catheter removed within 24 hours of diagnosis, 3/16 were dead at one month (18.8%). Two of three who had the catheter removed within 24 hours and died had infection with Zygomycetes species, which are resistant to most antifungal agents.

Chang et al 2010 conducted a retrospective single-centre study in Korea and related the survival rate of patients with fungal peritonitis to the timing of catheter removal. [36] Early removal (within 24 hours of diagnosis) was associated with a lower death rate (5/39, 12.8%) compared with 13/41 (31.7%) [P < 0.01] for delayed removal after a median duration of 3 days after diagnosis (range: 2-9 days). The PD catheter was not removed in 6 cases as the patients died before the diagnosis of fungal peritonitis was established and 2 patients refused catheter removal and died. Seven other catheters were removed because of recurrent peritonitis or clinical deterioration. On multivariate logistic regression, delayed catheter removal (more than 24 hours) (OR 13.73, 95% CI: 2.09-90.36, P < 0.01), presence of intestinal obstruction (10.90 [1.41-84.24], P < 0.05) and high white cell counts in blood (1.23 [1.04-1.46], P < 0.05) and the PD effluent (2.08 [1.12-3.86], P < 0.05) were independently associated with mortality in patients with fungal peritonitis.

Summary of impact on mortality of timing of catheter removal

The data from the registries and the single-centre studies strongly supports the urgent removal (within 24 hours) of the PD catheter. Delayed removal and attempting to treat the fungal peritonitis with the catheter in situ cannot be supported. Failure to remove the catheter leaves a foreign body in situ and an ongoing source of infection. The presence of biofilm impairs the effectiveness of antifungals. Direct invasion of the catheter wall by fungi as well as tracking of fungal infection along the PD tunnel with involvement of the cuffs and tissue of the track has been reported.

Fungal catheter invasion has been reported. Organisms identified include: Curvularia lunata [37]; Fusarium spp. [38]; Exophila jeanselmei [39]; Paecilomyces variotii [40]; Penicillium spp. [41]; Aspergillus spp. [42]; and Helminthasprium spp. [43] Erosion of the wall of the PD catheter due to Candida albicans has also been reported. [44]

It has been reported that fungal forms persisted on microscopy of the catheter lumen biofilm despite 4 weeks of therapy with high-dose fluconazole. [45] Removal of the catheter and the cuffs is the only way to remove the persisting source of infection. There are case reports of catheters being retained with the use of intra-catheter instillation of amphotericin in addition to IP administration [46] but the data relating to the increased mortality rates associated with delayed (more than 24 hours from diagnosis) [36] removal of the catheter should strongly discourage such an approach.
Antifungal therapy

The optimal choice of antifungals has not been established. Until recently, interpreting treatment data has been difficult due to the lack of standardised sensitivity testing. The degree of standardisation of testing across centres and countries remains uncertain.

In addition, some antifungals penetrate poorly into the peritoneal cavity and should be avoided if treating fungal peritonitis (e.g. ketoconazole) [47]. Itraconazole also has poor peritoneal penetration. As noted in the ISPD guidelines, intraperitoneal amphotericin should be avoided because it causes pain and increased fibrosis. [48]

Some general recommendations about which agents may be of use and which fungi are intrinsically resistant to particular agents is included in the treatment section but is not comprehensive (see Appendix A, Tables 2 and 3). This information provides some general guidance. Specific advice should be obtained from the local infectious disease team or microbiologists. The Sanford Guide to antimicrobial therapy contains additional information including tables that summarise suggested antifungal drugs that are effective against treatable pathogenic fungi. [49]

There are limited data from case reports indicating use of some of the newer antifungals for CAPD peritonitis (e.g. caspofungin, posaconazole, voriconazole). There is one report of using terbinafine in combination with voriconazole. This information is summarised in the case reports described below.

Madariaga et al 2003 reported the case of a 49-year-old woman with Trichosporon inkin peritonitis treated with caspofungin. [50] She had a 4-week history of cloudy bags and abdominal pain and had been treated initially for presumed bacterial peritonitis with vancomycin and gentamicin. She had her Tenckhoff catheter removed on her second hospital day when a budding yeast was reported on culture. She was initially given IV fluconazole for an uncertain period of time and then IV amphotericin but did not tolerate the amphotericin due to fever, rigors and hypotension. Caspofungin was then given with a 70 mg IV loading dose followed by 50 mg IV daily as maintenance for 14 days. This is not a pure case of caspofungin therapy and the MIC for caspofungin was high. Intraperitoneal caspofungin levels were not measured.

Fourtounas et al 2006 reported using the combination of caspofungin plus amphotericin B for a 65-year-old man with Candida albicans peritonitis. [51] The C. albicans was resistant to azoles. He had his PD catheter removed at an uncertain time after diagnosis and remained febrile and hypotensive despite amphotericin administration. Three days after the addition of caspofungin 50 mg daily he became afebrile. The combination was administered for a total of 15 days with no adverse effects noted.

Chang et al 2008 reported treating a man with Paecilomyces lichacinus peritonitis with oral voriconazole and terbinafine in combination. [52] He was initially treated with IV amphotericin (1 mg/kg/day) and oral fluconazole 6 mg/kg/day). His PD catheter was removed due to persistent cloudy bags; the exact timing is not detailed. He had a complicated course with persistent fevers and high CRP. At laparotomy, there were thickened leather-like plaques on the bowel wall and fungal hyphae were present. He was changed to oral voriconazole and amphotericin was ceased. His fever settled after 22 days of voriconazole but the ascites cultures still contained Paecilomyces lichacinus. He was discharged on 12 February 2006 (admission date 24 November 2005) on oral voriconazole with an elevated CRP. Ascitic taps showed persistence of Paecilomyces. Terbinafine was added (62.5 mg second daily). The combination therapy was continued for 3 months. His symptoms, elevated CRP and the ascites resolved and fungal cultures were negative. He remained on haemodialysis.
Voriconazole to treat Neosartorya pseudofischeri has been reported. [53] The catheter was removed one week after identification of the fungal peritonitis. Voriconazole 200 mg twice daily was commenced 15 days after presentation and then continued for 5 weeks.

Pimental et al 2006 report a case of Cunninghamella berthetiae treated with catheter removal (exact timing after presentation uncertain) and subsequent administration of voriconazole 200 mg twice daily for 90 days. Despite in vitro resistance to voriconazole, the patient survived what is usually a fatal infection. [54]

Ram et al 2008 reported a pseudo-aneurysm of the left colic artery after Tenckhoff catheter removal with initially unrecognised fungal peritonitis (Aspergillus flavus). [12] The patient was subsequently treated with both amphotericin (cumulative dose 3.0 g) and voriconazole (initially 400 mg twice daily then 200 mg twice daily for 4 weeks).

Sedlacek et al 2008 reported on a 57-year-old woman who survived Mucor peritonitis after her pet cockatoo bit through her transfer set in July 2004. [55] She failed to respond to more than 8 weeks of amphotericin but was given posaconazole on a compassionate basis for six months. The disease resolved and she remained well two years later at the time of the report.

Verghese et al 2007 reported the use of voroconazole for Aspergillus terreus when removal of the PD catheter did not result in clinical improvement. [56] While there was initial improvement, the effectiveness of the therapy cannot be evaluated as the patient discontinued therapy after one week and died 3 weeks later.

**Summary of treatment recommendations**

There are no established standard recommendations concerning antifungal selection, dose, duration of therapy or combination of drugs. Empirical treatment is required until the fungus is identified and sensitivities are available to guide choice of therapy.

Some practical considerations include:

- the key management is immediate removal of the peritoneal catheter
- flucytosine is always used in combination due to the risk of rapid development of resistance if used alone
- avoid ketoconazole and itraconazole due to extremely poor penetration into the peritoneal cavity.

There are no trial data related to the optimal timing of catheter reinsertion after fungal peritonitis. Immediate reinsertion of the catheter has been associated with colonisation of the new catheter. [39,57] Early catheter removal is associated not only with reduced mortality rates but may result in higher rates of return to PD.

Some reports have suggested waiting 4 to 6 weeks before reinserting a catheter after fungal peritonitis.

**The paediatric population**

Data relating to children were 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. [58] 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 end-stage kidney disease (ESKD), catheter type or orientation of the 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.

At 6-months of follow-up, 53% (27/51) of patients remained on PD and fewer – 24% (12/51) – were on haemodialysis. A further 4 patients (8%) received transplants and 3 died from causes unrelated to fungal peritonitis. No significant relationship between conversion to haemodialysis, specific type of fungal peritonitis, use of combination therapy, or time of catheter removal was found.

Another special consideration in children relates to the insertion of gastrostomy tubes in patients on PD. A retrospective report of 27 patients in 12 German centres over 10 years related the experience of the open insertion of gastrostomy tube at the same time (2 cases) as insertion of a PD catheter or PEG insertion after insertion of a Tenckhoff catheter. [59] Antibiotic and antifungal prophylaxis was given at the time of insertion and reintroduction of PD delayed 2-3 days so a good seal at the gastrostomy site was obtained. Ten of 27 (37%) developed peritonitis within 7 days of PEG insertion. Fungal peritonitis occurred in 7/27 (26%). Eight required replacement of their PD catheter, 4 transferred to haemodialysis and there were 2 late deaths and 14/27 had no problems. There were 4 patients with additional early peritonitis episodes who were successfully treated by IP antibiotics. For 18/27 (67%) patients, PD was successfully restarted shortly after PEG insertion. The authors suggested that antibiotic and antifungal prophylaxis, withholding of PD for 2-3 days and placement of the gastrostomy by an experienced team as precautions required to reduce the risk of peritonitis.

SUMMARY OF THE EVIDENCE

Evidence from non-randomised studies

Registry data

Using the ANZDATA registry data, Miles et al 2009 examined the predictors and outcomes of fungal peritonitis in PD patients in Australia. [27] The data was from 66 centres over a 4-year period (from 1 October 2003 to 31 December 2006) and included 4675 patients on PD. There were 162 episodes of fungal peritonitis in 158 individuals, which was 4.5% of all peritonitis episodes.

Candida spp. was the most common isolate with C. albicans causing 25% of cases and other Candida species causing 44% of cases; other fungi (n = 52). Independent predictors included prior treatment of bacterial peritonitis and also being an Aboriginal and Torres Strait Islander and living in Western Australia or the Northern Territory. Only 7% of people were prescribed antifungal prophylaxis during any peritonitis episode.

The majority of people received empirical antibiotics of either vancomycin or cefazolin IP in combination with gentamicin. Antifungal was administered in the initial empirical treatment in 33 episodes. A total of 105 people were treated with antifungals either alone or in combination with catheter removal. Forty-eight per cent were treated with catheter removal alone. Nine patients died before receiving antifungal therapy or catheter removal.

The most common antifungal treatment in the initial, second or third course was fluconazole alone (90%) followed by amphotericin monotherapy (20%), fluconazole and flucytosine (3%), amphotericin and fluconazole (2%) and ketoconazole (1%). Thirteen episodes initially treated with amphotericin monotherapy changed to fluconazole monotherapy in 4 episodes. Ninety-one
episodes initially treated with fluconazole monotherapy changed to amphotericin monotherapy in seven, combination amphotericin and fluconazole in two, and combination fluconazole and flucytosine in three cases. The median duration of antifungal treatment was 15 days. Heparin was administered in 22% of cases and streptokinase in 1%. There was no difference in management across the states.

Outcomes included hospitalisation for 98% and catheter removal for 88%. Permanent transfer to haemodialysis occurred in 74% and death in 9%. There was longer hospitalisation and the risk of death greater with antifungal alone (18%) than with catheter removal alone (6%) or catheter removal plus antifungal therapy. The risk of a subsequent fungal peritonitis episode was significantly lower with combined catheter removal and antifungal therapy than with antifungal therapy alone or catheter removal alone.

The data is consistent with reports from single-center studies, which have reported significant numbers of cases. Fungal peritonitis occurred in 5.8% of all peritonitis cases. Wang et al reported a higher mortality of 44% but that was in the context of a lower rate of removal of the PD catheter and lower rates of transfer to haemodialysis. [28] The outcome was also modified by higher numbers of non-C. albicans species, which are generally more resistant than C. albicans.

Overall, yeasts of the Candida species cause 70% to 90% of cases of fungal peritonitis in adults and 80% to 100% in the paediatric population. Filamentous fungi (moulds) result in 10% of cases. There are case reports of many different fungi causing peritonitis in CAPD and at least one case report of an algae. These are included in Table 1. For some, there are only one or two cases whereas others have been reported more frequently. The outcome for the filamentous fungi is generally worse than that for Candida species. C. albicans represents the most common Candida species but other more resistant Candida species are increasing in frequency (e.g. C. glabrata and C. parapsilosis) and the use of fluconazole as a prophylactic agent increases the incidence of the resistant species.

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. [58] 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.

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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 Renal Best Practice Guidelines: No recommendation.

International Guidelines: ISPD Guidelines/Recommendations, 2010: Fungal peritonitis is a serious complication and should be strongly suspected after recent antibiotic treatment for bacterial peritonitis. Catheter removal is indicated immediately after fungi are identified by microscopy or culture (Evidence).

Prolonged treatment with antifungal agents to determine response and attempt clearance is not encouraged.

Intraperitoneal Antibiotic Dosing Recommendations for CAPD Patients (ISPD guidelines)

<table>
<thead>
<tr>
<th>Antifungals</th>
<th>Intermittent (Per exchange, once daily)</th>
<th>Continuous (mg/l; all exchanges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>NA</td>
<td>1.5</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg IP every 24-48 hours</td>
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</tbody>
</table>


Prevention of fungal peritonitis

- Most episodes of fungal peritonitis are preceded by courses of antibiotics (Evidence).
- Fungal prophylaxis during antibiotic therapy may prevent some cases of Candida peritonitis in programs that have high rates of fungal peritonitis (Evidence).
- Recommended that each PD program examine their history of fungal peritonitis and decide whether such a protocol might be of benefit particularly for patients taking prolonged or frequent courses of antibiotics (such as those with foot ulcer and osteomyelitis).
- No recommendation made it relation to a particular prophylactic agent.

SUGGESTIONS FOR FUTURE RESEARCH

1. Randomized controlled trial of the use of nystatin prophylaxis during any antibiotic course for the prevention of fungal peritonitis and also the impact of antifungals prior to gynaecological procedures for CAPD patients.
2. Establish a registry of patients with fungal peritonitis and document the treatments given and the outcomes.

CONFLICT OF INTEREST

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


### APPENDIX A

**Table 1. Fungi reported to have caused fungal peritonitis in PD patients**

<table>
<thead>
<tr>
<th>Species</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acremonium spp.</strong></td>
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<tr>
<td></td>
<td>A. kiliense</td>
<td>Lopes et al 1995</td>
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<tr>
<td></td>
<td>A. strictum</td>
<td>Bibashi et al 2002</td>
</tr>
<tr>
<td><strong>Alternaria spp.</strong></td>
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<tr>
<td></td>
<td>A. alternata</td>
<td>Ryoo et al 2009</td>
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<tr>
<td><strong>Aspergillus spp.</strong></td>
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<tr>
<td></td>
<td>A. flavus</td>
<td>Carpenter et al 1982</td>
</tr>
<tr>
<td></td>
<td>A. fumigatus</td>
<td>Stein et al 1991; Tsoufakis et al 1995</td>
</tr>
<tr>
<td></td>
<td>A. oryzae</td>
<td>Schwetz et al 2007</td>
</tr>
<tr>
<td></td>
<td>A. thermomutatus</td>
<td>Matsumoto e al 2002</td>
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<tr>
<td><strong>Aureobasidium spp.</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>A. pullulans</td>
<td>Caporale et al 1996; Ibanez Perez et al 1997</td>
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<tr>
<td><strong>Bipolaris spp.</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>B. hawaiiensis</td>
<td>Gadallah et al 1995</td>
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<tr>
<td><strong>Blastobotrys spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. proliferans</td>
<td>Quirin et al 2007</td>
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<tr>
<td><strong>Candida spp.</strong></td>
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<tr>
<td></td>
<td>Note: Candida spp. is the most commonly associated species causing fungal peritonitis (Khanna et al 1980)</td>
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<tr>
<td></td>
<td>C. albicans</td>
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<tr>
<td></td>
<td>C. dubliniensis</td>
<td>Lo et al 2002</td>
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<td></td>
<td>C. famata</td>
<td>Gupta et al 2006</td>
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<tr>
<td><strong>Species</strong></td>
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<tr>
<td>C. guilliermondii</td>
<td></td>
<td>Saran et al 1996</td>
</tr>
<tr>
<td>C. glabrata</td>
<td></td>
<td>Cecchin et al 1984; Banerjee et al 1994</td>
</tr>
<tr>
<td>C. krusei</td>
<td></td>
<td>Saran et al 1996</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td></td>
<td>Garcia-Martos et al 1991</td>
</tr>
<tr>
<td>C. norvegensis</td>
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<td>Nielsen et al 1990</td>
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<tr>
<td>C. parapsilosis</td>
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<td>Kaitwatcharachai 2002</td>
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<tr>
<td>C. rugosa</td>
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<td>C. sake</td>
<td></td>
<td>Guclu et al 2008</td>
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<td>C. tropicalis</td>
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<td>Saran et al 1996</td>
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**Cephalosporium spp.**

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<tr>
<td>C. acremonium</td>
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<td>Landay et al 1982</td>
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**Chrysonilia spp.**

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<tr>
<td>C. sitophila</td>
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<td>Radix et al 1996</td>
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**Coccidioides spp.**

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<th><strong>Reference</strong></th>
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<tbody>
<tr>
<td>C. immitis</td>
<td></td>
<td>Ampel et al 1988</td>
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**Cryptococcus spp.**

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</thead>
<tbody>
<tr>
<td>C. laurentii</td>
<td></td>
<td>Sinnott et al 1989</td>
</tr>
<tr>
<td>C. neoformans</td>
<td></td>
<td>Morris et al 1992</td>
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**Cunninghamella spp.**

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<th><strong>Reference</strong></th>
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<tbody>
<tr>
<td>C. berthetiae</td>
<td></td>
<td>Pimental et al 2006</td>
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</table>

**Curvularia spp.**

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<th><strong>Reference</strong></th>
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<tbody>
<tr>
<td>C. geniculata</td>
<td></td>
<td>Vachharajani et al 2005</td>
</tr>
<tr>
<td>C. inaequalis</td>
<td></td>
<td>Pimental et al 2005</td>
</tr>
<tr>
<td>C. lunata</td>
<td></td>
<td>DeVault et al 1985</td>
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**Cylindrocarpon spp.**

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<th><strong>Type</strong></th>
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<tbody>
<tr>
<td>C. lichenicola</td>
<td></td>
<td>Sharma et al 1998</td>
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**Deschlera spp.**

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<tbody>
<tr>
<td>D. australiensis</td>
<td></td>
<td>Moulsdale et al 1981</td>
</tr>
<tr>
<td>Species</td>
<td>Type</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>D. spilicera</td>
<td>O’Sullivan et al 1981</td>
<td></td>
</tr>
<tr>
<td>Exophiala spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. jeanselmeii</td>
<td>Kerr et al 1983; Agarwal et al 1993</td>
<td></td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. dimerum</td>
<td>Gaur et al 2010</td>
<td></td>
</tr>
<tr>
<td>F. moniliforme</td>
<td>Rippon et al 1988</td>
<td></td>
</tr>
<tr>
<td>F. solani</td>
<td>Bibashi et al 2002</td>
<td></td>
</tr>
<tr>
<td>Geotrichum spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G. capitatum</td>
<td>Hernandez Jaras et al 1987</td>
<td></td>
</tr>
<tr>
<td>Histoplasma spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. capsulatum var capsulatum</td>
<td>Lopes et al 1994</td>
<td></td>
</tr>
<tr>
<td>Lecythophora spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. mutabilis</td>
<td>Ahmad et al 1985</td>
<td></td>
</tr>
<tr>
<td>Malassezia spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. furfur</td>
<td>Johnson et al 1996</td>
<td></td>
</tr>
<tr>
<td>M. pachydermatis</td>
<td>Fine et al 1983</td>
<td></td>
</tr>
<tr>
<td>Mucor spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucor spp. are responsible for zygomycosis (formerly mucormycosis). Zygomycosis may be caused by a number of fungi. These are presented in Table 2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neosartorya spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. pseudofischeri</td>
<td>Ghebremedhin et al 2009</td>
<td></td>
</tr>
<tr>
<td>Paecilomyces spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillium spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. parasiticum</td>
<td>Prasad et al 2004</td>
<td></td>
</tr>
<tr>
<td>P. obovatum</td>
<td>King et al 1993</td>
<td></td>
</tr>
<tr>
<td>Species</td>
<td>Type</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td><strong>Pichia spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>P. ohmeri</em></td>
<td>Choy et al 2000</td>
</tr>
<tr>
<td><strong>Rhodotorula spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>R. glutinis</em></td>
<td>Wood et al 1985</td>
</tr>
<tr>
<td></td>
<td><em>R. mucilaginosa</em></td>
<td>de Zoysa et al 2001; Unal et al 2009</td>
</tr>
<tr>
<td></td>
<td><em>R. rubra</em></td>
<td>Eisenberg et al 1983</td>
</tr>
<tr>
<td><strong>Saccharomyces spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. cerevisiae</em></td>
<td>Gomila Sard et al 2009; Snyder S 1992</td>
</tr>
<tr>
<td><strong>Scedosporium spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Syncephalastum spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trichoderma spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>T. harzianum</em></td>
<td>Guiserix et al 1996</td>
</tr>
<tr>
<td></td>
<td><em>T. longibrachiatum</em></td>
<td>Tanis et al 1995</td>
</tr>
<tr>
<td></td>
<td><em>T. pseudokoningii</em></td>
<td>Rota et al 2000</td>
</tr>
<tr>
<td></td>
<td><em>T. viridae</em></td>
<td>Loeppky et al 1983</td>
</tr>
<tr>
<td><strong>Trichosporon spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>T. asahii</em></td>
<td>Jian et al 2008; Rodrigues et al 2006</td>
</tr>
<tr>
<td></td>
<td><em>T. beigelii</em></td>
<td>Melez et al 1995</td>
</tr>
<tr>
<td></td>
<td><em>T. cutaneum</em></td>
<td>Carr et al 1987</td>
</tr>
<tr>
<td></td>
<td><em>T. inkin</em></td>
<td>Lopes et al 1997</td>
</tr>
<tr>
<td><strong>Verticillium spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wangiella spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>W. dermatididis</em></td>
<td>Greig et al 2003; Vlassopoulos et al 2001</td>
</tr>
<tr>
<td><strong>Zygomycetes spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Algae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prototheca spp.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>P. wickerhamii</em></td>
<td>O’Connor et al 1986; Sands et al 1991</td>
</tr>
</tbody>
</table>
Table 2. Fungi that cause zygomycosis

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoraceae</td>
<td>Absidia spp.</td>
<td>A. corymbifera</td>
</tr>
<tr>
<td></td>
<td>Apophysomyces spp.</td>
<td>A. elegans</td>
</tr>
<tr>
<td></td>
<td>Mucor spp.</td>
<td>M. circinelloides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. hiemalis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. racemosus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. ramosissimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. rouxianus</td>
</tr>
<tr>
<td></td>
<td>Rhizopus spp.</td>
<td>R. pusillus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. arrhizus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R. azygosporus</td>
</tr>
<tr>
<td>Cunninghamellaceae</td>
<td>Cunninghamella spp.</td>
<td>C. bertholletiae</td>
</tr>
<tr>
<td>Mortierellaceae</td>
<td>Mortierella spp.</td>
<td></td>
</tr>
<tr>
<td>Saksenaceae</td>
<td>Saksenaea spp.</td>
<td>S. vasiiformis</td>
</tr>
<tr>
<td>Syncephalastraceae</td>
<td>Syncephalastrum spp.</td>
<td>S. racemosum</td>
</tr>
<tr>
<td>Thamnidaceae</td>
<td>Cokeromycetes spp.</td>
<td>C. recurvatus</td>
</tr>
</tbody>
</table>
### Table 3. Azole antifungal agents

<table>
<thead>
<tr>
<th>Activity</th>
<th>Ketoconazole</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue penetration</td>
<td>Poor penetration into peritoneum</td>
<td>Good, including into the central nervous system</td>
<td>Poor penetration into peritoneum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interactions</td>
<td>Significant Via P450 QT interval prolongation</td>
<td>Significant Via P450 QT interval prolongation</td>
<td>Significant Via P450 QT interval prolongation</td>
<td>Weak CYP3A4 inhibitor Safety and efficacy in children not yet established</td>
<td>Significant Via cytochrome P450 QT interval prolongation</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Impairment of liver enzymes common. Stop if levels rise &gt;2-3 x upper limit of normal. GI upset Gynaecomastia and irregular menses Hypoadrenalism</td>
<td>Routine liver function monitoring is not required for short-term use Liver function monitoring should be considered.</td>
<td>Congestive heart failure Liver function monitoring should be considered.</td>
<td></td>
<td>Transient visual disturbances (20%-30%) Skin rashes (7%) including photo-sensitivity Use not recommended in people with severe hepatic impairment</td>
</tr>
</tbody>
</table>
The KHA-CARI Guidelines – Caring for Australasians with Renal Impairment

<table>
<thead>
<tr>
<th></th>
<th>Ketoconazole</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td>Acid-dependent oral absorption</td>
<td>Well absorbed following oral administration</td>
<td>Not altered by hypochlorhydria, PPIs or H2 receptor antagonists or antacids</td>
<td>Acid-dependent oral absorption</td>
<td>Decreased by proton pump inhibitors or histamine H2-receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Decreased by proton pump inhibitors or histamine H2-receptor antagonists</td>
<td></td>
<td></td>
<td></td>
<td>Administered with a meal, preferably containing fat</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Not significantly excreted in the urine</td>
<td>Renal: 90% unchanged</td>
<td></td>
<td></td>
<td>Renal dysfunction or dialysis IV formulation should be avoided</td>
</tr>
<tr>
<td><strong>Dosing adjustment</strong></td>
<td>(Loading dose required = normal dosing for first 2 days)</td>
<td>Renal impairment</td>
<td>Renal impairment</td>
<td></td>
<td>Dosage adjustment for renal failure by GFR</td>
</tr>
<tr>
<td>&gt; 50 mL/min normal</td>
<td>&gt; 50 mL/min normal</td>
<td>&gt; 50 mL/min normal</td>
<td>&gt; 50 mL/min normal</td>
<td>&gt; 50 mL/min normal</td>
<td></td>
</tr>
<tr>
<td>10 to 50 mL/min normal</td>
<td>10 to 50 mL/min normal 50% 24-hourly</td>
<td>10 to 50 mL/min normal</td>
<td>10 to 50 mL/min normal</td>
<td>10 to 50 mL/min normal</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mL/min normal</td>
<td>&lt; 10 mL/min normal 50% 24-hourly</td>
<td>&lt; 10 mL/min normal</td>
<td>&lt; 10 mL/min normal</td>
<td>&lt; 10 mL/min normal</td>
<td></td>
</tr>
</tbody>
</table>

**Doses for dialysis**

<table>
<thead>
<tr>
<th></th>
<th>HD normal</th>
<th>HD as for GFR &lt;10 mL/min, dose after dialysis</th>
<th>HD normal</th>
<th>HD normal</th>
<th>HD Oral: normal IV: not recommended</th>
</tr>
</thead>
</table>

Peritonitis Treatment and Prophylaxis (February 2014) Page 27
### Table: Peritonitis Treatment and Prophylaxis

<table>
<thead>
<tr>
<th>Method</th>
<th>CAPD</th>
<th>CAPD as for GFR &lt;10 mL/min (50 mg/day IP, oral 100 mg daily) 150 mg in single 2L dialysate bag every 48 hours. Paediatric 60 mg/kg IP or IV</th>
<th>CAPD</th>
<th>CAPD</th>
<th>CAPD Oral: normal IV: not recommended Voriconazole is partially removed by HD, while the vehicle is cleared less efficiently</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPD normal</td>
<td></td>
<td></td>
<td>CAPD normal</td>
<td>CAPD normal</td>
<td></td>
</tr>
<tr>
<td>CRRT normal</td>
<td>CRRT 200 to 400 mg 24-hourly</td>
<td>CRRT normal</td>
<td>CRRT normal</td>
<td>CRRT normal</td>
<td>CRRT Oral: normal IV: not recommended</td>
</tr>
</tbody>
</table>

* CRRT includes continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD) and continuous venovenous haemodiafiltration (CVVHDF).
APPENDIX B

Amphotericin: General product information

- Treatment of choice for most serious systemic fungal infections.
  - Prototheca wickerhameii algae also sensitive to amphotericin.
- Toxic drug
- Close observation during first dose. Regular monitoring of serum electrolytes, renal function and full blood count is essential.

Amphotericin B desoxycholate is the conventional form of amphotericin.

Amphotericin is also available as a lipid complex or liposomal formulation, which have different dosing schedules and infusion rates.

NOTE: Dosage and infusion rates are not interchangeable between the different formulations. Fatal errors have occurred when the dosage and infusion rates have not been appropriate for the product.

Conventional amphotericin B desoxycholate doses should not exceed 1.5 mg/kg/day.

Adverse reactions are common with amphotericin and various measures are used to minimise toxicity.

Pre-hydration not required for dialysis patients (for non-dialysis patients 0.5 to 1 L of sodium chloride 0.9% IV before amphotericin infusion is strongly recommended). Hydrocortisone, antihistamines, antiemetics, opioids or an antipyretic may provide symptomatic relief. If severe immediate reactions continue, or renal impairment develops rapidly, or the patient fails to respond, and other alternatives are not appropriate, then a liposomal or lipid formulation of amphotericin can be substituted with fewer toxic effects but much greater cost.

Amphotericin B desoxycholate: dosage adjustment for renal failure by GFR

<table>
<thead>
<tr>
<th>GFR Range</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 mL/min</td>
<td>normal</td>
</tr>
<tr>
<td>10 to 50 mL/min</td>
<td>avoid and consider using lipid complex or liposomal amphotericin. If essential, normal</td>
</tr>
<tr>
<td>&lt; 10 mL/min</td>
<td>avoid and consider using lipid complex or liposomal amphotericin. If essential, normal</td>
</tr>
</tbody>
</table>

Doses for dialysis

- HD: if essential, normal (avoid during acute renal impairment)
- CAPD: if essential, normal (avoid during acute renal impairment)
- CRRT: if essential, normal (avoid during acute renal impairment)
Amphotericin lipid complex: dosage adjustment for renal failure by GFR

- > 50 mL/min: normal
- 10 to 50 mL/min: normal
- < 10 mL/min: normal

Doses for dialysis

- HD: normal
- CAPD: normal
- CRRT: normal

Amphotericin liposomal: dosage adjustment for renal failure by GFR

- > 50 mL/min: normal
- 10 to 50 mL/min: normal
- < 10 mL/min: normal

Doses for dialysis

- HD: normal
- CAPD: normal
- CRRT: normal

Responsiveness to amphotericin

Resistant
- Trichosporon
- Alternaria
- Exophiala sp.
- Phialospora sp.

Some responsiveness
- Paecilomyces sp.
- Acremonium sp.
- Fursarium sp.

**Flucytosine**

Fluorinated pyrimidine converted in fungal cells to fluorouracil inhibitor of thymidine synthase – DNA replication

- Intravenously, orally, intraperitoneally
- Mainly used for its synergistic effect, in combination with amphotericin, against Cryptococcus neoformans.
- ~80% excreted unchanged in urine.
- Removed by haemodialysis and PD
- Toxicity
  - Bone marrow suppression
  - Rash
  - Severe enterocolitis
- Monitoring plasma concentrations is advised
  - Toxicity is associated with peak flucytosine plasma concentrations above 100 mg/L.
  - Monitoring recommended in patients with renal impairment and in all patients receiving concomitant amphotericin.
  - Trough concentrations should be kept above 25 mg/L to maintain efficacy.
  - Full blood counts should also be regularly monitored.

**Dosage adjustment for renal impairment**

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40</td>
<td>normal</td>
</tr>
<tr>
<td>20 to 40</td>
<td>100% 12-hourly</td>
</tr>
<tr>
<td>10 to 20</td>
<td>100% 24-hourly</td>
</tr>
<tr>
<td>&lt;10</td>
<td>100% 24- to 48-hourly</td>
</tr>
</tbody>
</table>

**Doses for dialysis**

- HD as for GFR <10 mL/min, dose after dialysis
- CAPD 0.5 to 1 g/day
- CRRT 100% 12- to 24-hourly
Nystatin

- Polyene antifungal
- Mainly active against *Candida* spp.
- Not active against dermatophytes
- Poorly absorbed from the gastrointestinal tract
- Not absorbed through skin or mucous membranes when applied topically
- No change for renal impairment or dialysis modality.

Echinocandins

Caspofungin, micafungin and anidulafungin: Inhibit the synthesis of β-(1,3)-D-glucan, an essential component of the cell wall of many fungi not present in mammalian cells.

Pharmacokinetics of anidulafungin, caspofungin and micafungin are similar

- IV only
- Half-life is 9-15 hours with once-daily dosing
- All highly protein bound (more than 95%)
- Renal clearance minimal. No dose alteration renal impairment or haemodialysis
- Distributed to most organs including the brain, however, cerebrospinal fluid (CSF) concentrations are low
- Reportedly minimal effects on cytochrome P450 system
  - BUT an interaction with cyclosporin with increased caspofugin levels and increased liver enzymes reported (AST, ALT).
- No reduction in renal impairment. Not dialysable.
- Dose reduction necessary in moderate hepatic dysfunction
- No experience of use in severe hepatic impairment
- Reported side effects
  - Fever (>10%)
  - Raised LFTs (1–10%)
  - Hypokalaemia (1–10%)
  - Nausea/vomiting (1–10%)
  - Possibility of histamine-mediated symptoms
  - No effect on ECG especially QT intervals.
- No reported cross resistance with azoles and without toxicity associated with polyene drugs
- Concurrent dosing with voroconazole and liposomal amphotericin B did not impact pharmaokinetics of either drug.
Spectrum of activity of echinocandins

Fungicidal activity against:
- *Candida* spp.: including triazole-resistant isolates
- Similar to each other in vitro activity against *Candida* spp.
  - miconafungin and anidulafungin similar (MICs) and generally lower than the MIC of caspofungin
- Resistance to echinocandins low to date but occasional reports of acquired resistance in *Candida* spp.

Fungistatic activity against:
- *Aspergillus* spp.

Inherently resistant fungi:
- *Cryptococcus neoformans*
- *Trichosporon* spp.
- *Fusarium* spp.
- *Zygomycetes*
- *Scedosporium* spp.
- *Pseudoallescheria* spp.
- *Rhodotorula* spp.

Terbinafine
- Monitor for myelosuppression.

Dosage adjustment for renal failure by GFR

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>Dosage (normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>normal</td>
</tr>
<tr>
<td>10 to 50</td>
<td>100% 48-hourly</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>100% 48-hourly</td>
</tr>
</tbody>
</table>

Doses for dialysis
- HD: as for GFR <10 mL/min, dose after dialysis
- CAPD: as for GFR <10 mL/min
- CRRT: as for GFR <10 mL/min
References for tables


