Review

J Ped. Nephrology 2017;5(1)
http://journals.sbmu.ac.ir/jpn

A Review on Fungal Infections and Their Treatments in Children with Renal Disorders

How to Cite This Article: Nateghian A. A Review on Fungal Infections and Their Treatments in Children with Renal Disorders. J Ped. Nephrology 2017;5(1)

Alireza Nateghian*

Pediatric Infection Diseases Department, Ali-Asghar Children Hospital, Iran University of Medical Sciences.

***Corresponding Author**
Alireza Nateghian, MD, Pediatric Infection Disease Department, Ali-Asghar Children Hospital, Vahid dasgerdi st., Tehran, Iran.
Email: nateghan.ar@iums.ac.ir
Tel: +98(21)23046211
Fax: +98(21)22220043

Fungal infections especially invasive ones (IFI), now are among well-known and hard to manage problems in various kidney diseases in children. Various databases including pubmed, scopus, ovid and Web of Science Core Collection were looked for keywords including antifungals, fungal infections, kidney diseases Since 1990 to 2017. Renal side effects were looked using the site WWW.DRUG.COM as well. For common cases with Identified Pathogens Infectious diseases society of America (IDSA) recommendations for antifungal therapy as the most acceptable plan has been summarized at the end of article; specific therapeutic issues have been also discussed in their sections.

Keywords: Fungal Infections; Renal Diseases; Acute Kidney Injury; Hemodialysis; CAPD, Kidney Transplantation.

Received: Jan-2017
Revised: Jan-2017
Accepted: Jan-2017

Running Title: Treatments of Fungal Infections in Renal Disorders

Introduction

Fungal infections especially invasive ones (IFI), now are among well-known and hard to manage problems in various kidney diseases in children. However, given the nonspecific presentation of these infections and introduction of new antifungal drugs with less experience in pediatric setting both from clinical efficacy and potential nephrotoxicity points of view, there is a need for periodic review of this issue.

Therefore, various databases including pubmed, scopus, ovid and Web of Science Core Collection were looked for keywords including antifungals, fungal infections, kidney diseases Since 1990 to 2017. Renal side effects were looked using the site WWW.DRUG.COM as well. For common cases with Identified Pathogens Infectious Diseases Society of America (IDSA) recommendations for antifungal therapy as the most acceptable plan has been summarized at the end of article; specific therapeutic issues have been also discussed in their sections.

Why children with kidney diseases are more prone to IFI?

Effects of immunosuppression and environmental exposure in various kidney disorders can make these patients vulnerable to IFI [1]. For example, after renal transplantation, T-helper cell activity is important determinant of rejection, for which Calcineurin inhibitors are prescribed and by this way the amount of interleukin 2 (IL-2) the major cytokine active for rejection is controlled [2]. Among patients with acute renal failure, although uremic state and acidosis may impair the immune response, but the role of other factors like invasive procedures specially having CVP line, hyperalimentation, impaired reticuloendothelial system as in collagen vascular diseases, presence of catheters and duration of previous antibacterial therapy makes the patient prone to IFI [3,4]. In case of obstructive ARF, including renal stone, there is increased risk of fungal infection specially candida infection of urinary tract [5].

Fungal infections in various renal disorders, Acute renal failure

Fungal infections are more common in kids with Acute renal failure (ARF) due to mentioned factors specially when they are on dialysis [3,6].

Candida infections are the most common type of fungal infections in these patients [7]; therefore, it is critical to remove the catheter and starting an appropriate less nephrotoxic drug like lipid preparations of amphotericin B or fluconazole; it would be much better to have local data regarding the types of candida spp and their sensitivity patterns. Some studies suggest to start with fluconazole and change it if there is no response to even high doses of this drug [6].

In the absence of other underlying risk factors, rhinocerebral mucormycosis and aspergillosis have rarely been reported in patients with ARF but they need to be treated more aggressively with AMB preparations.

Chronic renal failure, Hemodialysis

Patients on hemodialysis have many of previous risk factors more deeply and are quite prone to IFI especially with candidiasis and less frequently with other fungi like cryptococcosis and mucormycosis (especially with concurrent use of desferroxamine). These IFI are so aggressive and need prompt diagnosis and treatment [1]. non-albicans Candida species in an adult study was related to the presence of CVP line in patients undergoing chronic hemodialysis but again most of them were sensitive to fluconazole [8].

Skin and nail superficial dermatophytosis, most commonly due to Trichophyton rubrum is seen also in children with ESRD and hemodialysis for whom Terbinafine seems a good candidate but treatment should be adjusted according to creatinine clearance [9].

Chronic ambulatory peritoneal dialysis (CAPD)

A rare but potentially dangerous event in children is fungal peritonitis [10].

It comprises about 2-15% of peritonitis episodes [10] but may have a mortality rate around 30%. It may damage the peritoneal cavity so further dialysis may be impossible [11]. Other complications beside sclerosing peritonitis are adhesions with resulting bowel obstructions or stricture, invasion of the bowel wall, and abscess formation [1].

Candida species including C. albicans, C. tropicalis, and C. parapsilosis are the most common pathogens [10,11,12].

Peritoneal fluid usually is contaminated due to any problem with sterile techniques, exit site infection and transmission of fungi across the gut are also important in pathogenesis but recent or previous antibiotic therapy (especially during past 3 months), particularly for bacterial peritonitis is very important risk factors for fungal peritonitis [10,11,13].

The definition of fungal peritonitis is when there is isolation of fungi from PD fluid associated with fever, pain in abdomen (in 75% of cases), cloudy peritoneal fluid (in 90% of cases) containing at least 100 white blood cells/μl with at least 50% polymorphonuclear cells [12,1]. Sometimes there are lots of eosinophils in the peritoneal fluid which might be due to fungal peritonitis as well [1]. Other rare signs might be milky appearance of fluid, the presence of hyphal aggregates as black streaks in the fluid or Poor return of the dialysate specially due to non-candida organisms (particularly Fusarium and Aspergillus spp) [1].

In some adult studies, the presence of abdominal pain, bowel obstruction and late removal of the catheter have been associated with higher mortality and failure of further possibility for CAPD [11]. In a new study in adult it was shown that white blood cell (WBC) count greater than 3,000/mm [3] at presentation in peritoneal fluid can be a predictor of death [14].

Treatment of fungal peritonitis first include the removal of PD catheter as soon as possible (due to presence of biofilm); however rarely intraperitoneal injection of antifungal agents have been successful without catheter removal [15]. Conventionally for empirical treatment a combination of intravenous amphotericin B and flucytosine or oral fluconazole and flucytosine have been used. According 2010 update of ISPD guideline, Initial therapy as a combination of amphotericin B and flucytosine, until the culture results are available with susceptibilities is acceptable. Then other drugs like echinocandins (e.g., caspofungin or anidulafungin), fluconazole, posaconazole, or voriconazole may replace amphotericin B based on species identification and MIC values. Intraperitoneal use of amphotericin causes chemical peritonitis and pain; IV use leads to poor peritoneal bioavailability. Voriconazole or posaconazole are alternatives for amphotericin B especially when filamentous fungi have been cultured. Neither of them can be used alone for Candida peritonitis (with catheter removal) [16]. Voriconazole at a dose of 200 mg IV twice daily for 5 weeks after catheter removal has been used successfully [17]. Azole compound would be better to be associated

with flucytosine to avoid resistance and it's better to continue both drugs at least for 10 days after removal of catheter. 10 days after catheter removal. Posaconazole for 6 months has been used successfully for the treatment of liposomal amphotericin B-resistant PD related Mucor peritonitis [18]. Also, aspergillus and non-responding non-albicans Candida peritonitis can be treated by various echinocandins (e.g., caspofungin, micafungin, and anidulafungin) [10]. Caspofungin with or without amphotericin has been used successfully [19].

Bone marrow suppression should be monitored when using flucytosine [16].

There are some studies which show that prophylactic fluconazole during treatment of bacterial peritonitis may be effective for prevention of fungal peritonitis [12]. Also to avoid fungal peritonitis it is recommended that any fungal infection around dialysis site or even vaginal infection should be treated in CAPD patients [1].

Fungal Infections in Renal Transplant Patients

More effective immunosuppressive therapy has increased the survival of renal transplant recipients and also has made them prone to invasive fungal infections, specially candidiasis

And less frequently aspergillosis, cryptococcosis and other rare fungi like zygomycosis [2]. These infections mainly occur during first 6 months after transplantations [6,7]. Invasive aspergillosis especially as a nosocomial inhalational problem after constructional activities has a very high mortality [20].

Presentations and risk factors of invasive fungal infections after renal transplantation

Subtle presentation of fungal infections in these patients as well as non-specific and often normal laboratory data may make the diagnosis difficult. Any persistent fever after 5 days or relapsing fever specially when on treatment of effective antibiotics should be considered suspicious particularly if new or progressive pulmonary infiltration or hemoptysis is also present [2]. Diabetes and prolonged pre-transplant dialysis may predispose these cases to invasive fungal infections [21]. The most common candida infection after renal transplantation in children is urinary tract infection [20]. for invasive aspergillosis following risk factors are considered as risk factors: Prolonged and severe neutropenia, High dose corticosteroids, readmission in PICU and occurrence of acute renal failure or need to hemodialysis [22, 23].

Diagnosis of invasive fungal infections after renal transplantation

The gold standard is fungal isolation, and staining with fungal specific dies in tissues and fluids, but at least for invasive aspergillosis which has higher mortality, it may be impractical as blood cultures are rarely positive and the yield of BAL in those with respiratory symptoms is not sufficient [20]. So, Radiologic studies and antigen detection techniques like galactomannan antigen levels (as a polysaccharide in the Aspergillus cell wall that is released during fungal growth) should be considered in these cases [20]. The galactomannan assay can detect aspergillosis very early, but sensitivity and specificity in solid organ transplant patients may not be as good as in other immunosupressed hosts, so some studies recommend to repeat this test when it's negative [24]. This test is also helpful for response to therapy [20] and can also be done on BAL fluid, cerebrospinal fluid (CSF), and urine but with a high variation in terms of sensitivity and specificity among various studies [20].

Also Aspergillus polymerase chain reaction (PCR) in blood or BAL in children has good sensitivity and specificity (85% and 75% respectively) and can also be done for detection of resistant gene in the fungi [20].

A positive result of an India ink preparation of CSF or detection of capsular antigen in CSF instead of culture is enough for diagnosis of Cryptococcus infection [25].

Characteristic radiologic findings of invasive aspergillosis is less common in children but one should do his best to apply various imaging studies like. CT scans, chest radiographs, and abdominal ultrasonography for some evidences of fungal infections in various organs and starting antifungal treatment accordingly [20,2].

Overview of nephrotoxicity of various antifungal agents:

Amphotericin B (AMB)

Deoxycholate form of AMB is an old drug which is effective in most invasive fungal infections but nephrotoxicity of this drug has always been concerning specially in kids with kidney disorders [26,27]. Serum creatinine elevation to >1.5 x baseline and >2.5 x baseline values were seen in in a large study in children group in 24.8 and 8.8% of all patients, respectively: all 548 kid who

enrolled in this study were immunocompromised, around half with various cancers and half with solid organ transplants [28], more than two third of cases were also taking other nephrotoxic drugs; so conventional AMB was not tolerated or was ineffective in most cases, although no new need to hemodialysis was noted, a result which is in contrast to a large adult study in which more than half of cases had significant decrease in GFR and hemodialysis was used for 15% of cases [29]. Another retrospective study on various AMB products in children also showed that despite about occurrence of nephrotoxicity and hypokalemia, most of these events were rapidly controlled and were reversible [30]. Interestingly this study also showed that previous history of hypokalemia and neutropenia were associated with higher risks for hypokalemia.

Damage to glomerular filtration rate and distal tubulopathy with urinary loss of potassium and magnesium, sometimes Fanconi's syndrome and at last the loss of urine concentrating ability have been reported as various nephrotoxicities of conventional or Deoxycholate form of AMB [31]. Deoxycholate, the vehicle for amphotericin, can decrease the renal blood flow and glomerular filtration rate, increased salt concentrations at the macula densa: also interaction of amphotericin with ergosterol in the cell membrane, and apoptosis in proximal tubular cells and medullary interstitial cells may be important in pathogenesis [31].

Risk factors: higher cumulative doses, use of diuretics, abnormal serum creatinine (SCr) levels at baseline, dosing schedule and use of concomitant nephrotoxic drugs specially cyclosporine, tacrolimus, diuretics, aminoglycosides [26,29,31].

Intradialytic use of amphotericin B has been shown in an adult study to be generally effective and safe provided that a standard maintenance dose of 0.5 to 1.0 mg/kg amphotericin B intravenously thrice weekly during hemodialysis sessions is used [32].

Management of nephrotoxicity: Switching to less nephrotoxic more recently produced lipid formulations of AMB (including liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion) has been associated with much lesser nephrotoxicity in various studies including pediatric age group [2,26,27,28,33,34]. The efficacy may not change [35] however. A review comparing renal toxicity of this compound could not find a significant difference and proposed economic issues important when selecting one of these compounds [33]. When there is already a problem in kidney function or appears during AMB conventional course and in those with history of concurrent long term usage of nephrotoxic drugs, it's mandatory to use these products instead of AMB desoxycholate [27]. However, a retrospective study on adults failed to show any improvement in renal function at least immediately after switching to these compounds [26].

Adjuvant sodium supplementation which has been reported to be effective in protecting kidney function in adults might also be effective in extremely low birth weight infants when prescribing conventional AMB but needs more study [27]. Paying attention to volume repletion and usage of amiloride for serious potassium loss has also been recommended in a pediatric study to manage the renal side effects of AMB [31]. liposomal AMB has also been used in an adult ICU cases with hemodynamic instability and has shown to have little effect on renal function and can be used safely in clinically hemodynamically unstable patients [36], a finding which need more studies in pediatric population.

Voriconazole

As a broad specterum antifungal which is effective on most candida, Cryptococcus and Aspergillus spp, voriconazole has been increasingly used in clinical practice [37]. This drug has many interactions with other drugs and they should be considered before and during concurrent use with other drugs like CYP 450 isoenzyme related drugs and specially cyclosporine; so usually the dose of this drug is reduced by half the level of cyclosporine should be monirored as it's level me be higher [38]. This interaction may increase the risk of serious side effects such as kidney problems, diabetes, nervous system disorders, hyperkalemia (high potassium levels in the blood), high blood pressure, irregular heart rhythm, heart failure, infections, and various types of malignancies including lymphoma and skin cancer.

Overall it's safe for patients with normal renal function and even IV form of drug has not been associated with acute renal injury in patients with minimally compromised renal function [39]; however, The IV form should be avoided in moderate and severe renal insufficiency as there might be an accumulation of some toxic material (sulfobutylether-β-cyclodextrin) in the body [40]. Oral form of the drug is much safer for kidney function.

Fluconazole:
This is another tiazole antifungal with oral and IV forms which has lower specterum especially for aspergillus compared with voriconazole but has a safer profile. Caution should again be considered concurrent use with other drugs like CYP 450 isoenzyme related drugs and Calcineurin inhibitors specially cyclosporine; although both forms of drug may increase the cyclosporine level, sex and some ethnical factors might have a role in this interaction [41].
The level of urinary fluconazle is 10-20 folds higher than plasma level, making it a good candidate for fungal UTI providing the sensitive fungi is present [40].
Uncommonly (0.1% to 1%), Polyuria, renal pain and changes in renal function tests has been noted, rarely, membranous nephropathy and acute renal failure have been reported [42].

Itraconazole:
Although it has a wider spectrum than fluconazole [2] but the plasma level in children is lower than older children [40]. It has better activity on various types of aspergillus, blastomycosis and histoplasmosis than fluconazole. It has a safety profile like fluconazole and has both forms (oral and IV), a suitable drug for prophylaxis and lots of drug interactions. Limited data are available on the use of oral Itraconazole in patients with renal impairment. Renal monitoring would be better to be done periodically. Rare cases of Albuminuria have been reported as well.

Posaconazole:
A second generation of triazoles which has an exceptional activity on mucormycosis [40] as well as invasive candidiasis and aspergillusis [43].
Echinocandins (caspofungin, micafungin, anidulafungin):
These relatively new drugs which are all parenteral and have very good activity on various candida and aspergillus spp even resistant ones, have a different mechanism of action which has med them less toxic for human cells [40,44]. Renal dysfunction did not alter micafungin and caspofungin pharmacokinetics [45,46], so no dosage adjustment is necessary for caspofungin in patients with renal insufficiency. Since caspofungin is not dialyzable, no supplementary dosing is required after hemodialysis. These drugs are mainly indicated when the case is refractory to or intolerant of AMB-D, lipid formulations of amphotericin B and/or itraconazole [47]. Anidulafungin is not metabolized by or eliminated through the liver or kidney, so compared with caspofungin has a potentially wider spectrum, less toxic and better interaction profile but needs more study, similar to other echinocandins, anidulafungin can be given safely to patients with impaired renal function with no need for dosage adjustment [48].

Flucytosine:
This antimetabolite has activity against Candida and Cryptococcus, is used in conjunction of other drugs to avoid rapid resistance and as an oral agent has little renal side effect except in conjunction with AMB renal toxicity which may increase flucytosine toxicity as well [40]. Since renal impairment can cause progressive accumulation of the drug, at least kidney function should be monitored during therapy.
Summary of recommendations for more common renal related fungal infections
Although most guidelines for antifungal therapies have been published based on adult studies (Infectious diseases society of America (IDSA1-7), but there are some guidelines for children [40,49]; Overall it is believed that most general rules of antifungal therapies are the same in adults and children, however there are obviously some differences specially regarding pharmacologic issues which have been addressed in this review. Management of urinary tract infections due to candida or aspergillus spp are briefly explained according the last IDSA guidelines [50,51].

Treatment for Urinary Tract Infections Due to Candida Species

Treatment for Asymptomatic Candiduria:

Recommendations in this situation are:
1. Elimination of predisposing factors, such as indwelling bladder catheters, is recommended whenever feasible
2. Treatment with antifungal agents is NOT recommended unless the patient belongs to a group at high risk for dissemination; high-risk patients include neutropenic patients, very low-birth-weight infants (<1500 g), and patients
who will undergo urologic manipulation
3. Neutropenic patients and very low-birth-weight infants should be treated as recommended for candidemia
4. Patients undergoing urologic procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, OR AMB deoxycholate, 0.3–0.6 mg/kg daily, for several days before and after the

procedure

Treatment for Symptomatic Candida Cystitis?

Recommendations are:

1. For fluconazole-susceptible organisms, oral fluconazole, 200 mg (3 mg/kg) daily for 2 weeks is recommended

2. For fluconazole-resistant C. glabrata, AmB deoxycholate,0.3–0.6 mg/kg daily for 1–7 days OR oral flucytosine, 25 mg/kg 4 times daily for 7–10 days is recommended

3. For C. krusei, AMB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended

4. Removal of an indwelling bladder catheter, if feasible, is strongly recommended

5. AMB deoxycholate bladder irrigation, 50 mg/L sterile water daily for 5 days, may be useful for treatment of cystitis due to fluconazole-resistant species, such as C. glabrata and C. krusei.

Treatment for Symptomatic Ascending Candida Pyelonephritis:

Recommendations are:

1. For fluconazole-susceptible organisms, oral fluconazole, 200–400 mg (3–6 mg/kg) daily for 2 weeks, is recommended

2. For fluconazole-resistant C. glabrata, AMB deoxycholate,0.3–0.6 mg/kg daily for 1–7 days, with or without oral flucytosine, 25 mg/kg 4 times daily, is recommended. For fluconazole-resistant C. glabrata, monotherapy with oral flucytosine, 25 mg/kg 4 times daily for 2 weeks, could be considered

3. For C. krusei, AMB deoxycholate, 0.3–0.6 mg/kg daily, for 1–7 days is recommended

4. Elimination of urinary tract obstruction is strongly recommended.

5. For patients who have nephrostomy tubes or stents inplace, consider removal or replacement, if feasible

Treatment for Candida Urinary Tract Infection Associated with Fungus Balls?

Recommendations are:

1. Surgical intervention is strongly recommended in adults; antifungal treatment as noted above for cystitis or pyelonephritis is recommended

2. Irrigation through nephrostomy tubes, if present, with AMB deoxycholate, 25–50 mg in 200–500 mL sterile water, is recommended.

Treatment Recommendations for Renal Aspergillosis:

IDSA suggests a combined approach of medical and urologic management for renal aspergillosis. Obstruction of one or both ureters should be managed with decompression if possible and local instillation of AMB deoxycholate. Parenchymal disease is best treated with voriconazole

Recommendations for Antifungal Prophylaxis in Nonlung Solid Organ Transplant Recipients:

IDSA recommend prophylactic strategies in SOT recipients based on the institutional epidemiology of infection and assessment of individual risk factors. Prospective trials are lacking to address the need for routine anti-Aspergillus prophylaxis other than for

Lung transplant recipients. Individual risk factors have been identified in cardiac (pretransplant colonization, reoperation, CMV infection, renal dysfunction, institutional outbreak), liver (fulminant hepatic failure, reoperation, retransplantation or renal failure), and others with institutional outbreaks or prolonged or high-dose corticosteroid use. In such patients, the optimal duration of prophylaxis is not known.

Conflict of Interest

None declared

Financial Support

None declared

References

1. Gandhi BV, Bahadur MM, Dodeja H, Aggrwal V, Thamba A, Mali M.Systemic fungal infections in renal diseases. J Postgrad Med 2005 Vol 51 Suppl 1,530-536.
2. Khan A, El-Charabaty E, El-Sayegh S. Fungal Infections in Renal Transplant Patients. J Clin Med Res. 2015;7(6):371-378.
3. June- Mug sung, et al. Candidaemia in patients with dialysis dependent ARF etiology, predisposing and prognostic factors. NDT 2001;16:2348-56.
4. Nateghian A, Sedighi M. In-hospital Outcome and Main Determinants of Candida Septicemia in Children Admitted to Neonatal and Pediatric Intensive Care Units. ijca. 2016; 2 (4) :20-24 URL: http://ijca.iums.ac.ir/article-1-82-en.html
5. Weath H, Margensen P. Extracorporeal shock wave lithotripsy of a kidney stone complicated with candida albicans septicemia and endophthalmitis: case report. Scand J Urol Nephrol 1990;24:81.
6. Rex JH, Bennette TG. Candidaemia study group and the national institute of Allegy and infectious disease mycoses study group. A randomized trial company Fluconazole with Ampho B for treatment of candidaemia in patients without neutropenia. NETM 1994;331:1325-30.
7. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-ssociated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101-1111.

8. Serefhanoglu K, Timurkaynak F, Can F, Cagir U, Arslan H, Ozdemir FN. Risk factors for candidemia with non-albicans Candida spp. in intensive care unit patients with end-stage renal disease on chronic hemodialysis. J Formos Med Assoc. 2012 Jun;111(6):325-32. doi: 10.1016/j.jfma.2011.03.004.
9. Irimie, M; Tataru, A; Oanta, A; Moga, M. In vitro susceptibility of dermatophytes isolated from patients with end-stage renal disease; a case-control study.Journals@Ovid Full TextMycoses. 57(3):129-134, March 2014.
10. Matuszkiewicz-Rowinska J. Update on fungal peritonitis and its treatment. Perit Dial Int. 2009 Feb;29 Suppl 2:S161-5.
11. Wang AY, Yu AW, Li PK, Lam PK, Leung CB, Lai KN, Lui SF. Factors predicting outcome of fungal peritonitis in peritoneal dialysis: analysis of a 9-year experience of fungal peritonitis in a single center. Am J Kidney Dis. 2000 Dec;36(6):1183-92.
12. Kumar KV, Mallikarjuna HM, S. Jayanthi G. Fungal peritonitis in continuous ambulatory peritoneal dialysis: The impact of antifungal prophylaxis on patient and technique outcomes. Indian J Nephrol. 2014 Sep-Oct; 24(5): 297–301. doi: 10.4103/0971-4065.133005.
13. Hooman N, Madani A, Sharifian Dorcheh M, Mahdavi A, Derakhshan A, Gheissari A,et al. Fungal Peritonitis in Iranian Children on Continuous Ambulatory Peritoneal Dialysis,A National Experience. IJKD 2007;1:1-00.
14. Nadeau-Fredette AC, Bargman JM. CHARACTERISTICS AND OUTCOMES OF FUNGAL PERITONITIS IN A MODERN NORTH AMERICAN COHORT. *Peritoneal Dialysis International,* Vol. 35, pp. 78–84.doi: 10.3747/pdi.2013.00179.
15. Lee SH, Chiang SS, Hseih SJ, Shen HM. Successful treatment of fungal peritonitis with intracatheter antifungal retention. Adv Perit Dial. 1995;11:172–5.
16. Kam-Tao Li P, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A. ISPD GUIDELINES/RECOMMENDATIONS PERITONEAL DIALYSIS-RELATED INFECTIONS RECOMMENDATIONS: 2010 UPDATE. Peritoneal Dialysis International, Vol. 30, pp. 393–423.doi:10.3747/pdi.2010.00049.
17. Kiernan L, Kliger A, Gorban-Brennan N, Juergensen P,Tesin D, Vonesh E, et al. Comparison of continuous ambulatoryperitoneal dialysis-related infections with different "Y-tubing" exchange systems. J Am Soc Nephrol 1995;5:1835–8.
18. Sedlacek M, Cotter JG, Suriawinata AA, Kaneko TM,Zuckerman RA, Parsonnet J, et al. Mucormycosis peritonitis:more than 2 years of disease-free follow-up afterposaconazole salvage therapy after failure of liposomal amphotericin B. Am J Kidney Dis 2008; 51:302–6.
19. Fourtounas C, Marangos M, Kalliakmani P, Savidaki E,Goumenos DS, Vlachojannis JG. Treatment of peritoneal dialysis related fungal peritonitis with caspofungin plus amphotericin B combination therapy. Nephrol Dial Transplant 2006; 21:236–7.
20. Michael Green Marian G. Michaels. Infections in Pediatric Solid Organ Transplant Recipients. J Pediatric Infect Dis Soc (2012) 1 (2): 144-151.DOI:https://doi.org/10.1093/jpids/pir001.
21. Abbott KC, Hypolite I, Poropatich RK, Hshieh P, Cruess D, Hawkes CA, Agodoa LY, et al. Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis. 2001;3(4):203-211.
22. Wattier RL, Ramirez-Avila L. Pediatric Invasive Aspergillosis. J. Fungi 2016, 2, 19; doi:10.3390/jof2020019.
23. Gavalda J, Len O, San Juan R, Aguado JM, Fortun J,Lumbreras C, Moreno A, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a casecontrol study. Clin Infect Dis. 2005;41(1):52-59.
24. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis.Clin Infect Dis. 2006;42(10):1417-1427.
25. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis.2008;46(12):1813-1821.
26. Olga M. Klibanov; Ralph H. Raasch; John C. Rublein. Changes in Renal Function After Changes in Antifungal Drug Therapy, Am J Health Syst Pharm. 2004;61(1).
27. Bes DF, Rosanova MT, Sberna N, Arrizurieta E. Deoxycholate amphotericin B and nephrotoxicity in the pediatric setting. Pediatr Infect Dis J. 2014 Aug;33(8):e198-206. doi: 10.1097/INF.0000000000000299.
28. Wiley JM, Seibel NL, Walsh TJ. Efficacy and safety of amphotericin B lipid complex in 548 children and adolescents with invasive fungal infections. Pediatr Infect Dis J. 2005 Feb;24(2):167-74.
29. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. Clin Infect Dis. 2000 Nov;31(5):1155-63. Epub 2000 Nov 7.
30. Dutta A, Palazzi DL. Risk factors of amphotericin B toxicty in the nonneonatal pediatric population. Pediatr Infect Dis J. 2012 Sep;31(9):910-4. doi: 10.1097/INF.0b013e31825d649a.
31. Goldman RD, Koren G. Amphotericin B nephrotoxicity in children. J Pediatr Hematol Oncol. 2004 Jul;26(7):421-6.
32. WOOD JE, MAHNENSMITH MP; MAHNENSMITH RL, PERAZELLA MA. Intradialytic Administration of Amphotericin B: Clinical Observations on Efficacy and Safety. Am J Med Sci 2004;327(1):5–8.
33. Cannon JP, Garey KW, Danziger LH. A prospective and retrospective analysis of the nephrotoxicity and efficacy of lipid-based amphotericin B formulations. Pharmacotherapy. 2001 Sep;21(9):1107-14.
34. Saliba F, Dupont B. Renal impairment and amphotericin B formulations in patients with invasive fungal infections. Med Mycol. 2008 Mar;46(2):97-112. doi: 10.1080/13693780701730469.
35. Barrett JP, Vardulaki KA, Conlon C, Cooke J, Daza-Ramirez P, Evans EG et al. A systematic review of the antifungal effectiveness and tolerability of amphotericin B formulations. Clin Ther. 2003 May;25(5):1295-320.
36. Alvarez-Lerma F, Soriano MC, Rodríguez M, Catalán

M, Llorente AM, Vidart N. Impact of liposomal amphotericin B on renal function in critically ill patients with renal function impairment. Rev Esp Quimioter. 2012 Sep;25(3):206-15.
37. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clin Infect Dis. 2003;36(5):630-637.
38. Romero AJ, Le Pogamp P, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther.2002;71(4):226-234.
39. Lilly CM, Welch VL, Mayer T, Ranauro P, Meisner J, Luke DR. Evaluation of intravenous voriconazole in patients with compromised renal function. BMC Infect Dis. 2013 Jan 16;13:14. doi: 10.1186/1471-2334-13-14.
40. Allen UD. Antifungal agents for the treatment of systemic fungal infections in children.Paediatr Child Health 2010;15(9):603-8.
41. Mathis AS; DiRenzo T; Friedman G; Kaplan B; Adamson R. SEX AND ETHNICITY MAY CHIEFLY INFLUENCE THE INTERACTION OF FLUCONAZOLE WITH CALCINEURIN INHIBITORS 12. Journals@Ovid.2001;71(8):1069-1075.
42. Shin GT, Yim H, Park J, Kim H "Membranous nephropathy associated with fluconazole treatment." Am J Kidney Dis 49 (2007): 318-22.
43. Moore JN, HealyJR, ,Kraft WK. Pharmacologic and clinical evaluation of posaconazole. Expert Rev Clin Pharmacol. 2015 May; 8(3): 321–334.Doi: 10.1586/17512433.2015.1034689.
44. Van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis.2004;39(10):1407-1416.
45. Hebert MF, Smith H E., Marbury, TS, Swan SK et al. Pharmacokinetics of Micafungin in Healthy Volunteers, Volunteers with Moderate Liver Disease, and Volunteers With Renal Dysfunction.Journals@Ovid journal of Clinical Pharmacology. 45(10):1145-1152, October 2005.
46. Muilwijk E, Lempers V, Burger D,Warris A, Pickkers P, Aarnoutse R et al. Impact of special patient populations on the pharmacokinetics of echinocandins.Expert Rev. AntiInfect. Ther. 13(6), 799–815 (2015)
47. Maertens J, Raad I, Petrikkos G, Boogaerts M, Selleslag D, Petersen FB, Sable CA, et al. Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. Clin Infect Dis. 2004;39(11):1563-1571.
48. Dowell J, Stogniew M,Krause D .Anidulafungin dosage adjustments are not required for patients with hepatic and/or renal impairment [abstract P-1222]Program and abstracts of the 13th European Congress of Clinical Microbiology and Infectious Diseases (Glasgow, UK)2003,Basel, Switzerland .European Society of Clinical Microbiology and Infectious Diseases).
49. Lestner JM, Versporten A, Doerholt K, Warris A, Roilides E, Sharland M, Bielicki J, Goossens H, ARPEC Project Group. 2015. Systemic antifungal prescribing in neonates and children: outcomes from the Antibiotic Resistance and Prescribing in European Children (ARPEC) study. Antimicrob Agents Chemother .59:782–789. doi:10.1128/AAC.04109-14.
50. Pappas PG Kauffman CA, Andes DR, Clancy CJ, Marr et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America, Clinical Infectious Diseases® 2016;62(4):e1–50.
51. Patterson TF, Thompson GR Denning DW Fishman JA Hadley S et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America Clinical Infectious Diseases® 2016;63(4):e1–60.