



Systemic fungal infections in renal diseases

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ABSTRACT

Invasive fungal infections are a major challenge in the management of immunocompromised patients and those with renal dysfunction. These challenges are due to the immense morbidity and mortality in such situations. Also the management strategies for invasive mycosis in patients with renal dysfunction have narrow safety profile and involve high-cost. In this review we will discuss the issues involved in the management of invasive mycosis in the patients with renal dysfunction in the form of acute renal failure, chronic kidney disease, dialysis dependency of renal transplant recipients. We also emphasize that the use of Intravenous Liposomal Amphoterecin appears to be an effective alternative to the conventional Amphoterecin B for the treatment of invasive fungal infections in patients with renal dysfunction due to its greatly improved tolerability profile. Commercially two true liposomal preparations (Fungisome and Ambisome) are available. Judgement about the preferred formulation should be made on the basis of disease morbidity, severity of renal dysfunction and the cost involved.

KEY WORDS: Systemic fungal infections, Renal disease, Liposomal Amphotericin B

Invasive fungal infections have gained importance recently with increased incidence in patients with renal disease and kidney transplant recipients under effects of immunosuppression and environmental exposure. They also remain the major cause of death among these patients. These infections can be encountered in patients with acute renal failure, chronic renal failure on conservative therapy and on dialysis, and those undergoing renal transplantation. However, since they are frequently subtle in presentation and difficult to manage, early diagnosis and prompt therapy requires a high degree of suspicion and vigilance. While managing fungal infections in patients with renal failure, it is crucial to optimize the pharmacokinetics of antifungal drugs to reduce the risk of nephrotoxicity.

Epidemiological aspects

Causative agents^[1]

Very few fungal species are pathogenic and produce human illness under special circumstances – especially when patients' immune status has been altered by native disease or by therapy directed at some other diseases. Among these species are

Endemic or pathogenic fungi: These include Histoplasmosis, Blastomycosis, Coccidioidomycosis, Paracoccidioidomycosis, Sporothrix schenckii and Cryptococcus neoformans. These fungi exist in the environment as moulds. Following invasion of human tissue, they convert to their tissue-invasive form. These are capable of invading any immunocompromised host and producing an infection. Following inhalation and conversion to invasive form, they remain in lungs or disseminate systemi-

cally. In normal immunocompetent hosts, their propagation is checked by effective cell-mediated immunity. This course can be profoundly altered if the infecting dose is massive or if cell-mediated immunity is abnormal because of an underlying immunodeficiency state.

Opportunistic fungi: These are: *Aspergillus* species, *Rhizopus* (Mucorales) species and *Candida* species (most common). *Aspergillus* infections are perhaps ten times as common as mucor infections. When spores of these filamentous fungi are inhaled, neutrophils are able to dispose these off in normal circumstances. If there is some abnormality in their function, infection with opportunistic fungi occurs.

Predisposing factors

Systemic fungal infections are encountered commonly in immunocompromised settings like diabetes mellitus, HIV infection, haematological malignancy, neutropaenia secondary to chemotherapy, IgG deficiency states, long-term glucocorticoid therapy, prolonged antibiotic therapy and patients with renal dysfunction and renal transplantation.

Invasive fungal diseases are increasingly observed in immunocompromised patients especially those with protracted granulocytopenia and in patients with progressively declining CD4+ T cells and other perturbations in immune function. Current evidence indicates that adequate granulocytes in number and function, as well as intact cell-mediated immunity, are keys to successful outcome in patients with opportunistic yeast and mould diseases. Cellular immunity also plays an important role in the host's containment of the



endemic mycoses.

Immune mechanisms in renal failure

Immune defects observed in end-stage renal diseases, although poorly understood, may be related to metabolic and nutritional abnormalities resulting from the uremic milieu. Both cellular and humoral immunities are impaired, with the degree of impairment related to the duration of the uremic state.^[2] Defects in cellular immunity include lymphopenia, an imbalance in the relative quantities and activities of various T-lymphocyte subsets, decreased lymphocyte response to antigenic stimulation, and impaired phagocytosis. Defects in humoral immunity are mostly due to impaired helper T-cell function affecting antibody production.

Fungal infections in various renal-related conditions

Acute renal failure

Patients with renal failure have a higher incidence of fungal infections than normal hosts. These infections remain a major cause of death among patients with acute renal failure (ARF). There may be some host immune defects related to uremic state, but these defects are not well defined and a minor issue regarding risk. The most common risk factor associated with higher incidence of fungal infections in patients with ARF include invasive diagnostic/therapeutic procedures undertaken and use of broad-spectrum antibacterial agents. *Candida* spp. account for 8–15% of all hospital acquired infections of which patients with dialysis dependency (those on continuous renal replacement therapy) are more prone to fungal infections than those nondialyzed.^{[3],[4]} A study reported that the proportion of ARF patients on dialysis with candidemia was 5.7%, which was significantly higher than that found in the patients of ARF who were not on dialysis.^[3] Candidemia may become prevalent in patients with ARF as they survive longer due to advances in intensive care therapy and dialysis therapy (continuous renal replacement therapy).

Other factors that predispose to these infections include SLE, indwelling central venous catheter, multiple antibiotic usage for a long time, corticosteroid therapy, neutropeania, hyperalimentation, presence of urinary catheter, nasogastric tube, or endotracheal tube, surgery within 2 weeks prior to the episode, and metabolic acidosis.^[3]

It has been observed that in such patients prompt and aggressive antifungal therapy with catheter removal is mandatory.^[3] There continues to be debate over the antifungal agent to be used, appropriate dosage, and optimal duration of treatment for Candidemia infection. Amphotericin B has been historically the drug of choice for candidemia. However, its use is limited by its toxicity. In an effort to decrease the toxicity of conventional amphotericin B, Liposomal amphotericin was developed. Commercially only two (Fungisome and Ambisome) true liposomal preparations of amphotericin B are available. Both these preparations have been shown to be safe and effective in presence of acute renal failure in several clinical trials. However, a multicentric trial comparing Fluconazole with Am-

photericin B for invasive fungal infection showed comparable efficacy.^[4] Amphotericin being nephrotoxic, it is reasonable to try Fluconazole first in patients with candidemia in the ARF setting. If there is no clinical improvement, higher dosages of fluconazole may be tried (> 400 mg/day) or amphotericin B in dosages of 0.3–0.5 mg/kg/day. The mortality rate is high in ARF patients with candidemia, especially in those with APACHE II scores of ≥ 18 and in those who receive antifungal therapy for <48 h.^[4] A few cases of rhinocerebral mucormycosis have been reported in India in the ARF setting.^[5]

ARF secondary to obstructive lesions is known to predispose to candidemia as in patients with renal stones causing obstruction, prostatic hypertrophy, infected penile prosthesis, and chronic bladder catheterization. Cases have also been reported with renal aspergillosis giving rise to obstructive uropathy and recurrent anuric ARF. Shock wave lithotripsy has been related to fungemia and even *Candida* endocarditis and endophthalmitis in patients who have concomitant infection/colonization of urinary tract with yeast. Hence, such patients are candidates for peri-procedure antifungal therapy to prevent possible dissemination.^[6] In a series of studies on fungal infections of kidney by Raghavan *et al.*^[7] candidiasis was the most common mycoses encountered.

Chronic renal failure

Hemodialysis

Dialysis patients are at increased risk of fungal infection mortality compared to the general population. United States renal data system (USRDS) reported candidiasis (79%) as the dominant etiology of fungal infection in chronic dialysis patients. However, the frequency of cryptococcosis (6%) and coccidioidomycosis (4%) was higher than previously reported.^[8] These patients also appear predisposed to mucormycosis with the international registry reporting 59 cases among dialysis patients. Presentations include dissemination in 44%, rhinocerebellar in 31%, and other sites in 25%. Unfortunately, the diagnosis is made at autopsy in the majority of cases. Without treatment, the case fatality rate was 86% and remained high at 72% despite Amphotericin B treatment.^[9]

The major risk factor identified in this series was the concurrent administration of desferroxamine, primarily indicated for aluminum and iron overload. The desferroxamine-iron chelate, feroxamine, has been demonstrated to act as a siderophore to mucor and to stimulate both growth and pathogenicity in vitro.^[9]

Chronic ambulatory peritoneal dialysis (CAPD)

Peritoneal dialysis is an alternative to hemodialysis (HD) for CRF patients. Fungal Peritonitis (FP) is a rare complication of peritoneal dialysis (PD). It is often severe and carries higher mortality than bacterial peritonitis (BP). Incidence of FP comprises 2–15% of total peritonitis episodes as reported in the literature.^[10] In CAPD fungal infections; *Candida* species such as *C. albicans*, *C. tropicalis*, and *C. parapsilosis* are common etiological agents.^[11]

The most common reasons for contamination of peritoneal



fluid with fungi are breaks in sterile technique when connecting peritoneal catheters to dialysate bag, exit site infection, intestinal perforation, peritoneovaginal fistulae, and transmigration of fungi across the bowel wall into the peritoneum. Almost all published series have found an association with both recent antibacterial use and episodes of BP.^{[10],[12]}

The manifestations of FP in CAPD patients are cloudy dialysate (90%) and abdominal pain 75%. Rarely, the dialysate has been described as milky. There are also reports of black flecks observed in the returning fluid, a finding subsequently found to represent hyphal aggregates.

Poor return of the dialysate during episodes of FP seems to occur more frequently with infections by *Fusarium* and *Aspergillus* species, which can potentially block the tiny holes of the PD catheters. Although evidence of extra peritoneal fungal infection is almost always lacking, fungal skin infections or vaginal candidiasis should be looked for and if present treated aggressively since they represent potential sources of infection. With FP, the peritoneal white blood count is almost always greater than 200 cells/ml, with polymorphonuclear cell predominance. The finding of eosinophils in the peritoneal fluid of a patient on chronic PD with suspected infection should raise the consideration of fungi as the etiologic agents. Culture negative peritonitis in CAPD patients may be caused by *Malassezia furfur*, which requires addition of mineral oil or any other lipid over the agar for in vitro growth. Abdominal pain and fever in patients and catheter in site were identified as risk factors associated with mortality.^[12]

The FP carries a high morbidity and mortality than BP. Reported complications include sclerosing peritonitis, adhesions with resulting bowel obstructions or stricture, invasion of the bowel wall, and abscess formation.

At SGPGI (Lucknow), Prasad *et al.*^[12] observed that of 261 patients who underwent CAPD, FP was detected in 28 patients, one episode in each patient (14.3% of the total peritonitis). *Candida* species and diatomaceous fungi ± *Candida* species were responsible for 89.3% and 10.7% of episodes, respectively. Patients with preceding BP developed FP more frequently (25.6%) than de novo cases (2.9%).

In a prospective study at the University of Miami, FL, USA, six patients had FP (All *Candida* sp.; mean age = 6 years). Two of these patients were neonates with Tenckhoff catheter placement at less than 1 week of age.^[13]

Treatment

The treatment of FP is controversial. The goals of treatment should be twofold: the infection should be eradicated and the peritoneum should be preserved for future use for PD. With these goals in mind, the following general approach to treatment seems most reasonable.

Upon diagnosis of FP, the peritoneum should be lavaged until the returning fluid is clear. This lowers the fungal burden and prevents adhesions. It is also recommended that PD catheters be removed as soon as possible because retained catheter may serve as a nidus for persistent infection. Although there are several reports of patients with FP in whom the peritoneal fluid became sterile with antifungal therapy, heavy fungal colonization of the peritoneal catheter is found when these catheters were subsequently removed. Thus, sterile peritoneal fluid does not always indicate eradication of sequestered fungi.

Systemic antifungal therapy [Table 1] has variable penetration into peritoneal fluid and tissues, thereby resulting in a high rate of failure with systemic therapy alone. Amphotericin B given intravenously does not result in high levels in the peritoneal fluid but provides adequate levels in the peritoneal tissues. Although fluconazole penetrates well into the peritoneum (60–70% of serum levels can be achieved), the administration of this agent alone usually does not eradicate infection.^[14]

Some have advocated alternative regimens in which the catheter is initially not removed. Peritonitis treatment recommendations published in 2000 suggest that FP be treated with a combination of Fluconazole (200 mg/day orally or intraperitoneally) with Flucytosine (2 g loading dose followed by 1 gm daily as a maintenance dose) for 4–7 days. Dose of fluconazole may be increased to >400 mg/day with removal of catheter if there is no response after 4 days or fluconazole be substituted with amphotericin B in dosages of 0.3–0.5 mg/kg IV. Treatment should be continued for 4–6 weeks.^[15]

Instillation of Amphotericin B into peritoneal cavity has also occasionally been used as the sole or adjunctive therapy but often leads to painful exudative reactions. The choice of antifungal agent varies based upon the type of offending organism and the immune status of the patient.

If the fungus is a mold or an azole-resistant yeast, or if the patient is severely immunosuppressed, use of intravenous Amphotericin B for at least 2 weeks at a dose of 0.4–0.6 mg/kg/day for yeasts and 0.6–1.0 mg/kg/day for molds is advised.

Table 1: Dosages of antifungal agents used in the treatment of fungal peritonitis

Drug	CAPD intermittent dosing (once/day)		CAPD continuous dosing (per liter exchange)	
	Anuric	Nonanuric	Anuric	Nonanuric
Amphotericin	NA	NA	MD 1.5 mg	NA
Flucytosine	2 g LD, then 1 g q.d. p.o.	ND	As intermittent	ND
Fluconazole	200 mg q.d.	ND	As intermittent	ND
Itraconazole	100 mg q.12 h	100 mg q.12 h	100 mg q.12 h	100 mg q.12 h
V CZ	200 mg 12 h	200 mg 12 h	200 mg 12 h	200 mg 12 h

Na – Not applicable ND – No data.



Use of intravenous Liposomal Amphotericin B appears to be an effective alternative to conventional Amphotericin B in the management of immunocompromised patients. Use of this drug is facilitated by its greatly improved tolerability profile compared with conventional Amphotericin B. In an open label, randomized comparative phase III trial, an indigenously developed Liposomal Amphotericin B (Fungisome™) has been shown to be safe and effective in systemic fungal infections in patients not responding to plain Amphotericin B, resistant to flucytosine and ketoconazole. Because of this, Liposomal Amphotericin B should be preferred to conventional Amphotericin B in the management of suspected or proven fungal infections in immunocompromised patients with preexisting renal dysfunctions, Amphotericin B induced toxicity, or failure to respond to conventional Amphotericin B.

Infections due to diatomaceous molds should probably be treated with Itraconazole (200 mg/day) in addition to amphotericin B.

The patient should be maintained with hemodialysis during treatment with systemic antifungal agents. In some hemodynamically unstable patients who are unable to tolerate hemodialysis, the removal of the PD catheter may be exceedingly difficult since they are dependent upon PD for renal replacement therapy. In this situation, a temporary catheter can be placed with instillation of antifungal agents into the peritoneum; Miconazole (100 mg/l in 2 l) instead of Amphotericin B is better tolerated. A new peritoneal catheter can be placed once a full course of systemic therapy is finished and there is complete resolution.

Fungal infections after transplantation

Recipients of solid organ transplants have 6–10% incidence of opportunistic fungal infections with a very high mortality of 70–100% in the Indian subcontinent.^{[16],[17]} Reports of systemic mycoses from western countries among this population reveal a prevalence of 1.4–9.4%.^[18] Thus, systemic mycosis is a significant and often a lethal problem in renal transplant population through out the world; but is much more so in developing countries because of more intense immunosuppression, delay in diagnosis and management, and overcrowded environment.

Predisposing factors

Use of immunosuppressive agents (Cyclosporine, steroids Azathioprine, etc.), broad-spectrum antibiotics, indwelling catheters, number of surgical procedures, disruption of intestinal or bladder mucosa, hyperglycemia, Cytomegalovirus disease, and chronic liver disease are the common predisposing factors encountered.^{[16],[19]} The high rate of fungal infections in our patients is most probably related to the unhygienic and sanitary conditions that continue to be prevalent in the tropical environment of third world countries.^{[16],[17]}

Most fungal infections involve nosocomial or environmentally acquired pathogens, such as *Candida*, *Aspergillus*, *Zygomycosis* (*Mucor*), *Cryptococcus* species and *Pneumocystis carinii*, and the geographically restricted mycoses (coccidioidomycosis, histoplasmosis, etc.), presenting as either reactive or newly

acquired disease. *Aspergillus*, *Cryptococcus*, and *Candida* are the major causative pathogens.^{[16],[17],[19]} In data from USRDS registry, fungal infections in postrenal transplant patients were most commonly associated with secondary diagnoses of oesophagitis (23.9%), pneumonia (19.8%), meningitis (7.6%), and urinary tract infection (10.3%).^[19] Also, in this study most fungal infections (66%) had occurred by 6 months post-transplant but only 22% by 2 months.^[19] Fungal infections after transplantation appear to occur in two groups. In the initial 4 weeks after transplantation, Candidiasis of the oropharyngeal, vaginal, or intertriginous area may be seen and is related to intravenous lines, bladder catheters, or surgical wounds. After 4 weeks, net accumulation of immunosuppression allows opportunistic fungal infections such as *Cryptococcus neoformans*, *Aspergillus*, etc., to occur. The following fungal syndromes are observed:

Candidiasis

Mucocutaneous, disseminated, UTI, obstructing fungal elements of genitourinary system, pneumonia, peritonitis, and endocarditis. All species of *Candida* have been implicated, speciation important because of varying sensitivity to azoles and Amphotericin B

Cryptococcosis

Central nervous system (CNS), pulmonary, dermatologic, skeletal, and organ-specific disease

Aspergillosis

Pneumonia, genitourinary, CNS, rhinocerebral, gastrointestinal, and skin

Zygomycosis

Rhizopus and *Mucor* species

Pneumocystis

Pneumonia

Histoplasmosis

Pneumonia or disseminated disease

Other fungal pathogens observed are dermatophyte, etc. that may cause cutaneous lesions.

Treatment

For mucocutaneous candida infection, topical therapy with clotrimazole or nystatin is usually effective, but if this fails fluconazole therapy is suggested. In general, mucocutaneous overgrowth can be prevented by treatment of high-risk patients (those receiving antibiotic therapy, or high-dose immunosuppression) with nystatin oral washes. Penetration beyond the mucocutaneous border can be prevented by careful use of indwelling catheters. For this reason, candiduria should be aggressively treated with fluconazole or low-dose intravenous Amphotericin B with or without flucytosine. For disseminated disease, either Amphotericin B or fluconazole can be used.

For life-threatening infection, Amphotericin B is probably more effective because it controls the infection sooner, although fluconazole is less toxic. Fluconazole increases cyclosporine



levels and therefore cyclosporine levels must be frequently checked when patient is on fluconazole. Liposome Amphotericin has been used instead of Amphotericin B because there is less nephrotoxicity with similar efficacy; however, it is very expensive.

Post-transplant Mycoses: the Indian scenario

In a recently published study, prevalence of systemic mycoses was reported as 6.6%^[16] from Southern India similar to that in North India.^[17] Reports from western countries reveal a varying prevalence from 1.4 to 9.4%. This difference with the west is due to less intense immunosuppression resulting in lower systemic mycoses in western countries and the presence of poor hygienic and diagnostic facilities in developing countries.

The risk factors for mycoses include CMV disease, chronic liver disease, hyperglycemia and tuberculosis, and post-transplant period with CSA.^[16] The overall probability of survival was poor; however, survival has recently improved.^[16]

The major pathogens implicated here are *Aspergillus* (recently on upsurge), *Cryptococcus*, and *Candida* with 45% localizing to lungs.^[16] In another study by Gupta,^[20] 9.8% post-transplant patients had systemic mycoses with candidiasis (2.8%), aspergillosis (2.3%), mucormycosis (2%), and cryptococcosis (1.9%). He also reported a recent rise in angio-invasive infections like aspergillosis and mucormycosis, which are associated with high mortality.

Treatment of fungal infections: Special considerations in renal disease

Amphotericin B

Amphotericin B exerts its antifungal effect by disruption of fungal cell wall synthesis because of its ability to bind to sterols, primarily ergosterol. Reversible decline in GFR develops in up to 80% of patients receiving Amphotericin B, usually within 2 weeks after the initiation of therapy. It causes distal tubule damage that leads to decreased urinary concentration, distal renal tubular acidosis, potassium, magnesium wasting, and occasional renal vasoconstriction. Patients with advanced age, history of diuretic use (which causes hypovolemia or electrolyte imbalance), preexisting renal dysfunction, and hypokalemia are at risk of Ampho-B toxicity. This can be avoided by prior infusion of normal saline. The plasma creatinine concentration usually does not exceed 2.5 mg/dl (220 μ mol/l) in the absence of another insult such as volume depletion or concomitant nephrotoxic use. Measurements of renal function should be performed daily during initiation of therapy (up to 2 weeks) and at least weekly thereafter, if stable.

Amphotericin B is effective in patients with aspergillosis, candidosis, blastomycosis, coccidioidomycosis, cryptococcosis, fusariosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, and certain forms of mucormycosis, hyalohyphomycosis and phaeohyphomycosis. Its effectiveness is less in patients with aspergillosis and candidosis in neutropenic patients.

Standard dosage is 0.5–1.0 mg/kg/day IV for 10–14 days and up to 1.5 mg/kg/day can be used for disseminated infection.

Common adverse effects are chills, fever, vomiting, muscle, and joint pains, and deterioration of renal function and progressive normochromic anemia is indicative of bone marrow depression. Precaution to prevent side effects – to prevent precipitations, do not reconstitute with saline, maintain high fluid and salt intake, increase dose gradually, decrease dosage if renal function deteriorates substantially, and monitor renal function, potassium, and blood count regularly.

Some physicians recommend that Amphotericin B administration be held or a lipid-based formulation substituted if the plasma creatinine concentration exceeds 2.5 mg/dl (265 μ mol/l). It is not unusual for Amphotericin B to cause transient nephrotoxicity.

To decrease adverse effects, various forms of Amphotericin B are available like Liposomal Amphotericin B, Amphotericin B Colloidal Dispersion (ABCD), and Amphotericin B Lipid Complex (ABLC).^[21] Liposomal Amphotericin B is the only product that contains true liposomes. Liposomal Amphotericin B is definitely less nephrotoxic than normal Amphotericin B and even ABLC and ABCD. The chief advantage of Liposomal Amphotericin B is its greatly improved tolerability profile compared to conventional Amphotericin B. Clinical experiences are now sufficient to state that lipid formulations of Amphotericin B have a clear safety profile. All commercially available lipid formulations have well-defined size range, C_{max} , volume of distribution (V_d), and AUC. However, it is not clear whether these differences are clinically relevant (Dupont 2002). An Indian Liposomal Amphotericin B (FungisomeTM) has recently been approved for the treatment of life-threatening fungal infection. The cost of daily treatment with this preparation would be 8–10 times less than the commercially available Liposomal Amphotericin B. Thus, this preparation is an economical option for the treatment of systemic fungal infections in Indian patients. The comparative properties of Amphotericin B and commercially available lipid formulations of Amphotericin B are outlined in the table 2.

Caspofungin

It is a newer antifungal agent and is still not available in India. It is very effective against invasive forms of candidosis, candidemia, and invasive form of aspergillosis. The normal dose is 70 mg on the first day followed by 50 mg daily for 14 days. Response to this is 85.1% compared to 66.7%.^{*} It is well tolerated but can cause fever, rash, nausea, and vomiting, and transient elevation of liver enzymes.

Azole antifungals

They are non-nephrotoxic, and can be administered orally. The first such oral drug, ketoconazole, has largely been supplanted by newer, more effective, less toxic triazole derivatives such as fluconazole and itraconazole. The azole family of antifungals can be classified into two groups: the imidazoles (clotrimazole, ketoconazole, miconazole) and the triazoles (fluconazole, itraconazole, VCZ).



Table 2: Comparative properties of Amphotericin B and commercially available lipid formulations of Amphotericin B

	Amphotericin B (plain)	Ambisome	Fungisome™	ABCD	ABLC
Dose (mg/kg)	1	3	1	1.5	5
Peak blood level (µg/ml)	3.6	29	1.01	2.5	1.7
Area under curve	34.2	423	11.42	56.8	9.5
Half-life (h)	34	23	17.21	235	173.4
	Second phase	Second phase	Second phase	Third phase	
Clearance (ml/kg/h)	40.2	22.2	91.76	28.4	211

Fluconazole

Fluconazole is water-soluble and is absorbed almost completely after an oral dose. It is excreted largely unchanged in urine and has a half-life >24 h, facilitating use in single daily doses. Fluconazole pharmacokinetics is altered in patients with renal insufficiency as its elimination is predominantly via the kidney. Indeed, studies showed that the elimination half-life may increase to up to 98 h in patients with a creatinine clearance of <20 ml/min, whereas it is ~30 h in patients with normal renal function. Dosage reduction of fluconazole is thus mandatory in patients with renal impairment, i.e. patients with a creatinine clearance of <60 ml/min. In patients whose creatinine clearance is between 10 and 60 ml/min, it is recommended to reduce fluconazole maintenance doses by 50%, by halving the unitary dose or by doubling the dosing interval. The adaptation only concerns the maintenance dose and not the loading dose, which should be the same as for patients with normal renal function, as usually performed for most drugs.^[22] Fluconazole is dialyzable.

It has high penetration into CSF (>70% of serum levels) and has been especially useful for the treatment of cryptococcal and coccidioidal meningitis. It also provides an effective, less toxic alternative to amphotericin B for the treatment of candidemia in non-neutropenic patients. Although it was originally approved for the treatment of systemic mycoses in 200–400 mg daily doses, doses as high as 800 mg/day may be needed for some seriously ill patients with certain mycoses and daily doses of >1000 mg have been given in limited trials without apparent toxicity.

Itraconazole

Itraconazole has become the standard treatment for lymphocutaneous sporotrichosis as well as mild or moderately

severe histoplasmosis, blastomycosis, or paracoccidioidomycosis. It also has been proven effective in the treatment of mild cases of invasive aspergillosis, some cases of coccidioidomycosis, and certain types of chromomycosis. Because of its high lipid solubility and protein binding, itraconazole blood levels tend to be low, but tissue levels are generally high. Drug levels are negligible in urine or CSF. Itraconazole has been used successfully to clear some types of fungal meningitis, although it is not the drug of choice.

Voriconazole

The VCZ is a newer antifungal therapy and has a broad spectrum of activity against *Candida* species, *Cryptococcal neoformans*, *Aspergillus* species, *Fusarium* species, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Dermatophyte* species, and dematiaceous. It is ineffective against zygomycetes.

It is recommended in the treatment of serious fungal infection in immunocompromised patients with acute invasive aspergillosis (response rate 53%), invasive candidosis (response rate 71%), and in cases of infection due to fusarium (response rate 43%) and scedosporium.

The recommended initial adult IV dosage of VCZ in patients with invasive aspergillosis or infections caused by *Scedosporium apiospermum* or *Fusarium* spp. is 6 mg/kg by IV infusion every 12 h for 2 doses, followed by a maintenance dosage of 4 mg/kg by IV infusion every 12 h until the patient can be switched to oral therapy. In patients with moderate-to-severe renal impairment (creatinine clearance less than 50 ml/min), IV VCZ should be used only when clearly needed because of potential accumulation of the IV vehicle, sulfobutyl ether β -cyclodextrin sodium. No adjustment in oral VCZ dosage is necessary in

Table 3: Treatment regimens for various fungal infections

Infection	Drug	Dose/day	Duration
Candiduria	Ampho-B	0.3–0.5 mg/kg	Depends on clinical picture
	Fluconazole	100–200 mg	2–4 weeks
Candidemia/Disseminated candidiasis	Ampho-B	0.5–1 mg/kg	2–4 weeks
	Lipid-Ampho-B	1–5 mg/kg	2–4 weeks
Mucormycosis	Fluconazole	200–400 mg	For at least 2 weeks
	Ampho-B	0.5–1 mg/kg	6–8 weeks
Invasive Aspergillosis	Lipid-Ampho-B	1–5 mg/kg	(Cumulative dose 2–2.5 gm)
	Ampho-B +	1–1.5 mg/kg	Clinical picture
	Lipid-Ampho-B	3–5 mg/kg	Usually 8–12 weeks
Cryptococcosis	Itraconazole	400 mg/day	6 months (after Ampho-B)
	Ampho-B +	>0.7 mg/kg	For 2 weeks
	Lipid-Ampho-B	3–5 mg/kg	For 2 or more weeks
	Fluconazole	200–400 mg	For around 6 weeks



Table 4: Renal correction for various antifungal agents

Drug	Dose for normal renal function	GFR > 50 ml/min	GFR 10–50 ml/min	GFR < 10 ml/min	Supplement for dialysis
Amphotericin B	0.3–0.5 mg/kg/day	100%	100%	100%	None
Fluconazole	200–400 mg/day	100%	100%	50%	Hemo: dose after dialysis CAPD: as for GFR <10 CRRT: dose for GFR 10–50
Flucytosine	150 mg/kg/d in 3–4 divided doses	25–50 mg/kg 12 h	25–50 mg/kg 12 h	50 mg/kg 12 h	Hemo: dose after dialysis CAPD: 0.5 g/d. CRRT: for GFR 10–50
Itraconazole	100–200 mg 12 h	100%	50–100%	100 mg 12–24 h	None
VCZ	6 mg/kg 12 hrly 1st day followed by 4 mg/kg/day Orally 200 mg BD	No IV Rx 100%	No IV Rx 100%	No IV Rx 100%	

patients with renal impairment.

Adverse effects include transient visual disturbances (> 30%), GI upsets, exfoliative cutaneous reaction, and elevation in liver function tests in 13% of recipients.

Flucytosine (5-FC)

Due to a high incidence of both primary and secondary resistance, use of 5-FC as monotherapy is restricted to the treatment of chromomycosis and localized candidal infections, which are not life threatening. Combination therapy with amphotericin B is employed in severe, invasive fungal infections such as cryptococcal meningitis and candidal infections. Although the published dose range of 5-FC is 50–150 mg/kg/day, it is recommended that 100 mg/kg/day be given orally in four equally divided doses at 6-h intervals for adult and pediatric patients with normal renal function.

References

- Schrier (editor). Diseases of the Kidney and Urinary Tract. 7th edn. Philadelphia: Lippincott Williams and Wilkins; 2000.
- Weissgarten J, Modai D, *et al*. Induction of suppressor cells in normal lymphocytes by uremic serum. *Into Arch Allergy Appl Immunol* 1986;81:180.
- June- Mug sung, *et al*. Candidaemia in patients with dialysis dependent ARF etiology, predisposing and prognostic factors. *NDT* 2001;16:2348-56.
- Rex JH, Bennette TG. Candidaemia study group and the national institute of Allergy and infectious disease mycoses study group. A randomized trial comparing Fluconazole with Ampho B for treatment of candidaemia in patients without neutropenia. *NETM* 1994;331:1325-30.
- Talwerker NC, Acharya VN, Sheth SM. Rhinocerebral mucormycosis in a case of renal failure. *JPGM* 1981;27:190-3.
- 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.
- Raghavan R, Date A, Bhaktivijayan A. Fungal and nocardial infections of the kidney. *Histopathology* 1987;11:9-20.
- Abott KC, Hypolite I. Hospitalizations for fungal infections after initiation of chronic dialysis in the United States. *Nephron* 2001;89:426-32.
- Van Cutsem J, Boleacrt JR. Effects of desferoxamine and iron on experimental mucormycosis. *KI* 1980;36:1061.
- Nagappan R, Collins JF, Lee WT. Fungal Peritonitis in CAPD: the Auckland experience. *Am J Kidney Dis* 1992;20:490-2.
- Ping – Nam wong. A retrospective study of 7 cases of candida peritonitis in CAPD patients. The therapeutic options. *Peritoneal Dialysis International* 2000;20:76-9.
- Prasad KN, Prasad N, Gupta A. Fungal peritonitis in patients on CAPD, a single center India experience. *J Infect* 2004;48:703.
- Montane BS, *et al*. Fungal peritonitis in Pediatric patients. *Adv Perit Dial* 1998;14:251-4.
- Kease WF, *et al*. Peritoneal Dialysis related peritonitis: treatment recommendation. 1996;16:551
- Keane WF, Baile GR, *et al*. ISPD guidelines/recommendations. Adult peritoneal dialysis-related peritonitis recommendations. update. *Perit Dial Int* 2000;20:396-411.
- George IJ, V. Shankar. Epidemiology of systemic mycoses among renal transplant recipients in India. *Transplantation* 2003;75:1544-51.
- Chugh KS, *et al*. High mortality in systemic fungal infection following renal transplantation in 3rd world countries. *NDT*. 1993;8:168.
- Peterson PK, Ferguson R, *et al*. Infectious diseases in hospitalized renal transplant recipients: a prospective study of complex and evolving problem. *Medicine* 1982;61:360.
- Abott KC, Hypolite I, *et al*. Hospitalisation for fungal infections after renal transplant in the United States. *Transplant Infect Dis* 2001;3:203-11.
- Gupta KL. Fungal infections and the kidney. *Indian J Nephrol* 2001;11:147-54.
- Luke RG, Boyle JA. Renal effects of Amphotericin B lipid complex. *Am J Kidney Dis* 1998;31:780-5.
- Bodhe PV, Kotwani RN, Kirodian BG, Kshirsagar, Pandya SK. Open label, Randomized, comparative Phase Iii safety and efficacy study with conventional Amphotericin B and Liposomal Amphotericin B in patients with systemic Fungal infections. *JAPI* 2002;50:662-70.
- Gokhale PC, Barapatre RJ, Advani SH, Kshirsagar NA, Pandya SK. Pharmacokinetic and tolerance of Liposomal Amphotericin B in patients. *Jr Antimicrob Chem* 1993;32:133-9.
- Lucile Cousin, Marie Le Berre, Vincent Launay-Vacher, Hassane Izzedine, Gilbert Deray. Dosing guidelines for fluconazole in patients with renal failure. *Nephrol Dial Transplant* 2003;18:2227-31.

