

ARTICLE

Fungal infections and the kidney*

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Abstract

Invasive fungal infections have gained importance recently. The opportunistic pathogens such as *Candida*, *Aspergillus*, *Mucor*, *Cryptococcus*, and *Histoplasma* are particularly known to infect the kidneys in predisposed individuals with serious complications. At the same time there is a high incidence of invasive fungal infections in patients with renal disease and kidney transplant recipients under effects of immunosuppression and environmental exposure,

The clinicopathological features and outcome were analysed in 90 patients of systemic mycoses with renal involvement, seen at PGIMER, Chandigarh, during the period Jan 1981 – Aug 2001. The fungal infections comprised of candidiasis (30), mucormycosis (28), aspergillosis (27), cryptococcosis (4) and histoplasmosis (1). Mucormycosis had most severe presentation. Acute renal failure was the main clinical feature in all except one of the 23 cases with bilateral renal involvement (95.6%). In aspergillosis renal failure occurred in 55% of patients. Renal candidiasis presented with renal papillary necrosis in half of the patients and renal failure occurred in 40% in association with other comorbid conditions. There was no clinical evidence of renal involvement in those with disseminated cryptococcosis or histoplasmosis in which renal lesions were only found at autopsy. Outcome was very poor with 82% overall mortality.

We have also analysed the records of 850 patients who had undergone renal transplantation at his institute between 1977 and 2000. Systemic fungal infections were documented in 83 (9.8%) patients, These included candidiasis in 25 (2.8%), aspergillosis in 20 (2.3%), mucormycosis in 17 (2.0%), cryptococcosis in 16 (1.9%), and rare fungi including *phaeohyphomycosis* in 3 and *histoplasmosis* in 2 patients. Incidence of invasive fungal infection was found to be very high (52%) among the 79 autopsied renal transplant recipients. In addition our analysis showed overall incidence of 10.5% esophageal candidiasis in upper GI study of 89 patients. In another analysis we found evidence of fungal invasion in 21 of the 79 (26%) patients studied for CNS complications

To conclude fungal infections of the kidney may cause varied lesions depending upon the organism. Angioinvasive fungal infections such as aspergillosis and mucormycosis are associated with severe renal lesions and renal failure with a high morbidity and mortality. These infections may occur with increased frequency in patients with renal failure and following renal transplantation with ominous complications.

Introduction

Awareness of Invasive fungal infections has increased in clinical practice with the increased survival of patients having immunocompromised states^{1, 2}. These infections

are often insidious and their diagnosis is usually delayed because of the coexisting illnesses^{3,4}. Different fungi produce characteristic patterns of tissue injury, which are modified by the special structures of the tissues in which they invade⁵.

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The renal involvement by fungi has been found to be associated with increased morbidity and mortality particularly in cases of infections by angioinvasive fungi such as *aspergillus* and *mucor*⁶⁻⁸. The invasive fungal infections also occur with increased frequency in patients

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with renal failure and following renal transplantation⁹⁻¹¹. A knowledge of the clinicopathological features of these infections is essential to make an early diagnosis and provide timely therapy. The following paragraphs discuss renal involvement in fungal infection followed by short commentary on occurrence of fungal infections following renal transplantation.

Pathogenic fungi

The fungi that involve the kidneys may be primary or opportunistic pathogens, although this distinction may not be clearly delineated in the era of advanced immunosuppression¹. Primary pathogens are indigenous to the environment and exposure to their germ spores may cause infection in apparently healthy individuals or patients who have defective cell mediated immunity. The examples are blastomyces, coccidioides and histoplasma species. On the other hand opportunistic pathogens such as candida, cryptococcus and aspergillus may be found in the environment or as commensal organisms in humans. They cause infections in patients who have defective phagocytic function due to a variety of causes that include metabolic dysfunction, chronic disease or steroid or immunosuppressive therapy. A third group has also been identified and this includes the rare and unusual fungi such as zygomycetes or paecilomyces, which may cause serious infections in predisposed individuals¹. They are difficult to differentiate from the opportunistic infections.

PGIMER experience of renal mycoses

An analysis of the biopsy and autopsy records along with review of medical case histories of patients admitted to the Institute during the last two decades (Jan 1981-Aug 2001) revealed 90 cases with systemic mycoses and renal involvement. They included 79 males and 11 females with a mean age of 25.5±18.2 years. Their diagnosis was based on histological demonstration of tissue invasion and identification of fungi by their

characteristic morphological features in the sections stained with H and E, PAS and Grocott's stains or identification of fungus on culture of the pus from the infected tissue. Their relative frequency and extent of distribution is shown in Table 1.

As regards the predisposing conditions in the patients seen by us, majority of them (77%) had one or the other associated disease which included diabetes in 17 (19%), renal transplantation in 13 (15%), liver disease in 11 (12%) and septicemia and renal disease each in 8 (9%), and tuberculosis in 6 (7%). In addition there were isolated cases with AIDS, leukemia, prematurity, malnutrition and collagen vascular disease. There were 21 patients (23%) who had no underlying disease and these included 20 of the 28 (68%) with mucormycosis and one with aspergillosis.

Clinicopathological features of pathogenic fungi

The characteristic patterns of tissue injury and clinical manifestations of some of the fungal infection involving kidneys as seen by us are described below in order of their importance:

Mucormycosis

This refers to a serious fungal infection caused by fungi of the order Mucorales and genera Rhizopus, Absidia and Mucor¹². These ubiquitous fungi are found in decaying vegetative and organic matter. They have minimal intrinsic pathogenicity but can initiate grave and often fatal infection in certain clinical conditions with compromised host defenses. Such conditions include diabetic ketoacidosis, viral hepatitis and chronic renal failure^{9,12} although mucormycosis has been known to occur in the otherwise healthy individuals as well¹³.

Depending upon the portal of entry viz. infection through inhalation, ingestion, contamination of skin wounds or via vascular channels such as intravenous drips, well

known clinical presentations of mucormycosis are described¹². These include rhinocerebral, pulmonary, gastrointestinal, disseminated or miscellaneous forms involving isolated organs including bone, heart and kidneys. Renal involvement upto 22% has been reported in patients with disseminated mucormycosis¹⁴ but isolated involvement is rare^{8,15}. The characteristic features of mucor infection is a vascular invasion with thrombosis involving large and small arteries which results in infarction and necrosis of the infected organ. Diagnosis is made by histological examination of the infected tissue and

Table1 : Renal mycoses : Extent of involvement

	Fungal infection	Disseminated	Isolated	Total
1	Candidiasis	14 (47)	16 (53)	30
2	Aspergillosis	17 (63)	10 (37)	27
3	Mucormycosis	13 (46)	15 (54)	28
4	Cryptococcosis	4 (100)	0	4
5	Histoplasmosis	1 (100)	0	1
	Overall	49 (54)	41 (46)	90

Figures in parenthesis are percentages



Fig. 1 CECT showing bilateral enlargement of kidneys with perinephric collection

demonstration of characteristic broad aseptate hyphae branching irregularly at right angles. These features can distinguish them from the slender hyphae of aspergillus which have regular dichotomous branching and frequent septae.

Among the 28 patients of renal mucormycosis diagnosed at our Institute at autopsy¹⁶ or ante-mortum biopsy¹², 13 had disseminated disease and 15 had isolated renal involvement. Main clinical features at presentation were fever (82%), flank pain and oligoanuria (78%). Renal failure occurred in 22 of the 23 (95.6%) patients with bilateral renal involvement. Additional laboratory features were leucocytosis (73%), hematuria and pyuria (65%) with evidence of gross hematuria in half of them. Radiological findings were quite revealing in these patients. The kidneys were found to be enlarged on sonography and the CECT scans (available in 14 patients) showed lack of contrast excretion, presence of intrarenal and perinephric collections which have been found to be diagnostic of mucormycosis¹⁶ (Fig 1). The renal pathology showed evidence of vasculitis with infarction and necrosis of the kidneys as well as parenchymal infiltration by acute neutrophilic infiltrate. There was evidence of hilar vessel thrombosis¹⁷ (Fig 2). glomerular and tubular hyphal invasion (Fig 3) in 50% of the kidneys examined at postmortem. Only 3 patients with unilateral involvement who underwent nephrectomy followed by chemotherapy survived while the disease was fatal in rest of them.

Aspergillosis

Aspergillosis is primarily a pulmonary infection which can cause allergic alveolitis and bronchopulmonary aspergillosis. Disseminated infection may occur in debilitated patients particularly those with diabetes mellitus, neoplasia, obstructive uropathy, cirrhosis liver and AIDS. In a postmortem analysis of 98 patients¹⁸ with aspergillosis, pulmonary involvement occurred in 94% whereas less commonly involved organs were GIT (21%), brain (13%) liver and kidney (12%) and heart (7%).

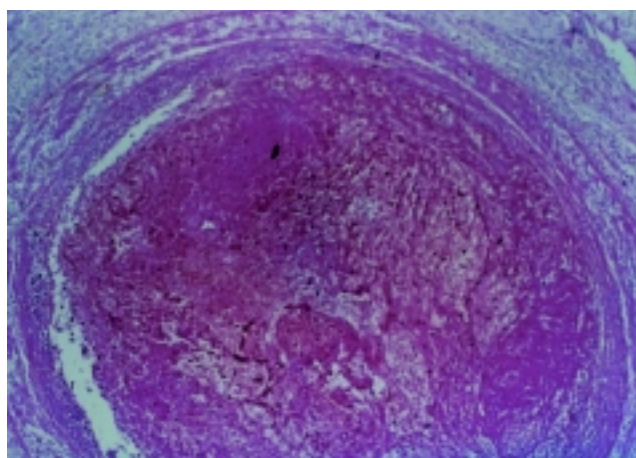


Fig. 2 Microsection of hilar vessel showing subtotal occlusion by thrombus and hyphae.

Aspergillosis of kidney may present in any other following three patterns¹⁹.

- 1 Disseminated aspergillosis with renal involvement. It results from haematogenous spread of fungi to the kidneys leading to formation of multiple focal abscesses..
- 2 Aspergillus cast of renal pelvis. It results in obstructive uropathy which may present with urinary retention or anuria and can be diagnosed by demonstration of filling defects on ultrasonography .
- 3 Ascending pan-urothelial aspergillosis It refers to the ascending infection involving the urethra, bladder, ureters and the kidney..

Among the 27 patients of renal aspergillosis seen at PGIMER, 17 had autopsy and 15 (88%) of them had disseminated infection involving lungs, brain, heart, GIT and liver. The remaining 8 patients were diagnosed by renal biopsy, and 2 of them had sloughed papillae. The pathology lesions were similar to mucormycosis but less extensive. They included microabscesses (80%), vasculitis with infarction (55%) and papillary necrosis (22%). Renal failure occurred in 15 (55%) patients. Bilateral renal aspergillosis may sometimes present with

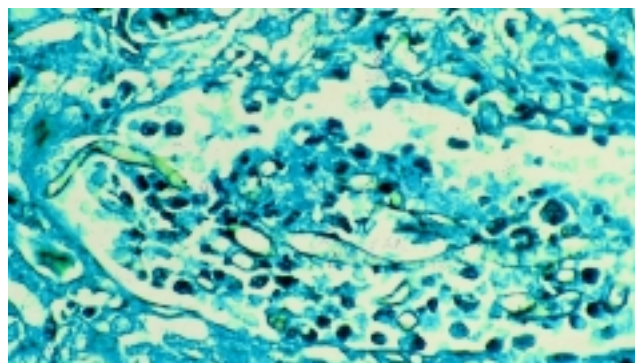


Fig. 3 Grocott's stained section of renal tubule showing in the lumen aseptate hyphae of mucor.

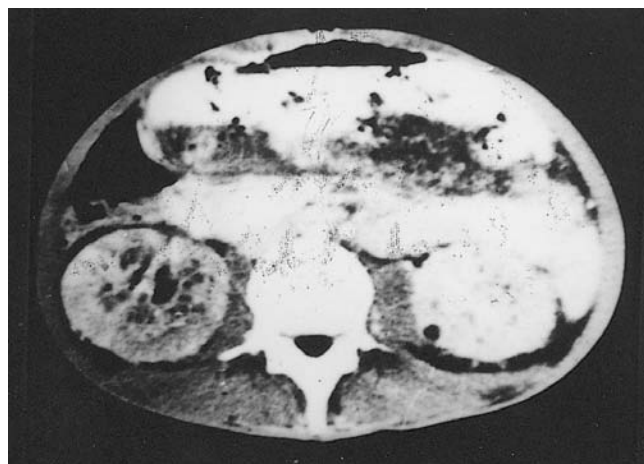


Fig. 4 CECT abdomen showing multiple low-attenuated areas in enlarged kidneys .

unexplained renal failure and is diagnosed by CT (Fig 4) or on renal biopsy in patients with a high index of suspicion⁷. Only half of 10 patients who received treatment survived whereas remaining 22 died (mortality 81%).

Candidiasis

Renal involvement in disseminated candidiasis has been increasingly recognised due to wide use of broad spectrum antibiotics, corticosteroids, prolonged urinary catheterisation particularly in patients with uncontrolled diabetes, congenital abnormalities and preexisting renal disease. *Candida* can exist in two morphological states including yeast (cellular form) and as filaments (hyphal or mycelial form, Fig 5) . It has been postulated that the hyphal form can cause invasive infection although this has not been definitely documented¹.

In an autopsy study of 39 patients with disseminated infection, renal involvement was found in 32 (82%)²⁰. The other organs involved included GIT (66%), brain (20%), lungs (61%) and spleen (19%). The pathological features of these patients have been described as microabscesses in the cortex and medulla. They are also been known to include papillary necrosis and emphysematous pyelonephritis^{21, 22}.

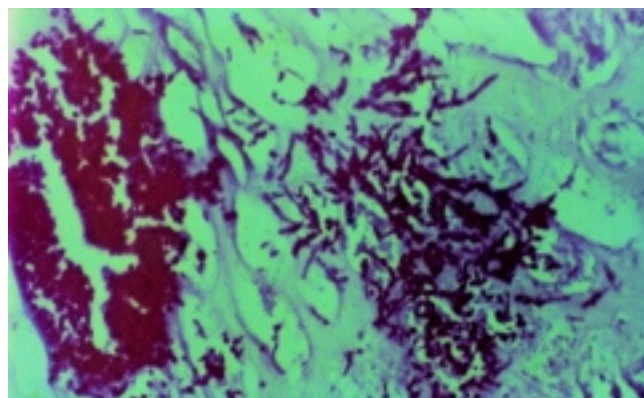


Fig. 5 Microsection of the kidney showing papillary necrosis with colonies of yeast and hyphal forms of candida.

Clinical manifestations of renal candidiasis include the fever, chills and flank pain associated with dysuria, pyuria, hematuria or candiduria. These patients may present with urinary retention or anuria or may have gradually progressive renal failure. Hence there is need of an early confirmation of diagnosis by demonstration of fungi in culture or by antigen demonstration. In addition imaging studies may show abnormalities on ultrasonography indicating evidence of filling defects in the collecting system as well presence of intrarenal abscesses which are better seen on contrast-enhanced computerised tomography²³.

In our analysis of 30 patients with renal candidiasis major pathology findings were acute pyelonephritis, microabscesses and pyonephrosis. Papillary necrosis occurred in half of the patients. Vasculitis was less common. Renal failure was documented in 12 (40%) cases but it was mainly the result of comorbid conditions these patients were suffering from. Among 11 patients who received treatment only 8 survived following antifungal therapy.

Cryptococcus

Cryptococcus neoformans is a fungus that can be found in bird excreta, decaying organic matter and soil. Initial focus of infection is usually the respiratory tract which occurs following inhalation of the fungal spores²⁴. Dissemination may occur with involvement of CNS, bones, spleen and gastrointestinal system. In a postmortem study of 39 patients with disseminated cryptococcosis 20 (51%) had renal involvement²⁵. The pathological changes in these patients ranged from sparse lymphocytic infiltration to intense granulomatous reaction in the renal parenchyma with caseation and formation of microabscesses. In no case could renal insufficiency be attributed to cryptococcal infection. Similarly in our analysis of 4 patients diagnosed at autopsy none had severe renal failure and the pathology was mainly in the form of microabscesses as well as destruction of the glomeruli (Fig 6). Diagnosis is made by identifying the

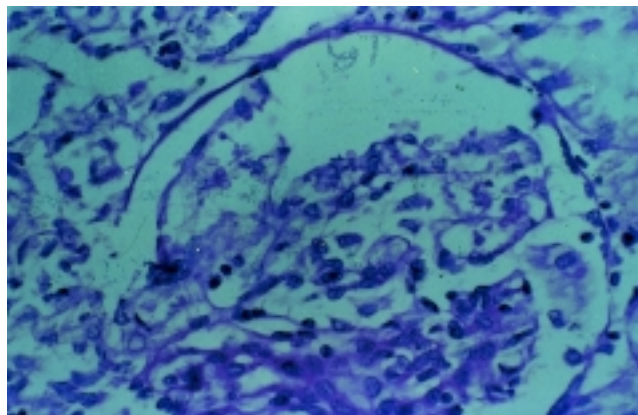


Fig. 6 Microsection of renal biopsy (PAS stain) showing partial destruction of the glomerulus with infiltration by cryptococcal spores

mucinous colonies of encapsulated yeast like organisms of varying size. Mucicarmine stain clearly identifies the capsule and wall of the fungus.

Histoplasma

The fungus *H. capsulatum* is also found world wide in the soil contaminated by bird excreta. Infection develops in the urbanites exposed to the construction excavations²⁶. Approximately 90% of these infections result in mild and clinically significant respiratory infections. The other 10% of the patients suffer serious pulmonary or disseminated infection. Progressive disease besides the lungs may involve reticulo-endothelial system with a high affinity for liver, spleen and bone marrow. Disseminated infection may involve genitourinary system as well. In a series 17 autopsy cases with disseminated histoplasmosis adrenal glands were involved in 14 (82%) kidneys in 3 (18%) and prostate in 1 (6%)²⁷. The renal lesions are usually in the form of microabscesses, not associated with significant renal symptoms.

Conclusions-Part I

The frequency of invasive fungal infections is increasing owing to the increasing number and improved survival of immunocompromised patients, although apparently healthy individuals are also reported to have these infections. The different fungi produce characteristic renal lesions, which may be associated with a variable outcome. Mucormycosis causes the most severe lesions with evidence of angioinvasion, renal infarction as well as parenchymal destruction and cortical necrosis. Renal failure is almost universal in patients with bilateral renal involvement. Aspergillosis also causes similar lesions though milder in severity. Candidiasis may present with papillary necrosis, pyelonephritis or pyonephrosis. Renal failure is seen in significant number of these patients but it often results from associated conditions. In view of the high mortality seen in patients with renal mycosis

(Table 2), a high index of suspicion is necessary in predisposed individuals to diagnose and treat the fungal infection so as to improve the prognosis in otherwise serious patients.

Fungal infections following renal transplantation

Recipients of solid organ transplants have 24-40% incidence of opportunistic fungal infections with a very high mortality of 70-100%^{10,28,29}. This is related to the environmental exposure and net state of immunosuppression. We had studied the records of 850 patients who had undergone renal transplantation at our Institute during 1977-2000. The immunosuppression protocol in these patients included conventional therapy with azathioprine and prednisolone in 105 patients (12.3%), triple- drug therapy including cyclosporine in 621 patients (73.0%) and only cyclosporine and azathioprine in 124 patients (14.6%). The treatment of acute rejection consisted of intravenous methylprednisolone and use of monoclonal antibodies when required.

The analysis showed occurrence of opportunistic fungal infections in 83 patients (9.8%) including candidiasis in 25 (2.8%), cryptococcosis in 16 (1.9%), aspergillosis in 20 (2.3%), mucormycosis 17(2.0%) and rare fungal infections in 5 others including pheohyphomycosis in 3 and disseminated histoplasmosis in 2 patients. Our results were in conformity with the reports from other centers in the country and abroad³⁰⁻³³ (Table 3). Rarely these fungi may be resistant to anti-fungal therapy as seen in case with a chronic indolent liver aspergilloma or even prove fatal due to massive pulmonary haemorrhage as described in a patient with pulmonary mucormycosis (Fig 7)³⁴. Often these patients have infections with multiple organisms and that makes their management more difficult³⁵. We also analysed the autopsy findings in 79 patients and documented higher incidences of angioinvasive fungal infections including aspergillosis in 11 (14%) and mucormycosis in 10(13%) compared with the relative low incidence for disseminated candidiasis seen in 5 (6%) and cryptococcosis in 4 (5%) patients. Histoplasmosis was less common in our patients³⁶. The underlying pre-disposing conditions in patients who had been autopsied were: CMV disease (35%), chronic allograft dysfunction (19%), leukopenia and hepatitis (16%) and diabetes (13%).

The analysis of endoscopic findings in 89 patients studied between 1985-1992 had shown an overall incidence of esophageal candidiasis in 10.5% and it was as high as 28.6% in those receiving triple-drug regimen including cyclosporine³⁷. An analysis of CNS manifestations in 79 renal transplant recipients revealed evidence of fungal infections in 21(26.5%), including cryptococcosis in more than half of them³⁸.

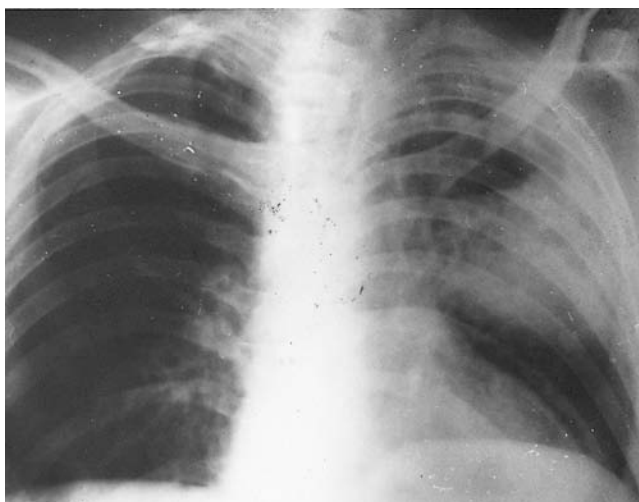


Fig. 7 Chest x-ray showing consolidation with cavity in pulmonary mucormycosis.

Table 2 : Outcome of Patients with Renal Mycoses

S.No.	Fungal infection	Untreated†	Treated (Ampho-B)	Survived
1	Candidiasis	19	11‡	8
2	Aspergillosis	17	10	5
3	Mucormycosis	17	11	3#
4	Cryptococcosis	4	0	0
5	Histoplasmosis	1	0	0

† Diagnosed postmortum, ‡ Fluconazole in 8, # unilateral nephrectomy

Conclusions-Part II

Systemic infections are an important cause of morbidity and mortality in renal transplant recipients. Whereas candidiasis and cryptococcosis are common and can be effectively treated, there has been a recent rise in angio-invasive fungal infections such as aspergillosis and mucormycosis, which are associated with a high mortality. A high incidence of CMV infections accompanies invasive fungal infections. Concomitant bacterial infections often complicate picture. Timely detection of the serious fungal infections and institution of therapy are important in reducing the mortality.

Treatment of fungal infections:

The treatment of deep-seated fungal infections can be difficult due to the limited number of drugs available and the undesirable toxicity of some of them. Important drugs used in the renal mycoses as listed in the Table 4.

In addition to the medical therapy surgical measures are also necessary to treat the fungal balls as well as removal of the infected tissues. Debulking of the bezoars seen in patients with candida and aspergillosis may be carried out by a percutaneous nephrostomy, endoscopic removal or open pyelotomy. In addition it may be combined with local irrigation by amphotericin B. For extensively damaged tissues in patients with angioinvasive infections such as mucormycosis debridement and excision of the tissue including nephrectomy may be necessary .

Table 3 Systemic fungal infections : Comparative Data

Authors (number)	Gallis et al ³⁰ (n-171)	Nampoory et al ³¹ (n-512)	John et al ³² (n-920)	Jaykumar et al ³³ (n-362)	PGI - CHD (n-850)
Fungal infection	13%	3.7%	5.6%	19%	9.8%
Candidiasis	2.3%	1.6%	1.4%	13.8%	2.8%
Cryptococcosis	5.8%	0.5%	2.4%	0.8%	1.9%
Aspergillosis	1.2%	0.9%	1 %	3 %	2.3%
Mucormycosis	1.2%	0.4%	1.1%	1.5%	2.0%
Others¶	0.6%	-	0.9%	-	0.5%

¶Histoplasmosis 1, Subhyphophycomycosis 3

Table 4 : Treatment of systemic fungal infections

Infection	Drug	Dose/day	Duration of Treatment
Candiduria	Ampho - B Fluconazole	0.3-0.5 mg/kg 100-200 mg	Depends on clinical picture 2-4 weeks
Candidemia/ Disseminated candidiasis	Ampho - B Lipid-Ampho-B Fluconazole	0.5-1mg/kg 1-5 mg/kg 200-400 mg	2-4 weeks - do- For at least 2 weeks
Mucormycosis	Ampho - B Lipid-Ampho-B	0.5-1mg/kg 1-5 mg/kg	6-8 weeks (Cumulative dose 2-2.5 gm)
Invasive Aspergillosis	Ampho - B+ Lipid-Amph B Itaconazole ^c	1-1.5 mg/kg 3-5 mg/kg 400 mg/day	Clinical picture must guide Usually 8-12 weeks Six months (After Ampho-B)
Cryptococcosis	Ampho - B+ Lipid -Amph B Fluconazole	>0.7 mg/kg 3-5 mg/kg 200-400 mg	For 2 weeks For 2 more weeks For around 6 weeks

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