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**Cryptococcosis in kidney transplant recipients: Current understanding and practices**

Meena P *et al*. Cryptococcosis in kidney transplant recipients

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**Abstract**

Cryptococcosis is the third most commonly occurring invasive fungal disease in solid organ transplant recipients (SOT). It is caused by encapsulated yeast, Cryptococcus species, predominantly Cryptococcus neoformans and Cryptococcus gattii. Though kidney transplant recipients are at the lowest risk of cryptococcosis when compared to other solid organ transplant recipients such as lung, liver or heart, still this opportunistic infection causes significant morbidity and mortality in this subset of patients. Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50% in SOT recipients with central nervous system involvement. The main aim of diagnosis is to find out if there is any involvement of the central nervous system in disseminated disease or whether there is only localized pulmonary involvement as it has implications for both prognostication and treatment. Detection of cryptococcal antigen (CrAg) in cerebrospinal fluid or plasma is a highly recommended test as it is more sensitive and specific than India ink and fungal cultures. The CrAg lateral flow assay is the single point of care test that can rapidly detect cryptococcal polysaccharide capsule. Treatment of cryptococcosis is challenging in kidney transplant recipients. Apart from the reduction or optimization of immunosuppression, lipid formulations of amphotericin B are preferred as induction antifungal agents. Consolidation and maintenance are done with fluconazole; carefully monitoring its interactions with calcineurin inhibitors. This review further discusses in depth the evolving developments in the epidemiology, pathogenesis, diagnostic assays, and management approach of cryptococcosis in kidney transplant recipients.

**Key Words:** Cryptococcosis; Kidney transplant recipients; Amphotericin B; Immunosuppression; Fluconazole

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**Core Tip:** Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients. As an opportunistic infection, it poses substantial morbidity and mortality in kidney transplant recipients. Mortality rates for cryptococcosis range from 10% to 25%. In immunocompromised patients, especially in cryptococcus-endemic areas, cryptococcosis must be suspected and diagnosed with a low threshold. Compared to India ink and fungal cultures, tests for the cryptococcal antigen detection in cerebrospinal fluid or plasma test are more sensitive and specific. The management of cryptococcosis poses considerable difficulties, mostly done with reduction or optimization of immunosuppression in addition to lipid formulations of amphotericin B and fluconazole.

**INTRODUCTION**

With the advent of a successful kidney transplantation way back in 1954, we have been able to ensure good initial graft outcomes with potent immunosuppression. Though potent, these drugs have their own side effect profiles[1]. Amongst these side effects, the most profound is higher rates of infections. Fungal infections occur in 15%-42% of organ transplant recipients. However, newer antifungal drugs have ensured a decline in these rates, especially invasive candidate infection. Cryptococcal infections generally are seen in the late post-transplant period, the time when anti-fungal prophylaxis is stopped[2]. Majority of these infections are due to the reactivation of pre-existing latent infections. Mortality rates are variable ranging from 33%-40% and are highest in those with central nervous system involvement[3]. Calcineurin inhibitors interestingly have anti-fungal activity in vitro. Tacrolimus showed more promising antifungal activity compared to cyclosporin and that might be due to efflux pump inhibition which is not present in cyclosporin[4]. Mammalian target of rapamycin inhibitors like rapamycin, and everolimus exhibit *in vitro* antifungal activity[5,6]. This however may not be truly protective against fungal infection in the real world. Considering the high mortality and even higher morbidity, there is a growing need for easily available highly specific diagnostic modalities for early diagnosis and treatment initiation. In this manuscript, we highlight the disease burden, the latest identification tools and outcomes in renal allograft recipients with present-day immunosuppression and anti-fungal therapy.

**MICROBIOLOGY OF CRYPTOCOCCUS**

Cryptococcus is a genus of basidiomycetous fungi with more than thirty species commonly found in the environment. There are only two species commonly known to be pathogenic, C neoformans and C gattii. C neoformans was first identified as human pathogen in the late 19th century but was recognized as a common human causative organism of human disease in late 1970s[7]. The pathogenic yeasts can be subclassified into four serotypes based upon capsular agglutination reactions and are designated A, B, C or D. From a clinical prospective it is reasonable to divide cryptococcus into two species complexes: C neoformans (serotype A, D) and c gattii (serotype B, C)[8]. Majority of cryptococcal infection (around 95%) are caused by C neoformans serotype A where as only 4%-5% infections are caused by C neoformans serotype D or C gattii serotype B, C. C neoformans is found throughout the world in association with birds excreta like pigeons, environmental scavengers like amoeba and in a variety of tree species. C gattii is commonly associated with several species of trees in tropical and subtropical climates[9-11]. The life cycle of cryptococcus involves both asexual and sexual forms. The asexual form exists as haploid encapsulated yeast and reproduces by budding. The yeasts are the only form of cryptococcus that have isolated from human infections. The sexual form is observed only in the laboratory[12]. Cryptococcus causes infection following inhalation of aerosolized infectious particles like desiccated yeast cells and basidiospores through the respiratory tract. Cryptococcal infection is acquired from the environment and the spread of infection from person to person has not been documented except with transplanted tissue[7,13].

**EPIDEMIOLOGY**

Cryptococcosis is an important opportunistic infection that leads to significant morbidity and mortality in transplant recipients. In solid organ transplant (SOT) recipients, it is the third most commonly occurring invasive fungal infection (IFI) after candidiasis and aspergillosis[14]. Though one recent retrospective observational study from Northern India highlighted the recent rise in angio-invasive fungal infections like mucormycosis and aspergillosis. Cryptococcosis was the fourth most commonly reported infection in this study preceded by mucormycosis, aspergillosis and pneumocystis jiroveci[15].

Cryptococcosis accounts for 8-10% of the invasive fungal infections in SOT recipients[15]. Its overall incidence in various cohorts of SOT recipients ranges from 0.2% to 5% depending on the type of organ transplanted[14,16,17]. As per a recently published retrospective analysis of the cohort of patients after organ transplantation from three states of the United States, the incidence of cryptococcosis was 0.32% after kidney transplantation which was lower than both lung and liver transplant recipients[18]. Shenoy *et al*[19] in their recent retrospective analysis showed a very low incidence of 0.04%.

Cryptococcosis primarily occurs due to the reactivation of the latent infection in the post-transplant period[20]. Two decades back, it occurred primarily amongst patients with human immunodeficiency virus (HIV), but now the majority of infections occur in non-HIV population, particularly immunosuppressed SOT recipients (60%-70% of the total cases)[21]. This may be explained by the emergence of highly active antiretroviral therapy for the treatment of HIV, along with an increase in the number of patients undergoing transplantation and the use of immunosuppressants. Calcineurin inhibitors (CNI) can affect the extent of the disease. Patients receiving CNIs were less likely to have disseminated disease due to their *in vitro* antifungal properties by targeting fungal homologs of calcineurin[22]. Steroids and T cell-depleting induction agents (antithymocyte or alemtuzumab) are associated with an increased risk of cryptococcosis[23,24].

Cryptococcosis is a late-occurring invasive fungal infection (after 1 year). It has a longer (574 d) median time to onset from the date of transplant as compared to invasive candidiasis (103 d) and aspergillosis (184 d)[25]. Based on the organ transplanted, the median time to onset is earlier after lung (191 d), heart (195 d) and liver (200 d) as compared to kidney transplantation (616 d)[18].

Mortality rates with cryptococcosis range from 10%-25%, while it can be as high as 50 % in SOT recipients with cryptococcal meningitis[26].

**PATHOPHYSIOLOGY**

C. neoformans is detected by a number of innate receptors, including Toll-like receptors, mannose receptors and -glucan receptors in the body during infection. Cells of innate immunity such as natural killer cells, dendritic cells, macrophages and neutrophils are primarily involved in C. neoformans killing in the host[27]. In particular, the establishment of Th1 and Th17 responses following the activation of macrophages is responsible for fungus clearance. Th1 and Th17 cells produce inflammatory cytokines such as IFN-, IL-17, and IL-22 in response to C. neoformans infection, resulting in robust antimicrobial and phagocytic responses[28]. Recently, studies have shown that mediators of death receptor-triggered extrinsic apoptosis, FADD and RIPK3 (immune regulators) control excessive inflammation during C. neoformans infection[29]. Replication of C. neoformans inside macrophages has been shown to be directly correlated with the susceptibility of the host to infection. Factors and conditions that modulate macrophage function causing T-cell function impairment such as in recipients of SOT can result in cryptococcal disease as a result of the reduced antifungal capacity of cells, facilitating the intracellular growth of C. neoformans[30]. C. neoformans releases an array of molecules such as prostaglandins and leukotrienes and virulence-associated enzymes that alter the local immune response of the host by having direct effects on inflammatory cells. Cryptococcal polysaccharides interfere with the migration of leukocytes toward chemoattractants[31]. The robust immune responses can at times be destructive to the organs of the host, especially to the lung parenchyma. Mouse models suggest CD4+ T cells mediates inflammation and host damage in the setting of C. neoformans infection[32]. Rarely, transmission can also occur from a donor allograft[33].

**CLINICAL MANIFESTATION**

Depending on the host's immunological condition, clinical signs of cryptococcal infection in a kidney transplant recipients (KTR) might range from asymptomatic colonization of the respiratory tract to wide dissemination[34]. The central nervous system (CNS) is the primary target site. C. neoformans is typically acquired through inhalation into the lungs, where it can spread to the skin, bone, myocardium, transplanted kidney and other organs. The cryptococcal infection in kidney transplant recipients might be the result of a recent acquisition or the recurrence of a latent or dormant infection. Epidemiological data has long suggested that cryptococcal infections exhibit dormancy and reactivation[22]. Cryptococcus neoformans possess the traits required for dormant infection in humans. In an analysis, of 52% of transplant recipients with cryptococcosis, there was evidence of a latent infection before the organ transplant[35]. Figure 1 shows various organ involvement of the human body in cryptococcal infection.

Up to 70% of patients with cryptococcal illness have involvement of the central nervous system. Leptomeningeal or parenchymal lesions, as well as hydrocephalus, can be seen. Frequent clinical signs of CNS involvement include fever, headache, altered mental status, vomiting, seizure, and visual and auditory complaints[36].

Other major organs affected include the lungs, skin, soft tissues, and osteoarticular. Generalized lymphadenopathy with constitutional symptoms and weight loss can be a presentation that can mimic post transplant lymphoproliferative disease.

The typical signs of pulmonary involvement in a cryptococcus infection include fever, lethargy, night sweats, weight loss, sputum-producing cough, dyspnea, hemoptysis, and rarely severe respiratory failure. Only about one-third of people with cryptococcosis have a lung-only disease, which is usually part of an infection that has spread to other parts of the body[30]. A chest X-ray may reveal multiple or a single nodule, nodular or alveolar infiltrates, a cavitary lesion, a consolidation, a mass, or a pleural effusion. One-third or more of patients with pulmonary cryptococcosis may be asymptomatic[37]. Compared to patients with consolidations, pleural effusions, and infiltrates, patients with nodular densities or mass lesions were less likely to be symptomatic. Rarely severe cryptococcal infection especially with lung involvement can be complicated by the development of hemophagocytic lymphohistiocytosis (HLH) associated with very high mortality. A high index of suspicion is needed to make an early diagnosis which can help to incorporate specific therapy for HLH earlier which may improve outcomes[38].

Rarely, skin involvement is also seen with cryptococcal infection. Studies have shown that skin involvement can be the first sign of a disseminated cryptococcal illness[39]. Primary cutaneous cryptococcosis may act as a portal of entry for secondary disseminated cryptococcosis. Skin lesions might include cellulitis, panniculitis, subcutaneous nodules, abscesses, and acneiform papules. Umbilicated papules resembling Molluscum contagiosum are often present in hemogenous cryptococcal skin changes.

Another condition for the disease's localized form is cryptococcoma[33]. Most of them are recognized radiologically. Localized cryptococcal lesions typically coexist with a systemic illness. These are more typical in infections caused by Cryptococcus gattii. Cryptococcoma mainly affects the CNS and very infrequently the lungs and the transplanted kidney.

Both symptomatic cryptococcal pyelonephritis and graft involvement have been reported in cryptococcal infection[40]. Laryngeal cryptococcus and renal arterial rupture related to cryptococcus have also been described[41,42].

**DIAGNOSIS OF CRYPTOCOCCAL INFECTION**

Diagnosis can be challenging, especially in transplant recipients. One must have a high index of suspicion and a low diagnostic threshold to diagnose cryptococcosis, especially in regions with high prevalence. Any clinical signs of disease like subacute headache, fever, cough and weakness should prompt rapid cryptococcal testing. All transplant recipients with suspected or proven cryptococcosis should undergo a thorough evaluation for extrapulmonary sites of infection including a lumbar puncture [large volume cerebrospinal fluid (CSF) sample] and blood/urine cultures. This is important to delineate the site and extent of disease in order to decide the duration of antifungal treatment. The methods used to confirm the infection include direct microscopic examination, culture, histopathology, serology and molecular detection. Antigen tests from blood or culture are rarely positive unless there is disseminated cryptococcal infection.

***Imaging: CNS and chest***

Cerebral cryptococcosis are more common with C gatti than with C neoformans infection. Normal brain imaging always does not exclude meningoencephalitis. Magnetic resonance imaging (MRI) (magnetic resonance imaging) brain is the preferred modality of imaging to diagnose cerebral cryptococcosis. The MRI findings of CNS cryptococcosis are leptomeningeal/pachymeningeal enhancement, dilated perivascular space, cryptococcal granuloma, hydrocephalus, miliary nodule and plexitis which can occur in isolation or in various combinations[43]. Chest imaging in pulmonary infection is non-specific with solitary/ multiple nodules or diffuse interstitial infiltrates[37].

CSF examination: The CSF picture in cryptococcal meningoencephalitis classically demonstrates increased opening CSF pressure, low white cell count with a mononuclear predominance, and slightly elevated protein with low/normal glucose concentration[44]. Neuroimaging should be done prior to lumbar puncture to exclude hydrocephalus and mass lesions. Cryptococcal antigen testing from the CSF or serum is the preferred strategy to diagnose infection. India ink testing on CSF is no longer recommended because it can miss low burden infections due to the low sensitivity and specificity.

***Microscopy and culture***

Visualization of encapsulated yeast forms with narrow budding in the sputum, bronchoalveolar lavage (BAL) or lung tissue biopsy specimens is suggestive of cryptococcal infection. The pellet from pleural fluid or BAL can be mixed with India Ink and observed under a microscope[45]. A lung biopsy from a nodule of uncertain aetiology requires a fungal culture to be done, in addition to a histopathology examination. Samples for culture should be placed on Sabouraud dextrose agar at 30°C for 7 d, in aerobic conditions, and observed daily[46]. Cryptococcus appears as mucoid creamy colonies. C. neoformans are identified generally as smooth colonies while C. gattii mostly appears as mucoid colonies. Canavanine-glycine-bromothymol blue (CGB) agar can be used to differentiate between C. neoformans and C. gattii.Colonies of C. neoformans will not cause changes in CGB agar. On the other hand, C. gattii produces a blue colour in CGB agar.

***Histopathology***

A lung biopsy is the best diagnostic option when sputum or bronchoscopy specimens are unavailable or negative. Gamori’s methenamine silver or periodic acid Schiff stain identifies the organism as narrow-based budding yeasts (4-10 μm), usually surrounded by thick capsules in the lung tissue. Mucicarmine stain can be used to highlight the cryptococcal capsule as rose burgundy. Histopathological methods and cryptococcal antigen testing cannot differentiate between C neoformans and C gattii[47]. Lung histopathology in pulmonary cryptococcal infection varies from well-formed granulomas to minimal inflammation. Positive histology does not always correlate with culture result. A negative culture might be caused by nonviable organisms in the sample[30]. Figure 2 shows the histopathology of a patient with pulmonary cryptococcosis (H & E stain) and Figure 3 shows the histopathology of a patient with pulmonary cryptococcosis (Alcian blue -PAS stain). India Ink of Cryptococcus neoformans is provided in Figure 4.

***Cryptococcal antigen testing***

Capsular polysaccharides of Cryptococcus can be detected by using specific anti C. neoformans antisera in the serum, CSF, BAL, and urine by two formats- the latex agglutination test and the recently approved lateral flow immunoassay (LFA)[48]. LFA is the preferred method recommended for diagnosis given its low cost and high sensitivity. These cryptococcal antigen (CrAg) detection tests are rapid, sensitive and specific for diagnosis. These tests have not been standardised for respiratory specimens such as BAL, pleural fluid, or sputum. Pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of Cryptococcus[37]. Serum CrAg titres are typically higher in patients with disseminated diseases/CNS involvement. A prozone effect can occur in high cryptococcal burden states and recognition of this with appropriate dilution of the sample may be required.

***Molecular detection***

This may be required in specific situations where other diagnostic tests have failed to confirm the diagnosis. These molecular methods include pan-fungal polymerase chain reaction (PCR), deoxyribonucleic acid sequencing for identification, multiplex PCR, isothermal amplification method, and probe-based microarrays. Species identification of cryptococcus is also important as it may affect the choice of antifungal therapy and affect the clinical outcomes. Where possible, isolates should be subjected to either PCR or matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) for genotypic identification. Antifungal susceptibility testing is routinely not recommended for cryptococcal infection[49]. However, in patients with C neoformans infection who have failed primary therapy or relapsed, or in patients with recent antifungal exposure (*i.e.* antifungal prophylaxis), antifungal susceptibility testing for fluconazole is recommended[50]. Table 1 shows modalities for the diagnosis of post-transplant cryptococcosis.

**TREATMENT**

Much of the data on the treatment of patients with cryptococcal infections has been extrapolated from trials on HIV Infected patients[51] and also retrospective data from kidney and other SOT patients as there are no randomized controlled trials for the therapy[52-54]. Recommendations herein are consistent with the guidelines of the American Society of Transplantation Infectious Diseases[50].

***Management of cryptococcus has 3 main aspects***

**Antifungal therapy:** As discussed, earlier patients with Cryptococcal infections can present with either isolated pulmonary involvement, neurological Involvement or disseminated disease. The Therapy thus also depends on the site and extent of involvement. (1) In patients with CNS disease, Disseminated Disease or Moderate to severe pulmonary involvement the antifungal therapy of choice in kidney transplant recipients would be Liposomal Amphotericin B Conventional amphotericin B is nephrotoxic and found to be inferior to the liposomal form on comparison of 90-d mortality between the two forms[54,55]. The addition of 5-flucytosine as a part of induction therapy reduces the chances of treatment failure[56]. The induction therapy is usually followed by a consolidation phase and maintenance phase. Doses of flucytosine and Fluconazole should be adjusted according to the glomerular filtration rate*.* Monitoring of flucytosine level is recommended (2 h post-dose 30-80 mcg/mL). Extended doses may be required as per clinical status. Figure 5 shows therapy for patients with CNS disease, Disseminated Disease or Moderate to severe Pulmonary involvement; and (2) In patients with mild pulmonary disease use of fluconazole 400 mg/d for 6-12 mo is recommended. Even asymptomatically detected (Cryptococcus positive on Sputum culture) pulmonary disease needs to be treated with the same regimen. In all these cases extrapulmonary disease should be excluded. Longer duration of Induction should be considered for patients who are clinically deteriorating, persistent comatose state, and persistently elevated intracranial pressure[16]. In case flucytosine is not available an extended duration of amphotericin B can be used lasting 4-6 wk. Use of extended-spectrum azoles like itraconazole, Voriconazole, Posaconazole, Isavuconazole, do not offer any advantage over fluconazole, but should be used in fluconazole-resistant C. gatti[57,58].

**Supportive therapy:** (1) Management of elevated Intracranial Pressure: 50% to 70% of patients with cryptococcal meningitis have elevated intracranial pressure due to reduced CSF absorption secondary to a film formed over the pial layer due to significant inflammatory response. This is a significant factor in morbidity and mortality of the patient as it can lead to hydrocephalous, blindness deafness or death[59]. Lumbar puncture should be done in all patients and opening pressure should be noted. If pressure is above 25 mmHg then a large volume of CSF should be removed, and attempts should be made to keep it below 20 mmHg using repeated lumbar puncture or by using drains from CSF cavities to the peritoneum[60]. Maintaining pressures below 25mmhg was associated with 69% relative survival protection[61]; and (2) Use of Dexamethasone: When Dexamethasone was added to adjunctive therapy on HIV patients showed slower clearance of CSF, Increased serious infections and no impact on mortality compared to placebo. But can be used after clearance of infection[62,63].

**Change in immunosuppression:** As this disease is a direct result of the immunocompromised state of the patient there should be an attempt to reduce the immunosuppressive medications. Although nothing can be done about the T cell depleting agents given in the beginning slow reduction in dose of other immunosuppression with a low threshold for diagnosis of rejection should be done aiming for eradication of the fungus and preservation of allograft. The overall immunosuppression should be minimized during therapy; however, the specific approach to achieve this must be tailored to each individual instance. The expeditious decrease in the administration of immunosuppressive drugs may give rise to unfavorable consequences, including the occurrence of organ rejection and/or immune reconstitution inflammatory syndrome (IRIS). Therefore, it is advisable to strategically implement a progressive decrease in dosage with the administration of antifungal therapy. The primary objective is to achieve complete elimination of the infection while simultaneously ensuring the maintenance of allograft functionality. The interaction of azoles with CNI should be kept in mind and frequent monitoring of levels along with dose reduction should be done. The reduction of immunosuppression in KTR along with antifungal therapy initiation can also lead to the development of IRIS[64]. The incidence of this is 5%-12% in SOT recipients and it mimics a worsening cryptococcal disease and can also lead to rejection and graft loss[21,24,65]. It occurs 4-6 wk after initiation of the therapy and is found to be associated more with CNS disease and stoppage of CNI[16,66]. After ruling out the presence of fungi in the body IRIS can be tackled by increasing the dose of corticosteroids[64,67].

***Prognosis and outcomes***

Mortality rates in organ transplant recipients with cryptococcosis range from 33%-42% and may be as high as 49% in those with CNS disease and as low as 2.8% in those with isolated pulmonary involvement[2,21,50,51]. Recently, Ponzio *et al*[65] demonstrated an overall mortality rate of 49%. Independent risk factors for mortality include abnormal mental status, renal failure at baseline, fungemia and disseminated infection[24]. Patients receiving tacrolimus are less likely to have central nervous system involvement and more likely to have skin, soft-tissue, and osteoarticular involvement. Improved outcomes with the use of calcineurin-inhibitor agents may be attributable in part to their synergistic interactions with antifungal agents[5,68]. A significant percentage of patients (up to 20%) progress to graft loss after the infection[55]. Risk factors for graft loss after cryptococcosis include disseminated infection, higher baseline creatinine levels, graft dysfunction concomitant with amphotericin B deoxycholate therapy and an additional nephrotoxic condition[56]. Therefore, the clinical focus should be on the use of less nephrotoxic lipid formulations of amphotericin B in this specific population.

**CONCLUSION**

Cryptococcal infection accounts for < 10% of IFI and is seen in the late transplant period. Mortality rates are higher for those with meningeal involvement. The advent of newer diagnostic modalities and treatment has reduced infection-related morbidity but has not yet been able to reduce mortality beyond a level. Newer therapeutics with liposomal Amphotericin B. Fluconazole, and 5-flucytosine have improved survival. However, a significant proportion of these patients progress to graft loss either due to reduced immunosuppression, infection or nephrotoxic therapeutic agents. Early detection however has resulted in better survival in the subset of patients.

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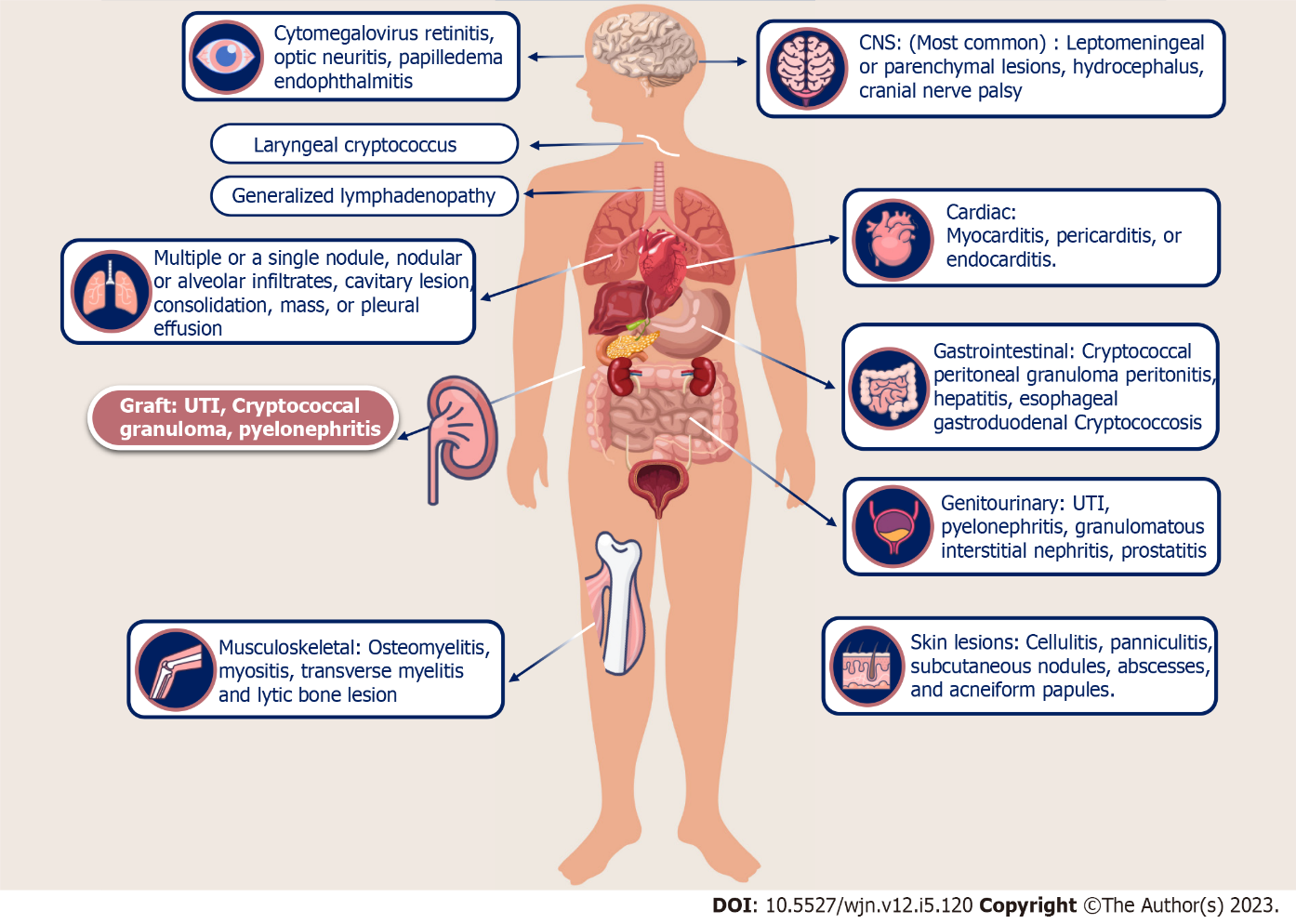
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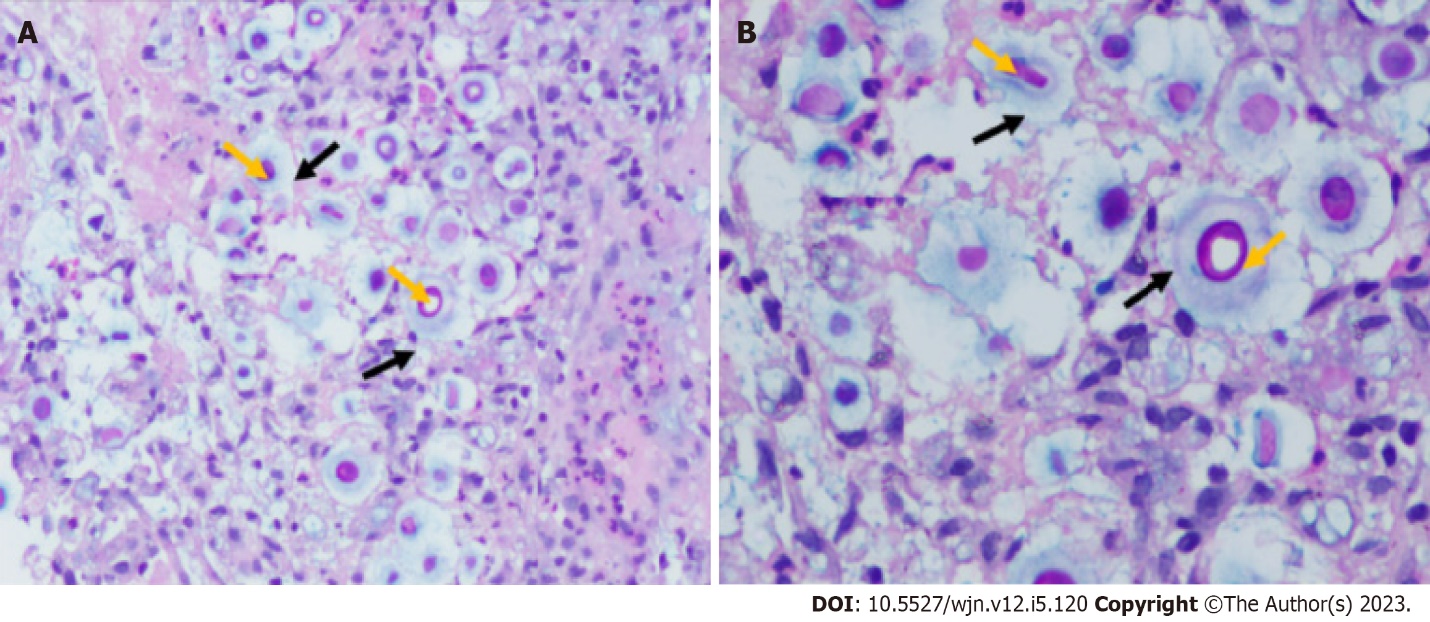
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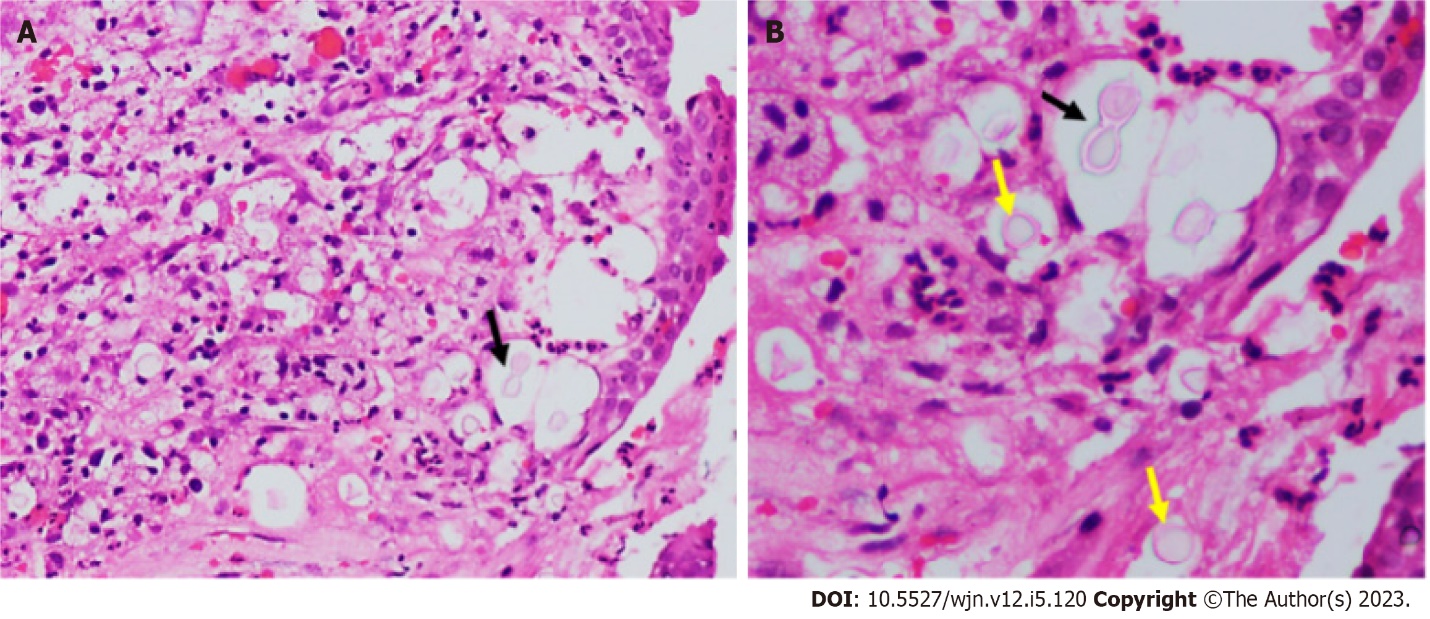
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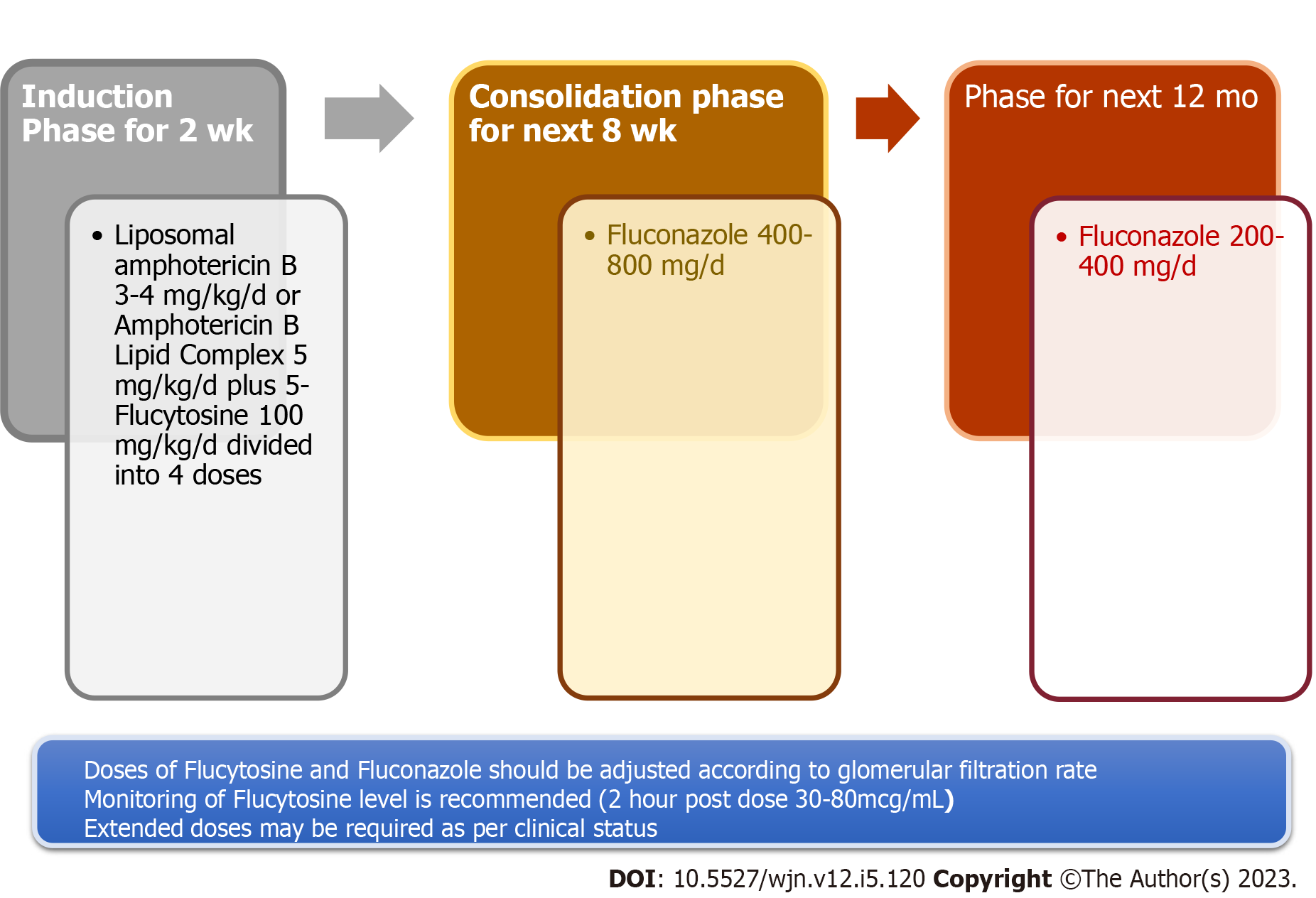
**Figure 1 Various organ involvement of the human body in cryptococcal infection.** UTI: Urinary tract infection; CNS: Central nervous system.

**Figure 2 Histopathology of a patient with pulmonary cryptococcosis, hematoxylin and eosin stain and Alcian blue stain.** A: At ×100 magnification; B: At ×200 magnification. Alcian blue-PAS stain atains the yeast forms of cryptococcus. Alcian blue stains the capsule blue colour (black arrow) and PAS stains the cell wall of the yeast magenta colour (yellow arrow).

**Figure 3 India ink of cryptococcus neoformans.** Endobronchial mucosa shows squamous metaplasia and the sub epithelium shows inflammatory exudates along with variably sized round to oval encapsulated yeast (yellow arrow) with thin walls and narrow based budding (black arrow).A: At ×100 magnification; B: At ×200 magnification.



**Figure 4 India ink-stained cryptococcus neoformans.**



**Figure 5 Therapy for patients with central nervous system disease, disseminated disease or moderate to severe pulmonary involvement.**

**Table 1 Modalities for the diagnosis of post-transplant cryptococcosis**

|  |  |  |
| --- | --- | --- |
| **Method** | **Advantages** | **Disadvantages** |
| **Direct microscopic examination** | Cryptococcus is identified as narrow budding encapsulated yeasts after mixing sample with India ink. | Direct microscopic examination |
| **Culture** | Identify the species and susceptibility patterns | Time consuming. More than 1 wk must elapse for fungal growth to occur |
| **Histopathology** | Gomori methenamine silver, and periodic acid-Schiff are used to detect Cryptococcus that appears as narrow-based budding yeasts (4-10 μm), usually surrounded by thick capsules in the lung tissue | Histopathology |
| Antigen detection | Inexpensive point-of-care testing, simple, cheap and rapid diagnosis in developing country, high sensitivity and specificity | Isolated pulmonary cryptococcal infection is usually associated with false negative serum CrAg, probably because of the low fungal burden outside the lung or the capsule-deficient strain of Cryptococcus. One must be aware of the prozone effectwhile interpreting these tests |
| **Molecular detection** | Required in specific situations where other diagnostic tools have failed to confirm a diagnosis of cryptococcosis, highly specific (almost 100%) | Expensive and not routinely available |

CrAg: Cryptococcal antigen.



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