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Review article

Fungal pneumonia in kidney transplant recipients

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ABSTRACT

Fungal pneumonia is a dreaded complication encountered after kidney transplantation, complicated by increased mortality and often associated with graft failure. Diagnosis can be challenging because the clinical presentation is non-specific and diagnostic tools have limited sensitivity and specificity in kidney transplant recipients and must be interpreted in the context of the clinical setting. Management is difficult due to the increased risk of dissemination and severity, multiple comorbidities, drug interactions and reduced immunosuppression which should be applied as an important adjunct to therapy. This review will focus on the main causes of fungal pneumonia in kidney transplant recipients including *Pneumocystis, Aspergillus, Cryptococcus*, mucormycetes and *Histoplasma.* Epidemiology, clinical presentation, laboratory and radiographic features, specific characteristics will be discussed with an update on diagnostic procedures and treatment.

1. Introduction

Pneumonia is a common complication encountered after kidney transplantation. Among them, fungal pneumonia is particularly dreaded and can be life-threatening [1,2]. Indeed, diagnosis and management can be challenging because (1) the clinical presentation is similar to that of bacterial and viral pneumonia (2) the diagnostic tools have limited sensitivity and specificity in these patients and must be interpreted in the context of the clinical setting (3) dissemination is frequent and can involve the central nervous system requiring adjustment of treatment (4) and treatment is challenging because it must take into account interactions with calcineurin inhibitors (CNI)/mammalian target of rapamycin inhibitors (mTORi), dose adjustment to glomerular filtration rate (GFR) and reduced immunosuppression which should be applied as an important adjunct to therapy.

This review will focus on the main causes of fungal pulmonary infection in kidney transplant recipients (KTR) including *Pneumocystis, Aspergillus, Cryptococcus*, mucormycetes and *Histoplasma.* Epidemiology, clinical presentation, laboratory and radiographic features, specific characteristics will be discussed with an update on diagnostic procedures and treatment. Some issues not specifically reported in KTR will be derived from published data in solid organ transplant (SOT) recipients (SOTR).

2. Diagnostic tools in suspected fungal pneumonia

In KTR, invasive sampling techniques as bronchoalveolar lavage (BAL) and lung biopsies are often required to allow a rapid diagnosis. Although fungal isolation from culture is for most of the pathogens the gold standard for diagnosis, it has limited sensitivity and may be time-consuming [3]. Microscopy of respiratory samples can give valuable arguments for the initiation of fungal therapy. Staining by Grocott methenamine silver stain (GMS) or periodic acid Schiff stain (PAS) should be undertaken and whenever possible, wet mounts of specimens should be stained with a fluorescent dye (eg, calcofluor or blankophor) [4]. The development of antigen detecting tests has improved substantially the diagnosis of some of these infections. (1 → 3)-b-D-glucan (BDG), a component of the fungal cell wall can be detected in the serum and in the BAL of infected patients in most of the herein described fungal infections. There are different commercially available tests, which were recently included in a Cochrane Systematic review about BDG testing for the detection of invasive fungal infections in immunocompromised or

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critically ill people. The authors concluded that due to a wide variation of sensitivities and specificities, accuracy of this test cannot be estimated [5]. Data concerning the performance of these tests to diagnose invasive fungal infections in SOTR is rare [6–9]. Additionally, its use is limited by several disadvantages. First, mucormycetes and cryptococci release not enough BDG in serum to be detected by current detection tests, and second, these tests lack specificity and may be positive in different non-fungal related states. For example, BDG may be increased in the serum of patients undergoing hemodialysis with cellulose membrane, receiving human blood products as immunoglobulins or albumin, suffering from serious bacterial infections or severe mucositis, and after surgeries if gauzes containing glucans were used [10–13]. Additionally, BDG may be positive in BAL if fungal colonization occurs [9].

Other detection tests for antigens specific for *Aspergillus* and *Histoplasma* have been developed [14–20]. Their advantages and limitations will be discussed in the corresponding sections.

Amplification of fungal DNA from BAL, sputum and lung biopsies by broad-range and specific polymerase chain reaction (PCR) is gaining importance in the management of fungal pneumonia [3,21]. Also, application on formalin-fixed paraffin-embedded (FFPE) samples is increasingly used in practice, even if sensitivity is lower than on fresh clinical samples [22].

Radiographic diagnosis is best achieved using chest computed tomographic scan (CT scan). It allows the characterization of lesions that might be too small to be detected on the chest radiograph [4,23,24]. Nodular or mass like opacities (with or without the halo sign) are the most common radiographic findings and may progress to cavitary lesions. Ground-glass opacities (GGO), and lobar infiltrates can also be seen [24,25]. The interpretation of images may be complicated by concurrent bacterial or viral pulmonary infection. Central nervous system (CNS) extension is a feared complication and should be quickly investigated by CT scan or magnetic resonance imaging (MRI) even in the absence of symptoms for some of these infections.

3. Treatment particularities

Treatment should be initiated as soon as the diagnosis of fungal pneumonia is considered. It remains challenging because patients are under immunosuppressive treatment and suffer from different comorbidities needing medication that potentially interact with the antifungal drugs. Additionally, they are prone to develop nephrotoxicity. Randomized comparison for the treatment of fungal infections in SOTR, and especially in KTR are rare. Moreover, a concomitant reduction of the immunosuppressive treatment is an important adjunct to treatment.

Triazoles are for most of the fungal diseases the cornerstone of treatment. The correct handling of these drugs may be complicated. As the metabolism is depending on the cytochrome P450 (CYP450) system, the blood levels are subject to an important inter- and intra-patient variability and the treatment may lead to significant drug interactions (Table 1).

Intra-patient variability may be due to drug-drug interactions (concomitant treatment by other inducers or inhibitors of the metabolizing cytochrome P450 isoforms), variating distribution volumes (e.g. in the setting of the treatment in intensive care units, decreased renal function) and liver failure. Significant inter-patient variability of voriconazole (VCZ) can be due to genetic single-nucleotide polymorphism

Table 1
Azole antifungal drugs: bioavailability considerations, therapeutic drug monitoring, potential for drug interactions and recommendations for dose adjustment of immunosuppressants during concomitant administration of azole antifungal drugs.

triazole	bioavailability considerations in oral administration forms [209–213]	TDM: trough level timing and aims [30]	interaction with CYP3A4 [214]	interaction with CYP2C9/CYP2C19 [214]	adjustment of CNI/mTORi [214,215]
fluconazole	excellent bioavailability of the oral formulations (tablets, oral suspension)	n.a.	inhibition (++)	inhibition (++/+)	cyclosporine: reduce by 21–50% tacrolimus: reduce by 40% sirolimus: reduce by 50–70%
itraconazole	capsules: very variable, should be given with food or acidic beverages; oral solution (better than tablets): empty stomach	day 5–7; treatment: 1–2 mg/L	inhibition (+++) substrate of CYP3A4 (+++)	inhibition (+/0)	cyclosporine: reduce by 50–60% tacrolimus: reduce by 50–60% sirolimus dose: reduce by
posaconazole	tablets: oral solution: with a high fat meal (decreased by a low gastric acidity)	≥ day 7; prophylaxis: >0.7 mg/L, treatment: >1 mg/L	inhibition (++)	none	cyclosporine: reduce by 0–30% tacrolimus: reduce by 75–80% sirolimus: coadministration contraindicated
voriconazole	tablets: empty stomach	after 2–5 days; treatment: 1–6 mg/L*	inhibition (+) substrate of CYP3A4 (+)	inhibition (++/+++) substrate of CYP2C9 (+)/CYP2C19 (+++)	cyclosporine dose: reduce by 50% tacrolimus dose: reduce by 66% sirolimus dose: coadministration contraindicated
isavuconazole	capsules: good bioavailability	limited data	inhibition (+) substrate of CYP3A4	none	cyclosporine, tacrolimus and sirolimus: no empirical reduction

TDM: therapeutic drug monitoring; CYP: cytochrome P450; CNI: calcineurin inhibitors; mTORi: mammalian targets of rapamycin inhibitors; n.a.: not applicable; (+++) = strong interaction; (++) = moderate interaction; (+) = weak interaction; *A higher target (2–6 mg/L) should be used, if there is disease with poor prognosis (eg. cerebral dissemination, bulky disease, infections with pathogens exhibiting high MICs) [120].
Inhibition of different isoforms of the cytochrome P450 system by the different triazoles, which may increase the serum concentrations of their substrates. Some examples of commonly used substrates (not exhaustive-readers are advised to check the manufacturer's prescribing information) for CYP3A4: cytochrome P450 3A4: antiarrhythmics (amiodarone, digoxin …), antibiotics (dapsone, some macrolides, rifabutin …), anticoagulants (apixaban, rivaroxaban), antidepressants (amitriptyline, citalopram, venlafaxine …), oral antidiabetics (linagliptin, nateglinide), antiemetics (cisapride, domperidone …), antiepileptics (carbamazepine, phenytoin..), antifungals (isavuconazole, voriconazole), antihypertensive (eplerenone), antiplatelet medication (clopidogrel, ticagrelor, …), anxiolytic (buspirone), benzodiazepines (alprazolam, clobazam, diazepam, midazolam), beta-blocker (propranolol), calcium channel blockers (e.g. amlodipine, diltiazem, …), calcineurin inhibitors (cyclosporin, tacrolimus), colchicine, glucocorticoids (deflazacort, dexamethasone, hydrocortisone), proton pump inhibitors (esomeprazol, omeprazole, pantoprazole), mTOR inhibitors (everolimus, sirolimus, temsirolimus), statin (atorvastatine …), for CYP2C9: cytochrome P450 2C9; anticoagulant (warfarin), antidepressants (amitriptyline, fluoxetin, venlafaxine..), antiepileptics (phenytoin, valproic acid), antifungals (voriconazole), antiplatelet drugs (clopidogrel), non-steroidal anti-inflammatory drugs (celecoxib, diclofenac, ibuprofen ….), oral antidiabetics (glibenclamide, glimepiride, glipizide …), sartans (azilsartan, irbesartan, losartan); for CYP2C19: cytochrome P450 2C19; antibiotics (chloramphenicol, dapsone), anticoagulant (warfarine), antidepressants (amitriptyline, citalopram, escitalopram, venlafaxine …), antiepileptics (diazepam, phenobarbital, phenytoin …), antifungals (voriconazole), antihypertensives (labetalol, propranolol) antiplatelet medication (clopidogrel), proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole).

in the gene encoding for the cytochrome P450 2C19 [26–29] or higher elimination capacity, as encountered in children [30].

Studies have suggested significant relationships between serum concentrations and efficacy of itraconazole (ITZ) [31,32], VCZ [33,34] and posaconazole (PCZ) [35–37]. All these points underline the importance of the therapeutic drug monitoring of triazoles, especially for ITZ, VCZ and PCZ (Table 1).

Additionally, some of these azoles are potent inhibitors of cytochrome P450 3A4 (CYP3A4) and accessory of cytochrome 2C9 (CYP2C9) and 2C19 (CYP2C19), which may result in an increase in blood levels of their substrates including CNI and mTORi, thereby resulting in toxicities [38–40]. Consequently, doses of immunosuppressive agents should be adapted at initiation of the azole treatment, and their serum concentrations should be closely monitored at the beginning, during, and after treatment (Table 1). In contrast, mycophenolic acid (MPA) is metabolized via the uridine diphosphate glucuronosyltransferase (UGT) pathway, which is mildly inhibited by isavuconazole (ISA) [41–43], inhibited by fluconazole (FCZ) and not affected by VCZ. In general, as immunosuppression must be reduced, MPA is usually stopped and trough levels of CNI or mTORi are reduced.

4. Pneumocystis jirovecii

4.1. Epidemiology

Pneumocystis jirovecii (PJ) is a unicellular organism that may be found in the human respiratory tract and cannot be cultured in the routine microbiology laboratory. Infection is worldwide, and around 80% of children have antibodies by the age of 4, whereas up to 20–50% of healthy adults are colonized [44–46]. However, the reservoir for human disease has not been discovered yet.

Pneumocystis jirovecii pneumonia (PJP) generally occurs after acquisition of a new infection rather than reactivation of latent PJ infection [47]. Since clusters of PJP have been described, especially among KTR at individual care centers, molecular genotyping studies have suggested nosocomial outbreaks, possibly due to inter-human transmission [48–54].

In KTR, the incidence of PJP varies between 0,6%–14% depending upon whether prophylaxis is given or not [55]. When prophylaxis is not given, the highest risk lies between the second and the sixth month after transplantation. Increased risk is also observed during periods of increased immunosuppression, as encountered after treatment with high-doses of corticosteroids or lymphocyte-depleting antibodies [56–59], or in patients with long duration corticosteroid therapy (15–20 mg prednisone equivalent during 3–6 months). When prophylaxis is given, most cases are reported after its discontinuation, predominantly during the second year post-transplantation [60–62]. Risk factors for the so called “late-onset” PJP in the second year after transplantation include: age $\geq$65 years, low total lymphocyte count ($<$500–1000/mm^3) during more than 1 month, hypogammaglobulinemia, corticosteroid boluses, graft rejection, detectable CMV viremia and administration of mTORi [56,60,61,63,64]. Due to primary prophylactic treatment, incidence of the disease has decreased to 0.3–2.6% of KTR, but PJP remains an important cause of morbidity and mortality (up to 30%) in SOT, and is associated with graft failure [64–69].

4.2. Clinical features

Non-HIV-infected patients with PJP typically present more acutely ill than those with HIV [67]. They are often more dyspneic and hypoxemic, needing intensive care [67,70]. Symptoms are non-productive cough, dyspnea, weakness, fatigue and high-grade fever, though fever and cough may be absent [47,56,67]. However, these symptoms may also be discrete and could be mistaken for a sirolimus-induced interstitial pneumonitis [71]. The progression to respiratory failure is rapid and the outcome of patients with respiratory failure requiring mechanical ventilation is worse in HIV-negative patients than in patients with HIV infection [56,61].

4.3. General laboratory findings

Serum lactate dehydrogenase (LDH) is usually increased over 300 IU/ml, but this test is not specific. An unexplained hypercalcemia ($>$10.5 mg/dL) in association with an increased level of 1,25 dihydroxyvitamin D and 25 hydroxyvitamin D may occur in as much as 36.7% of the KTR [72]. Hypoxemia with a PaO_2 $<$70 mm Hg on room air and a respiratory alkalosis are often encountered. An increased alveolar-arterial PAO_2.PaO_2 gradient over 30 mm Hg may be seen and should be considered as a sign of severity and may be an indication of an adjunctive corticosteroid therapy [56].

4.4. Focused diagnostic testing

Specific diagnosis relies on visualization of the organism in respiratory samples including BAL, transbronchial or open lung biopsy and induced sputum. The most sensitive microscopic diagnostic assay is a rapid and easy to perform immunofluorescence microscopy [73]. Without antibody staining, routine stains (GMS, calcofluor, toluidine-blue O stain or Wright Giemsa) can also be used to visualize PJ [74,75]. However, in patients receiving prophylaxis and non-HIV patients, the microorganism load is lower resulting in a decreased sensitivity of microscopic examination and an increased false negative rate (up to 25%) [76].

Standard PCR tests are very sensitive and specific in detecting PJ in respiratory specimens, especially BAL, but cannot distinguish between infection and colonization. On BAL, quantitative real-time PCR (qPCR), aiming the large-subunit ribosomal RNA of PJ, has the advantage of rapidity and quantification of the DNA and can help differentiate colonization from infection [77]. However, grey zones exist, meaning that for some quantification results, both colonization and infection are possible. These qPCRs can also be done on oral wash samples, sputum and nasopharyngeal aspirates [78,79]. Negativity of these tests in these non-invasive samples, however, does not exclude PJP.

Sensitivity of BDG in serum for PJP has been estimated as $>$90% and specificity at $<$80% [8,80–83]. A positive test result in serum and in BAL must be interpreted with caution, as many factors are likely to produce false positive as explained above. Based on studies including different populations suffering from PJP, the American Society of Transplantation Infectious Diseases suggests that a negative test result may reasonably exclude the diagnosis of PJP [80]. However, large studies in KTR with PJP to define sensitivity and specificity in serum and BAL are lacking. As none of these diagnostic methods is both sensitive and specific, the best strategy would be to combine qPCR with other diagnostic tests such as immunofluorescence staining on BAL and BDG dosage.

In the case of clustering of PJP cases in a KTR unit, a nosocomial outbreak should be suspected and molecular genotyping considered. Different techniques have been tested, and multi-locus sequence typing (MLST) is currently the preferred one [84,85]. A recent study suggested a four gene MLST scheme based on two mitochondrial genes (mitochondrial large ribosomal subunit, *cytochrome b oxidase*) and two nuclear genes (*β-tubulin*, *superoxide dismutase*) [84].

4.5. Radiographic findings

The chest radiograph images are non-specific and may even seem normal. Bilateral reticulation is seen in up to 95% of KTR [24]. In patients with breakthrough PJP under aerosolized pentamidine prevention, these signs are classically present in the upper lobes [56]. In high-resolution computed tomography (HRCT) the findings are dominated by multifocal consolidation, solid nodularities and extensive GGO (Fig. 1) [86,87]. Pulmonary cysts are more uncommon in this patient population [24] (Table 2).

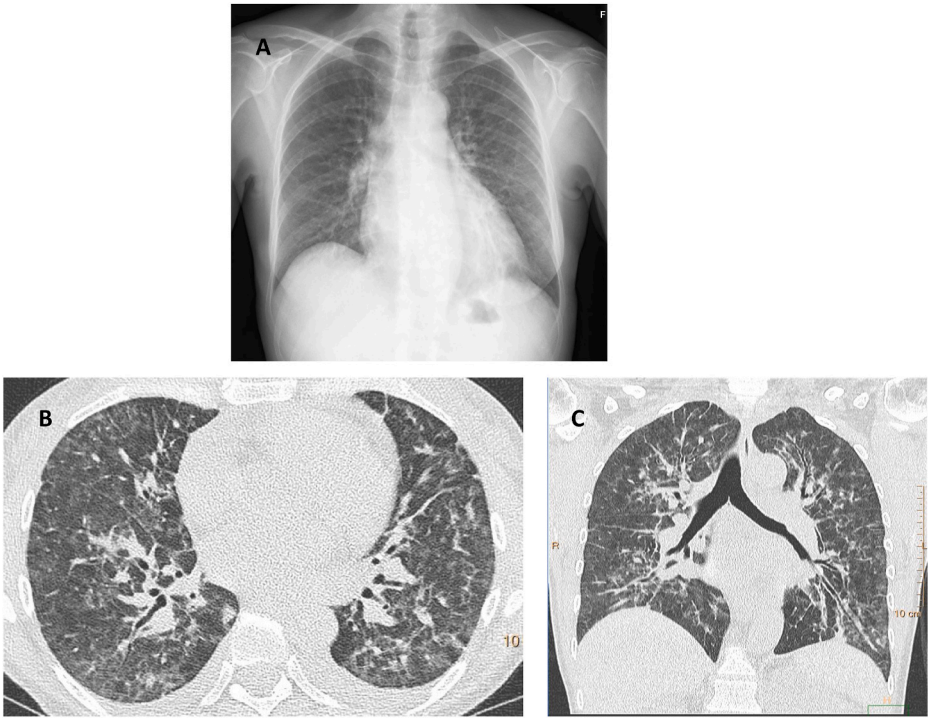

Fig. 1. A 54-year-old woman transplanted with a kidney 3 years ago, presented with dry cough, dyspnea and mild fever for 4 days. **A.** Poster-oanterior chest X-ray performed at day 0 revealed no significant parenchymal abnormalities. A slightly enlarged heart and increased pulmonary vasculature is noted. **B.** CT performed at Day 3. Axial view displayed at the level of the middle lung zones revealed extensive areas of ground glass opacities with discreet increase of interlobular thickening. The distribution of lung abnormalities was heterogenous with a mosaïc appearance. **C.** Coronal CT reformatted image on a plane passing through the division of the main bronchi illustrates well the symmetrical and heterogeneous distribution of the lung abnormalities.

4.6. Treatment

Trimethoprim-sulfamethoxazole (TMP/SMX) is the drug of choice for PJP prophylaxis and treatment [56]. For treatment of mild disease, oral TMP/SMX can be given at a dose of 2 double-strength tablets (160 mg TMP and 800 mg SMX) every 8 h for 21 days. For more severe disease with hypoxemia (paO2 <70 mm Hg), intravenous therapy is preferred (15–20 mg/kg TMP and 75–100 mg/kg SMX every 6–8 h for 21 days) [88] (Table 3). The treatment by TMP may increase serum creatinine by 35% in patients with pre-existing renal impairment, due to the inhibition of the tubular creatinine secretion. This effect is reversible and does not alter the renal clearance, but may rise concerns regarding the renal function [89]. Optimal dose adjustment of TMP/SMX in renal impairment remains a critical issue (Table 3).

In patients with a history of intolerance to TMP/SMX or with inherent side effects (bone marrow suppression, rash, Stevens-Johnson syndrome, interstitial nephritis, aseptic meningitis, pancreatitis, hyperkalemia), treatment with pentamidine, atovaquone, dapsone with trimethoprim and primaquine are alternative treatments [56,90] (Table 3). Pentamidine therapy remains the second line treatment, even if its use can be complicated by numerous side effects as pancreatitis, hypo- and hyperglycemia and electrolyte disturbances [56]. In all patients in whom dapsone is prescribed, glucose-6-phosphate dehydrogenase (G6PD) levels should be measured and be normal before initiation. Besides the risk of haemolytic anemia, the risk of methemoglobinemia in KTR receiving dapsone as a curative or prophylactic treatment may be as high as 46% [91]. Methemoglobin should be monitored in these patients. Another important point to mention is that dapsone is metabolized partially by CYP3A4 and CYP2C19, which both might be inhibited by azoles, especially VCZ. Treatment should be continued for 21 days. In mild disease, 14 days may be sufficient [56].

The concomitant administration of glucocorticoids should be considered within 72 h of initiating antimicrobial therapy in patients with moderate to severe disease presenting with hypoxemia (arterial blood gas showing partial pressure of oxygen < 70 mmHg or alveolar-arterial oxygen gradient ≥ 35 mmHg). The anti-inflammatory property of the corticosteroids decreases the pulmonary inflammation that occurs in response to dead or dying organisms and prevents the clinical deterioration that is often seen after several days of treatment. Prednisone can be administered orally at a dose of 40–60 mg twice daily for 5–7 days, before being tapered over a period of 14 days [56,88,92–95].

4.7. Prevention

Prophylaxis is recommended for 6–12 months posttransplant with TMP/SMX (Table 3) [56]. If the recipient is allergic or if there are important side effects under this treatment, alternative regimens include atovaquone, dapsone (not in patients with severe side effects with TMP/SMX) and inhaled pentamidine (Table 3) [56].

Prevention should be reinitiated or continued during the later post-transplant period if supplementary risk factors occur, such as increased immunosuppression for graft rejection (T-cell depleting agents, alemtuzumab, rituximab, belatacept, anti-thymocyte globulin, …), higher-dose corticosteroid therapy (>20 mg daily of prednisone for more than two weeks), corticosteroid bolus and eventually chronic lymphopenia (<1000/mm^3) [56,62,68,96–99]. The duration of this targeted prevention depends on the indication [62]. Another argument for the reintroduction of a prophylactic regimen for 6–12 months could be PJP outbreak in the renal transplant center [53]. Finally, after treatment, effective secondary prophylaxis is recommended, but the standard regimen, duration and validity have not been well-studied [100].

5. Aspergillus

5.1. Epidemiology

Aspergillus is a ubiquitous filamentous fungus present in soil, decomposing vegetable material, on farming locations, in household dust, in building materials, ornamental plants, items of food and water [101]. The spores of *Aspergillus* enter the lungs by inhalation and can cause, depending on the immune status and the presence of other risk factors, a wide spectrum of disease, including allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis and invasive pulmonary aspergillosis (IPA). In regards to KTR, IPA is the only relevant

Table 2
Overview of the routes of contamination, radiological patterns, diagnostic tests, treatment and distinctive features of the microorganisms causing pneumonia.

microorganism	route of contamination	radiological pattern	diagnostic tests	treatment	distinctive features
Pneumocystis jirovecii	inhalation, reactivation, outbreaks have been described in kidney transplant units	GGO, consolidation	(immunofluorescence) microscopy, PCR/qPCR, serum BDG	TMP-SMX with prednisone* alternatively: pentamidine OR atovaquone OR dapsone + TMP** OR primaquine + clindamycin** with prednisone*	dyspnea, hypoxemia, elevated LDH second year post-transplant or no prophylaxis
Aspergillus	inhalation	nodules±cavitation, infiltrates	microscopy, culture, *Aspergillus* GM (serum, BAL), PCR/qPCR (plasma, serum, whole blood, BAL)	VCZ or ISA alternatively: AMB, CAS or PCZ	consider antifungal susceptibility testing
Cryptococcus	inhalation, reactivation	nodules, cavitation, GGO, consolidation, pleural effusion	microscopy, culture, serum CrAg, PCR	mild to moderate lung disease: FCZ disseminated disease: induction: AMB + 5-FC (≥14 days) consolidation and maintenance: FCZ (6–12 months)	exclusion of CNS disease by lumbar puncture mandatory
Mucormycetes	inhalation	consolidation, nodules, cavitation, pleural effusion, invasion of adjacent structures	microscopy, culture, PCR/qPCR	AMB, ISA or PCZ and surgical debridement	reverse halo sign; may be rapidly progressive; dissemination should be excluded by CT of the brain and sinuses
Histoplasma	inhalation, reactivation, donor-derived	multiple nodules, bilateral infiltrates	microscopy, culture, *Histoplasma* antigenuria, serologic antibody detection test, PCR/qPCR	AMB then ITZ	often disseminated; BSL-3 fungus; TD
Coccidioides	inhalation, reactivation, donor-derived	nodular alveolar infiltrates, reticular interstitial disease, lobar infiltrates, miliary interstitial disease, hilar AP or cavities	microscopy, culture, *Coccidioides* antigenuria, serologic antibody detection test, PCR/qPCR	FCZ in uncomplicated pneumonia AMB then FCZ CNS disease: FCZ, intrathecal AMB as rescue therapy	often disseminated; residency or travel history to endemic regions in America; BSL-3 fungus; TD
Blastomyces	inhalation	diffuse bilateral infiltrates, mediastinal AP, nodular mass and cavities	microscopy, culture, *Blastomyces* GM, PCR/qPCR	AMB then ITZ	often disseminated (skin, CNS); TD
Talaromyces marneffei	inhalation	solitary mass, mediastinal AP, patchy consolidations or bilateral multiple lung nodules	microscopy, culture, *Aspergillus* GM (serum)	AMB then ITZ	often disseminated (skin, bones); residency or travel history to endemic regions in Asia; TD

GGO: ground glass opacities; BDG: (1–3)-β-D-Glucan; CNS: central nervous system; TMP: trimethoprim; SMX: sulfamethoxazole; VCZ: voriconazole; ISA: isavuconazole; PCZ: posaconazole; CAS: caspofungin; AMB: amphotericin B; ITZ: itraconazole; FCZ: fluconazole; 5-FC: flucytosine; CrAg: cryptococcus antigen; AP: adenopathies; GM: galactomannan; BSL-3: biosafety level 3; TD: thermally dimorphic; * in hypoxemic patients (paO2 < 70 mm Hg): 40–60 mg of prednisone po/iv bid-tid with taper after 5–7 days over a period of 1–2 weeks in adolescents and adults. In children: 1 mg/kg po bid for 5 days, then 0,5 mg/kg po qd for 10 days. **not studied adequately in children to recommend.

disease process. Although there are more than 250 species, only a small number has been related with human diseases. Among these, *Aspergillus fumigatus is* the most common species recovered from cases of IPA, followed by *A.nidulans, A niger* and *A terreus* [102].

Even if KTR have one of the lowest risks (0,7%–4%) among SOTR [103–105], it is the most common invasive mold infection and accounts for almost 60% of all proven or probable fungal infections in this population [106]. Aside from a high dose and prolonged duration of corticosteroids, graft failure (with increasing immunosuppressive treatment), the need of hemodialysis, broad-spectrum antibiotic therapy, viral co-infections (CMV and HCV) and environmental factors have been reported to be risk factors [105,107–110]. A recent multinational case-control study including 112 KTR showed that more than half of IPA occurred beyond the sixth month after kidney transplantation (median interval from transplantation to diagnosis: 230 days), in some cases even after more than ten years [110]. Risk factors for early IPA were pre-transplant diagnosis of chronic obstructive pulmonary disease (COPD), delayed graft function and acute graft rejection. Previous occurrence of immunosuppression-related events such as pneumonia, tuberculosis, CMV disease and/or de novo malignancy was identified as an independent risk factor for IPA occurring after 180 days of transplantation [110].

Mortality rates among KTR with IPA remain high, over 30%-reaching 61%, and in surviving recipients, one in four to one in two experiences graft loss [110,111]. Independent predictors for 6-week all-cause mortality are the early occurrence of IPA within the first 6 months after transplantation, and bilateral involvement at diagnosis. The initial use of VCZ-based regimen showed a protective effect [110]. Independent predictors of mortality among SOTR with IPA infection are hepatic insufficiency, malnutrition and CNS involvement [112].

5.2. Clinical features

The most common presentation of aspergillosis in KTR is pneumonia [111]. Symptoms include fever, chest pain, shortness of breath, cough and/or hemoptysis. Fever is not always present in SOTR compared with neutropenic patients (22% vs 80%, respectively) [113]. Other symptoms, such as cough and chest pain are also less frequently seen in non-neutropenic patients [114]. Symptoms of CNS dissemination are alterations of the mental status, either progressive or acute, seizures or

Table 3
Pneumocystis pneumonia treatment and prevention with adjustment to renal function in adults and adolescents.

antiinfective agent	dosage	dose adjustment for CrCl
trimethoprim (TMP)-sulfamethoxazole (SMX)	treatment: mild disease: (160 mg TMP and 800 mg SMX oral) tid severe disease: (15–20 mg/kg TMP and 75–100 mg/kg SMX intravenous) tid to qid prevention: either 80 mg TMP/400 mg SMX or 160 mg TMP/800 mg SMX qd or thrice a week	if CrCl 30–50 ml/min: 5 mg/kg TMP tid, if CrCl 10–30 mL/min: 5–10 mg/kg TMP bid
clindamycin	treatment (in combination with primaquine): IV: 600–900 mg tid-qid	If CrCl <10 ml/min: not recommended
primaquine	treatment (in combination with clindamycine): oral: 15–30 mg qd	none
pentamidine	treatment: IV: initially 4 mg/kg/day with dose reduction to 2–3 mg/kg/day if needed	none
atovaquone	treatment and prevention: oral: 750 mg bid (higher doses to 1500 mg bid commonly used)	none
dapsone	treatment (in combination with TMP) oral: 100 mg qd prevention: oral: 50–100 mg qd	none
pentamidine	prevention: 300 mg administered through nebulizer every 3–4 weeks	if CrCl >10 ml/min: no adaptation, but use with caution if CrCl < 10 ml/min: 50–100 mg qd, but use with caution

CrCl: creatinine clearance; IV: intravenous; qd: once daily; bid: twice daily; tid: thrice daily; qid: four times daily.

focal motor deficits [115].

5.3. General laboratory findings

Microscopy of respiratory samples is seldom helpful due to its limited sensitivity of 50% at its best (on BAL examination) and *Aspergillus* is grown from sputum specimens in only 8–34%, and from BAL specimens in 45–62% of patients [113,116]. As *Aspergillus* is a ubiquitous organism, it may be difficult to distinguish between colonization and invasive infection. However, a positive culture from respiratory samples associated with suggestive patterns at the lung CT scan makes the diagnosis of aspergillosis probable in KTR [4]. To prove an IPA, transthoracic biopsies with histopathological study after staining by GMS or PAS would be necessary. On microscopic examination, small angular dichotomously branching septate hyphae, and tendency of hyphae to invade small and large arteries and veins, causing inflammation, thrombosis and infarction are very characteristic but not specific of this fungal genus. However, lung biopsies are invasive and often not possible in patients with suspected IPA, because mass-like lesions are lacking in most cases, or patients are severely ill with thrombocytopenia and other contraindications. The diagnosis relies then on a bundle of clinical suspicion and non-invasive biomarkers [117].

If CNS disease is suspected, lumbar puncture (LP) should be done after CNS imaging (brain CT scan or, more sensitive, IRM) and analysis should include microscopy and culture. However, the negativity of these tests does not exclude the presence of a CNS dissemination, especially in the presence of a probable or proven pulmonary aspergillosis associated with mental alterations and abnormal CNS imagery.

5.4. Focused diagnostic testing

Serum BDG may be elevated in KTR with IPA. However, as it has not been extensively studied in KTR and because of its low specificity as a non-specific marker of fungal infection, it is not recommended as a screening or diagnostic tool. The detection and quantification of galactomannan (GM), a component of the cell wall of *Aspergillus* spp., is considered specific of aspergillosis, even if many other fungi, such as *Paecilomyces*, *Penicillium*, *Talaromyces marneffei*, *Fusarium*, *Histoplama* and *Blastomyces* may have GM in their cell wall and may lead to a false positive result. The detection of GM in serum is less useful in KTR than in neutropenic patients with a sensitivity of about 58–68% [110,118]. Detection of GM in BAL has been advocated as a sensitive test for diagnosing IPA [18–20]. False positive results are higher at a low cut-off value of 0.5 [119]. In one retrospective study including 81 SOTR who had undergone BAL, GM testing sensitivity and specificity at a cut-off of $\geq$1.0 was 100% and 90,8% respectively [20]. The American Society of Transplantation Infectious Diseases Community of Practice recommends to use a BAL GM index value cut-off of $\geq$1.0 in combination with other fungal diagnostic modalities [120]. *Aspergillus* PCR by broad-range and specific PCR's may enhance the diagnosis of these infections but efficiency in KTR has been insufficiently studied so far [121–123]. The sensitivity of these PCRs is higher in BAL than in blood, however they may be positive during colonization by *Aspergillus* or after recovery from an invasive aspergillosis.

More standardized PCR methods have been marketed. Combined use of PCR together with BAL culture and GM may have a negative predicted value of 99% in immunocompromised patients [124–126].

5.5. Radiographic findings

Chest radiograph can fail to detect the early stages of pulmonary lesions, but thin-section lung CT at optimized dose -the imaging modality of choice-demonstrates nodules with or without cavitation and/or infiltrates [23] (Table 2). Compared with neutropenic patients, SOTR are also more likely to exhibit peribronchial consolidation or GGO in lung CT scan, but less likely to have macro-nodules, mass-like consolidation, halo-sign, or air-crescent sign [127]. In one retrospective study analysing prognostic factors on lung CT scan in SOTR and including 46 adult patients with IPA, consolidation or mass was significantly less frequent in survivors than in patients who died (62% versus 93%) [128].

If CNS disease is suspected, a brain CT scan or preferably a MRI should be done [23]. Mycotic aneurysm, haemorrhagic lesions, stroke, meningeal enhancement, empyema or cerebral abscesses may be seen [23,115].

5.6. Treatment

A substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of invasive aspergillosis. Species identification and antifungal susceptibility testing, especially for azoles, should be considered on all clinically relevant *Aspergillus* isolates, as acquired and intrinsic resistance is a global concern [23,129]. Current guidelines endorse for treatment VCZ (loading dose of 6 mg/kg IV twice daily, or 400 mg twice daily orally during 24 h, then 4 mg/kg IV twice daily intravenously or 200 mg twice daily orally) or ISA as the first-line choice for primary IPA [23] (Table 4).

The triazole agents are strong inhibitors of the CYP3A4 isoenzymes, leading to an increase in the serum levels of CNI and sirolimus (Table 1). A 50–60% reduction in the dose of these immunosuppressive agents may be necessary. Liposomal amphotericin B (LAmB; intravenously 3–5 mg/kg once per day) or amphotericin B lipid complex (ABLC; intravenously 5 mg/kg once per day) is recommended for species with high minimum inhibitory concentrations (MIC) values for azoles or in case of relapse or important side effects under VCZ (Table 4) [23,130].

Combination therapy is not recommended, but may be considered in

Table 4
Dosage of antifungal treatments described in this article, with their adjustment to renal function.

anti-infective agent		dosage	dose adjustment for CrCl
polyenes	amphotericin B lipid complex	IV: 5 mg/kg qd	none
	liposomal amphotericin B	IV: 3–7 mg/kg qd (depending on the fungal disease)	none
azoles	fluconazole	cryptococcosis treatment for mild to moderate pulmonary disease and for consolidation therapy in patients with CNS disease: oral or IV: 400–800 mg qd maintenance therapy: oral: 200 mg qd	if CrCl 10–60 mL/min, the fluconazole dosage should be decreased by 50%
	itraconazole	treatment in adults and adolescents: oral or IV: 200 mg tid day 1–3, then 200 mg bid prevention in adults and adolescents: oral: 200 mg qd	none; but IV not recommended if CrCl<30 ml/min and should be used with caution in patients with CrCl of 30–80 ml/min*
	posaconazole	adults and adolescents (>13 years): IV: 300 mg bid day 1, 300 mg qd from day 2 oral suspension: 200 mg qid oral DR tablets: 300 mg bid day 1, then 300 mg qd	none, but IV should be used with caution in patients with diminished CrCl*
	voriconazole	adults and adolescents (>50 kg): IV: 6 mg/kg bid day 1, then 4 mg/kg bid oral: 400 mg bid day 1, then 200 mg bid	if CrCl<50 mL/min, prefer the oral formulation*
	isavuconazole	IV or oral: 200–300 mg tid day 1–2, then 200–300 mg IV or oral qd from day 3	none
flucytosine	flucytosine	oral: 100 mg/kg in four doses	if CrCl 20–40 mL/min: 37.5 mg/kg bid if CrCl <20 mL/min: 37.5 mg/kg qd single doses of 25–30 mg/kg after each hemodialysis
echinocandines	anidulafungin	IV: 200 mg qd day 1, 100 mg qd from day 2	none
	caspofungin	IV: 70 mg qd day 1, 50 mg qd from day 2	none
	micafungin	IV: 100 mg qd	none

CrCl: creatinine clearance; IV: intravenous; qd: once daily; bid: twice daily; tid: thrice daily; qid: four times daily; DR delayed release; *cyclodextrin is present in the IV formulations of voriconazole, posaconazole and itraconazole which may accumulate in renal disease.

selected circumstances. The American Society of Transplantation Infectious Diseases Community of Practice recommends to consider a combination therapy when the *Aspergillus* species is unknown, until susceptibility testing is available, when a loading VCZ dose is not given or metabolism is unpredictable until serum trough levels are documented, in patients with disseminated or CNS disease and as salvage therapy [120]. In CNS disease, VCZ is the preferred azole agent [120] (a monotherapy with ITZ, PCZ or echinocandins should be avoided [131]), and the combination of a LFAmB with VCZ may be the best choice [120]. In other cases, the combination of an echinocandin with a triazole or lipid amphotericin B formulation is preferred [120,132].

The evidence to support any duration of therapy is weak and antifungal therapy is usually continued for 12 weeks until all signs and symptoms of active infection have disappeared and radiographic abnormalities have stabilized [23,120]. Failure to respond to VCZ therapy should prompt search for resistance and treatment switch [133]. Alternatives include LAmB, PCZ, and caspofungin (CAS) [134].

5.7. Prevention

KTR should avoid activities that are at increased risk for exposure to *Aspergillus* as mulching, raking leaves or visiting construction or excavation sites [120].

6. Cryptococcus

6.1. Epidemiology

Cryptococcus sp. is a ubiquitous encapsulated yeast, which is saprobe in nature. The primary environmental niche is certain trees and rooting wood. The fungus has frequently been isolated from soil contaminated by bird guano, especially from pigeons, turkeys and chickens. *C. neoformans* var. *grubii* and *C. neoformans* var *neoformans* affect primarily immunosuppressed patients worldwide [135]. In contrast, *C. gattii* has historically been found in tropical and subtropical regions. Its geographical range has expanded in the last decade, starting with a 2001 outbreak on Vancouver Island followed by associated outbreaks in nearby regions of the United States and Canada, as well as in Europe [136]. Although *C. gattii* causes disease predominantly in immunocompetent persons, new risk groups have been recognized as patients with underlying HIV, cancer, SOT, and other immunodeficiencies [137,138].

Cryptococcosis is the third most common fungal infection in SOTR after candidiasis and IPA and its incidence is higher in kidney and heart transplant recipients probably related to the use of high doses of corticosteroids or monoclonal antibodies such as alemtuzumab [139]. In KTR, cryptococcosis is recognized as the second most common fungal infection with incidences ranging from 0.3 to 5.8% [140].

Cryptococcus pneumonia in SOTR is considered to be secondary to a reactivation of a quiescent infection contracted by inhalation of the organism from an environmental source [141]. However, acquisition of primary infection or reinfection with a new strain is also possible as illustrated by the findings of identical genotypic profiles in isolates from a pet cockatoo and a KTR with cryptococcosis [135,142,143].

Cryptococcosis is more often seen after the first posttransplant year and occurrence even 3 years after transplantation is not uncommon [111,144,145]. Very rarely, transmission can occur through donor organ and should be considered in early presentations (within 30 days) [146].

Overall mortality in SOTR with cryptococcosis is reported to be 14%, but is lower when restricted to pulmonary involvement (3–4%) [2]. However, for infection with *Cryptococcus gattii* strains (VGIIc) treated according to current treatment guidelines, with high FCZ MIC, mortality rates reaching 70% have been reported [138].

In KTR, the mortality at 6 months, all presentation forms included, was evaluated in one retrospective study at 34% by 6 months [111]. In the same study, graft failures were recorded in 21% by 6 months.

6.2. Clinical features

Symptoms of pulmonary disease are cough, fever, chills, night sweats, chest pain, malaise, weight loss, shortness of breath and

hemoptysis [141,147]. But patients may also be asymptomatic and diagnosis relies on the incidental finding on a routine chest radiograph [148]. Acute respiratory distress syndrome (ARDS) can occur, often associated with disseminated infection [149] or after cessation or reduction of immunosuppressive therapy in the context of antifungal treatment with immune reconstitution syndrome (IRIS) [150].

In SOTR, extrapulmonary dissemination is common (50–75%) [141]. The most common presentation of cryptococcosis is CNS disease [111]. In patients with associated meningitis, frequent symptoms are prolonged headache, altered mental status, fever and malaise [151]. Absent headache in the context of a cryptococcal meningitis was described to be a risk factor for mortality, probably linked to a delayed diagnosis and delayed subsequent treatment [152].

The most common dissemination sites besides CNS include skin, soft tissue, bones and joints [145]. Cutaneous manifestations of disseminations include cellulitis, papular, nodular and ulcerative lesions, predominantly on the lower extremities [153].

6.3. General laboratory findings

Fifty to 75% of transplanted patients with cryptococcosis have extrapulmonary or disseminated disease [140,151]. As the additional diagnosis of cryptococcal meningitis or disseminated disease changes the dose and duration of induction therapy, a LP (after brain CT scan) and blood and urine culture should be done in all KTR suspected or diagnosed with cryptococcal disease [141]. LP should be associated to an opening pressure measurement, as overall 50–70% with cryptococcal meningitis have elevated intracranial pressure [154]. Cerebrospinal fluid (CSF) analysis should include Gram's and fungal stains, cell count, glucose, protein, fungal cultures and *Cryptococcus* antigen detection [141]. If meningitis is diagnosed, there is a need of intracranial pressure monitoring [155]. KTR with cryptococcosis do present with high rates of fungemia (38.3%) [140].

After meningitis has been excluded, and only pulmonary lesions have been documented, a BAL with or without biopsy should be considered [141]. The diagnosis of pulmonary cryptococcosis is based in one third of the cases on a positive respiratory tract (including BAL) or pleural fluid culture (39%) and in one third (30%) on a biopsy of the pulmonary lesion. GMS or PAS staining shows round to oval-shaped yeasts with narrow-based budding. As the capsule cannot be stained by these methods, there can be seen a halo around these cells.

Interestingly, patients receiving CNI are less likely for a CNS involvement [141,145].

6.4. Focused diagnostic testing

The preferred strategy to diagnose cryptococcosis is the detection of cryptococcal antigen. However, in isolated pulmonary disease serum antigen titers are less often positive and are lower than in disseminated and neurological diseases [2]. On the other side, a negative serum cyptococcal antigen detection test does not exclude meningitis. There are different detection tests commercially available: monoclonal lateral flow assay tests (LFA), monoclonal and polyclonal latex agglutination tests (LAT) and an enzyme immunoassay (EIA). The LFA has several advantages in comparison to the LAT's: it does not need any specimen preparation and is more sensitive across all cryptococcal strains, including *C. gattii* [156]. This increased sensitivity of the LFA may lead to low false positive results (1:2; 1:5) [157,158]. Monitoring of cryptococcal antigen testing is not recommended after antifungal induction therapy [141]. Despite fungemia leading to the diagnosis in only 4.5% of cases, blood cultures and serum antigen detection are the main diagnostic tool in SOT population [2,139].

As antifungal susceptibility may vary depending on the species and genotype of the *Cryptococcus*, thereby affecting the antifungal treatment, species identification should be tempted [138,141,159–161]. For identification of *C. gattii* strains, canavanine-glycine-bromothymol (CGB) agar may be used. Whenever possible, strains should be sent to reference laboratories for genotypic identification [141].

Even if clinical breakpoints of MICs are not defined by the Clinical and Laboratory Standards Institute (CLSI) and by the European committee on antimicrobial susceptibility testing (EUCAST) (except for amphotericin B for *C. neoformans*), susceptibility testing is recommended in patients who fail primary therapy, who have relapse of disease, who had prior antifungal exposure or in patients with a *C. gattii* infection [141].

6.5. Radiographic findings

The radiological findings on lung CT scan are variable. Patients with *C. gattii* pneumonia are more likely to present with cryptococcoma in the lungs [141]. Most of the patients have pulmonary nodules (either solitary or multiple: 68.7%). GGO and consolidations with or without cavitation can also be seen as well as reticular nodules, enlarged lymph nodes and pleural effusions [147,162]. Miliary pulmonary disease has also been described [163] (Table 1). Prior to LP a brain CT should be done to exclude a hydrocephalus and to detect mass lesions. However, to detect cryptococcomas, MRI is more sensitive.

6.6. Treatment

There have been no randomized trials on cryptococcosis treatment in SOTR. Choice of antifungal therapy is dependent on the site and extent of disease, net state of immunosuppression and severity of illness. Distinguishing between disseminated disease and localized disease is important prior to initiating therapy.

In patients with disseminated disease or moderate to severe respiratory disease, induction fungicidal therapy with LFAmB (LAmB 3–4 mg/kg/day or ABLC 5 mg/kg/day) and flucytosine (5-FC) (100 mg/kg/day) is recommended for a minimum of 14 days. If 5-FC cannot be used, the induction therapy by LFAmB should be extended for at least 4–6 weeks. A lack of 5-FC as induction therapy has been shown to be an independent risk factor for treatment failure at week 2 in SOT patients [155,164]. If the CSF fungal culture is positive initially, a LP should be repeated after two weeks and if still positive, the induction therapy should be extended [155].

For consolidation phase, a treatment by FCZ (400–800 mg/day; 6–12 mg/kg/day) is recommended for a duration of 8 weeks, and then a maintenance therapy by decreased doses of FCZ (200–400 mg/day; 3–6 mg/kg) for 6–12 months (Table 2) [155]. In high-fungal burden disease or relapse, a treatment by LAmB (6 mg/kg/day) might be considered [155].

In patient with CNS disease associated with an initial opening pressure above 25 mm Hg, a large volume of fluid should be removed to normalize the intracranial pressure. Then, LP should be performed regularly. Sometimes, if repeated LP are insufficient, temporary lumboperitoneal or external ventricular drains may be necessary for normalizing and monitoring the intracranial pressure, [155,165].

The recommendation for patients with focal mild-to-moderate pulmonary disease (in the absence of diffuse pulmonary infiltrates and in the absence of severe immunosuppression) and incidentally detected pulmonary disease in otherwise asymptomatic patients is FCZ orally 400 mg/day (6 mg/kg) for 6–12 months [155].

Amphotericin B deoxycholate (AmBd) is not recommended as first line therapy due to the high risk of nephrotoxicity. The tolerated dose is uncertain, but a dose of 0.7 mg/kg/day is suggested with a close monitoring of the renal function [155].

If FCZ cannot be used, or if isolates have high FCZ MIC's, newer triazoles as VCZ, PCZ or ISA may be considered as alternative therapy [141]. Discontinuation of therapy must be made on the basis of signs, symptoms and level of immunosuppression.

In the presence of persistent radiographic abnormalities or symptoms, surgery should be considered [155].

Whenever possible, a reduction in immunosuppression should be done during therapy. A gradual tapering of immunosuppression is preferred to avoid acute organ rejection or emergence of immune reconstitution inflammatory syndrome (IRIS) [141,155]. Thereby, it may be helpful to start with the stepwise tapering of corticosteroids, as CNIs have a direct anticryptococcal activity. IRIS occurs typically 4–6 weeks after initiation of antifungal treatment, and may mimic worsening of cryptococcal disease. Clinical symptoms, as headache, and radiological signs may increase despite appropriate antifungal therapy, but repeated microbial workup does not show positive *Cryptococcus* cultures. Treatment with the association MPA-tacrolimus-prednisone, CNS disease and discontinuation of CNI has been described as increasing the risk for IRIS, and subsequently the risk for allograft rejection [150,155]. If major complications appear, as ARDS, a treatment with 0.5–1 mg/kg of prednisone or equivalent may be considered [155].

6.7. Prevention

Primary antifungal prevention is not recommended for KTR. However, in patients having experienced a cryptococcosis and needing increased immunosuppression, secondary prevention may be considered [141].

In case the allograft function fails, retransplantation may be considered in patients with the possibility of a hemodialysis bridge after several months of treatment and resolution of symptoms and signs of active disease along with negative cultures from the initial site of infection [141].

7. Mucormycetes

7.1. Epidemiology

Mucormycosis refers to a group of opportunistic mycoses that occur in immunocompromised or diabetic patients and in otherwise healthy individuals in India and China, e.g. in the forms of renal mucormycosis and chronic (sub-)cutaneous infections [166]. The number of published cases in KTR has increased considerably since the 2000s, but remains uncommon [167,168]. Mucormycetes (formerly zygomycetes) encompass *Mucor*, *Lichtheimia* and *Rhizopus* among others. The commonest causes of human infection are *Rhizopus* spp. *(R. oryzae*, *R. arrhizus* and *R. microspores), Mucor* spp. and *Lichtheimia* spp. These organisms are usually found in the soil and on decaying vegetation, grow rapidly and release easily spores that once inhaled may lead to a mucormycosis. They all have a propensity to invade blood vessels, frequently causing arterial and venous thrombosis and subsequent ischemic or haemorrhagic infarction. Incidence in SOTR have ranged from 0.4% to 16.0% depending on the transplanted organ and the geographical area [169]. The range is 0.2–1.2% in KTR [170]. Risk factors in this population group are increased immunosuppression (following antirejection treatment with high doses of steroids), neutropenia, renal failure, diabetes mellitus, and prior VCZ and/or CAS use [168,171]. In KTR, mucormycosis develop a median of 2–2.5 months post transplantation [168,171]. In most cases, the infection is rapidly progressive and results in death unless underlying risk factors are corrected and aggressive treatment with antifungal agents and surgical excision is instituted. Mortality rates among SOTR are very high (>50%) despite antifungal therapy [171,172].

7.2. Clinical features

Rhino-orbital-cerebral and pneumonia with infarction and necrosis are the major syndromes caused by these fungi [167,168,171]. Symptoms of pulmonary mucormycosis are nonspecific and consist in fever that is unresponsive to broad-spectrum antibiotics. Non-productive cough is common, and haemoptysis, pleuritic chest pain and dyspnea are possible.

7.3. General laboratory findings

Direct microscopy of clinical specimens, preferably using optical brighteners (as calcofluor white), may allow a rapid presumptive diagnosis. Even if culture has low sensitivity, it is essential as it allows identification and susceptibility testing (for epidemiological purposes) of the isolate in case of growth [166]. Mucormycetes may now be reliably identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) techniques [173] or molecular tools [174]. Histopathological examination of stained tissue specimens (GMS, PAS) may allow differentiation between hyphae of *Aspergillus* or morphologically related fungi, and hyphae of mucormycetes, that form characteristic broad, non-septate or sparsely septate hyphae and a ribbon-like appearance.

7.4. Focused diagnostic testing

In patients with a possible invasive fungal infection, negative galactomannan test results in serum and BAL increase the likelihood of invasive mucormycosis, but positive results do not exclude the diagnosis, as mixed fungal infections are possible [121]. BDG testing is not a reliable marker and is not recommended for the diagnosis of invasive mucormycosis. PCR-based techniques have been used to detect and to identify mucormycetes from cultures, biopsies, BAL and more recently from plasma and serum samples. This allows an effective treatment by identifying causative mucormycetes and could be useful as a follow up tool to assess the fungal burden, which reflects the evolution of mucormycosis [174].

7.5. Radiographic findings

The signs on chest images are nonspecific and indistinguishable from those of pulmonary aspergillosis. Most frequently, consolidation, nodules, cavitations, infiltrates, atelectasis, effusion, air crescent sign are described [175]. The reverse halo sign, an area of central ground-glass necrosis surrounded by a ring of consolidation, multiple nodules and pleural effusion are suggestive of pulmonary mucormycosis in lung CT scan [119,166]. Pulmonary mucormycosis can also invade lung-adjacent organs such as the mediastinum and the heart, or disseminate hematogeneously to other organs [170] (Table 1). Therefore, whenever mucormycosis infection is suspected, CT of the brain, sinuses, and chest should be performed.

7.6. Treatment

Extensive early surgical debridement is recommended in combination with antifungals and is reported to be an independent predictor of successful therapy in SOTR with pulmonary mucormycosis [170,175]. In general, a diagnosis-driven antifungal treatment is applied as soon as possible. Polyenes are the preferred therapeutic agents for mucormycosis. LAmB is preferred at 5 mg/kg/day, which can according to some experts, be increased to 10 mg/kg/day, especially if there is a CNS involvement [166,172]. Alternative treatments are ISA (3 × 200 mg day 1 and 2, then 200 mg qd from day 3), oral PCZ delayed release tablets or PCZ IV (2 × 300 mg day 1, 1 × 300 mg from day 2) [166] (Table 4). The optimal duration of treatment is unknown and should depend on the clinical and radiological evolution of the infection [166]. Generally, antifungal treatment is given for weeks to months [166].

8. Histoplasma

8.1. Epidemiology

Histoplasma is a thermally dimorphic fungus, endemic in North America (particularly in the Ohio and Mississippi River valleys), Latin America, Africa, Australia and Asia [176,177]. Two humans infecting

varieties of *H. capsulatum* are recognized (var. capsulatum and var. duboisii) differing in their parasitic phenotype. With the larger implementation of whole genome sequencing, the genus is currently undergoing substantial taxonomic reviews [178]. The fungus has been recovered most frequently from soil enriched with bird or bat droppings.

Although histoplasmosis is the most common endemic mycosis among immunocompromised patients in general, the frequency of histoplasmosis among SOTR appears to be low. The incidence of clinical histoplasmosis is < 0,5% in SOTR in endemic regions in North America [179,180]. In contrast to immunocompetent hosts, the disease tends to disseminate [181]. Although uncommon in Western Europe, physicians treating immunocompromised patients should be aware of this pathogen, given the increasing immigration of patients from regions of the world where histoplasmosis is endemic and the increasing number of transplant recipients visiting endemic regions [182,183].

KTR have the highest incidence of *Histoplasma* infection compared to other SOTR [184]. In the largest series of histoplasmosis in SOTR, median time from transplantation to infection was 27 months, but one third of the cases occurred during the first year following transplantation. In this study the mortality was 10%, and highest within the first three weeks following diagnosis. Higher antigen concentration as well as older age and fungemia were associated with higher death rates in univariate analysis [185].

In a small retrospective study, the mean interval from transplantation to diagnosis among 14 KTR was 5.1±2.1 years. In this study, infection was complicated by graft failure in 21% by six months and led to death in 38% of patients by six months [111].

8.2. Clinical features

Clinical manifestations can vary and are not specific, which can cause a delay in diagnosis. Patients may present with pneumonia or more often with progressive disseminated histoplasmosis [111,186]. Tuberculosis is a common differential diagnosis in endemic regions. The most common clinical manifestations are fever and shortness of breath, followed by diarrhoea, cough, diaphoresis and headache [179]. When dissemination occurs, ulcerations and granulomas of the oronasopharynx are the most frequent lesions, while skin lesions are present in only 6% of patients [187]. Patients can also present with adrenal insufficiency, gastrointestinal and CNS involvement, in addition to hepatosplenomegaly and bone marrow involvement [186].

8.3. General laboratory findings

It is important to underline that none of the available tests has an absolute diagnostic accuracy and thus, a combination of various tests should be used to optimize the diagnostic yield [184]. The diagnosis of proven histoplasmosis is established with culture or histopathological or direct microscopic demonstration of characteristic intracellular yeast forms [4]. The intracellular yeast form (usually 2–4 μm in size narrow-based budding yeasts, clustered within macrophages) can be detected by microscopy either in fresh clinical samples by the use of calcofluor, or in histopathological samples after special staining methods (GMS, PAS) [188]. The differential diagnosis of these yeast cells includes *Talaromyces marneffei, Candida glabrata*, *Emergomyces* spec. and endospores of *Coccidioides* [188]. Culture from BAL or lung biopsy of this biosafety level 3 fungus needs special safety precautions and may take as long as 4–8 weeks to grow on appropriate media (Sabouraud, Brain Heart Infusion Agar). The fungus is growing at 26 °C as mold and at 37 °C as yeast. The sensitivity of cultures varies substantially [188]. *Histoplasma capsulatum* can grow in cultures from different specimens (BAL, biopsies, CSF), but bone marrow and blood give highest sensitivity. This sensitivity can improve by using lysis centrifugation technique [189].

8.4. Focused diagnostic testing

A substantially faster diagnosis can be obtained by detection of *Histoplasma* polysaccharidic antigen (HPA) through EIA in urine, especially if the disease is disseminated. Cross-reactions are possible with antigens of other fungi as *Coccidioides* spp., *Emergomyces* spp, *Blastomyces* spp, *Talaromyces marneffei* and *Paracoccidioides* spp [184,190,191]. Also rabbit antithymocyte globulin has been reported to result in false positive *Histoplasma* antigen results [184]. Data from diverse immunocompromised patient groups suggest that the sensitivity of HPA in disseminated histoplasmosis may be comparable in serum and urine, and that the magnitude of antigenuria may correlate with disease severity [192]. In non-transplant patients, a study reported a sensitivity and specificity of more than 90% of BAL antigen assays in patients with pulmonary histoplasmosis [193]. If urine antigen is positive at baseline, levels should be followed, expecting a fall in response to therapy and a rise in relapsed infection. However low-level urinary antigens may persist even after a successfully completed treatment in SOTR [192]. False-positive results for *Aspergillus* galactomannan can occur [194].

Detection of *Histoplasma* antibodies may be a valuable additional tool in the diagnosis of histoplasmosis in SOTR. However, caution is required because the impaired antibody production in these patients decreases the sensitivity of these tests. In one retrospective study including 152 cases of histoplasmosis in SOTR, one third of the serological tests were negative, and only one case was diagnosed solely with a positive antibody test [185]. Available tests include immunodiffusion (ID) and complement fixation (CF). However positive tests results may be caused by crossreactions with other fungal diseases and granulomatous diseases and a negative test is common even in immunocompetent patients in the first four to eight weeks after infection [188]. The diagnosis of histoplasmosis is increasingly helped by PCR performed on fresh clinical material and on formalin fixed paraffin embedded samples [195–199]. Different molecular methods have been used and show variable sensitivities and specificities.

8.5. Radiographic findings

Chest radiograph is often negative, but lung CT scan is more sensitive. The most common abnormalities are multiple nodular lesions and diffuse bilateral infiltrates. In addition, lesions consistent with histoplasmosis such as splenomegaly (with or without focal lesions) and lymphadenopathy can be found on abdominal CT scan [179].

8.6. Treatment

Antifungal treatment is mandatory in KTR and should be started as soon as possible. The optimal duration of treatment is unknown. For mild to moderate disease, 12 weeks treatment is recommended. However, most SOTR develop progressive disseminated disease or severe disease, which should be treated during 1–2 weeks by LAmB (3 mg/kg daily) followed by oral ITZ (200 mg 3 times daily for 3 days, then 200 mg twice daily) for a total of at least 12 months (Table 2). For patients who develop respiratory distress or hypoxemia, methylprednisolone (0.5–1.0 mg/kg daily intravenously) during the first 1–2 weeks of antifungal therapy is recommended. Whether or not secondary prevention is necessary is still debated [200]. Relapse occurs in 6% of SOTR with histoplasmosis supporting the safety of discontinuing antifungal therapy following a 12-month course of treatment [185]. Despite sparse data, PCZ or ITZ may be efficient second line treatments [185,192,201,202]. Awareness should be risen, that cases of increased MICs to VCZ have been described in *Histoplasma* strains found in relapsing histoplasmosis of HIV patients treated by FCZ [200,203] and that in a retrospective study, VCZ treatment was associated with increased mortality in the first 42 days compared to ITZ [204]. Heightened awareness of findings consistent with relapse should be maintained during the first two years following the initial episode, and continued awareness of the

risk of relapse for the remainder of the patient's life.

8.7. Prevention

Screening for prior histoplasmosis and primary prophylaxis in endemic regions is not recommended. However, in patients who have recovered from an active histoplasmosis 2 years prior to the initiation of immunosuppression, azole prevention may be considered (ITZ 200 mg qd). In patients with previous histoplasmosis and during intensive immunosuppression, serial *Histoplasma* antigen detection tests should be performed [201].

KTR should be counselled to avoid at-risk exposures as close contact with bat and bird guano or spelunking in endemic regions [201].

9. *Coccidioides, Blastomyces* and *Talaromyces marneffei*

Coccidioides, Blastomyces and *Talaromyces marneffei* are endemic fungi that can cause pneumonia in humans residing in or travelling to their specific geographic area, characterized by an increased risk of severity and dissemination in KTR [201,205–208]. Their characteristics are briefly summarized in Table 2.

10. Conclusion

Fungal pneumonias are dreaded infections in KTR, with a high rate of mortality. Early diagnosis combined with targeted therapy are key points in reducing mortality. Diagnostic tools have limited sensitivity and specificity and must be interpreted in the context of the clinical setting. Invasive sampling techniques as bronchoalveolar lavage and lung biopsies are often required to permit a rapid diagnosis. Treatment should be initiated as soon as the diagnosis is considered but may carry risks of toxicity and drug interactions requiring close monitoring of immunosuppressive agents. Reducing immunosuppression levels is also an important adjunct to treatment that should be considered.

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Declaration of competing interest

None.

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